Hospital Drug Safety – Role of the Pharmacists

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1 Zusammenfassung

Medikationsfehler und unerwünschte Arzneimittelwirkungen (UAW) treten bei hospitalisierten Patienten häufig auf. Meine Dissertation sollte die Häufigkeiten von Medikationsfehlern und UAW bei hospitalisierten Patienten aufzeigen und Massnahmen zu derer Reduktion beschreiben.

Das Hauptziel meiner Dissertation war dem entsprechend die existierenden Daten über Medikationsfehler und UAW in der Literatur zu reviewen, mit einem besonderen Augenmerk auf Frequenz und Risikofaktoren, und Massnahmen zu derer Verhütung vorzuschlagen. Etwas detaillierter:

- Die Literatur zwischen 1990 und 2003 nach Studien betreffend Medikationsfehler/UAW bei hospitalisierten Patienten zu durchsuchen und zu reviewen
- Design und Mithilfe bei einer grossen Studie, in der potentielle Arzneimittelinteraktionen bei dyslipidämischen, mit einem Statin behandelten Patienten untersucht wurden
- Das Generieren von Richtlinien zur Dosisadaptation von Chemotherapeutika bei Patienten mit Leberleiden zu erstellen. Diese Studie regte ich an, weil Anfragen aus diesem Gebiet in Spitalapotheken nicht selten sind und weil das Nicht-Angleichen der Dosis ein Medikationsfehler ist

In der ersten Studie analysierte ich die Originalpublikationen über Medikationsfehler und/oder UAW bei hospitalisierten Patienten die zwischen 1990 und 2003 veröffentlicht wurden. Dabei fokussierte ich auf die Häufigkeit, Risikofaktoren und Massnahmen für die Vermeidung solcher Fehler oder Reaktionen. Zuerst führte ich einen Search in Datenbanken durch (Medline, Embase), wobei ich die Ausdrücke „medication error“, „adverse drug reaction“, “adverse event”, „hospital“ verwendete. Ich schaute auch Reviews an, um die aufge-

fundenen Arbeiten zu komplettieren. Die Analyse zeigte, dass Medikationsfehler mit einer Häufigkeit von ungefähr 5% aller Applikationen vorkommen, allerdings mit einer hohen Variabilität zwischen den 29 gefundenen Studien. Diese Variabilität ist erklärt durch die Art des Erfassen der Medikationsfehler (systematische Erfassung vs. Spontanmeldungen) und durch die Art und Weise, wie die Medikamente verabreicht werden(intravenöse Arzneistoffe haben die höchste Fehlerrate). Fehler ereignen sich während des gesamten Medikationsprozesses, wobei Applikationsfehler mehr als 50% der Fehler ausmachen. Wichtige Risikofaktoren sind schlechte pharmakologische Kenntnisse oder Arbeitsüberlastung des Pflegepersonals und der Ärzte, nicht-computerisierte Verarbeitung der Verschreibungen und das Fehlen von Klinischen Pharmazeuten auf den Abteilungen. UAW betrafen ca. 6% aller Patienten pro Hospitalisation, wobei auch hier eine grosse Variabilität zwischen den 31 gefundenen Studien bestand. Diese Variabilität kann erklärt werden durch Unterschiede im Erfassen der Frequenz der UAW und durch die verschieden Abteilungen, welche studiert wurden. Risikofaktoren waren weibliches Geschlecht, Alter > 65 Jahre, Polypharmazie und Medikationsfehler. Diese Befunde erlaubten mir, Massnahmen zur Reduktion von Medikationsfehlern vorzuschlagen, insbesondere die Verbesserung der Kenntnisse in Pharmakologie aller im Medikationsprozess involvierter Personen, Computerisierung des gesamten Medikationsprozesses und Anstellung von Klinischen Pharmazeuten auf den Abteilungen.

In einer zweiten Arbeit übernahm ich das Design und teilweise die Durchführung einer grossen Studie, in der wir die Prävalenz von Arzneimittelinteraktionen bei dyslipidämischen Patienten untersuchten, welche mit einem Statin behandelt werden. Die Medikationsprofile und andere klinische Daten von mit Statinen behandelten Patienten wurden von 242 Praktikern in der Schweiz erhalten. Die Medikationen wurden dann elektronisch mittels eines Interaktionsprogramms auf potentiell schwerwiegende Interaktionen geprüft. Insgesamt prüften

wir 2742 ambulante Patienten (mittleres Alter 65.1 ± 11.1 [SD] Jahre, davon 61.6% männlich) mit 3.2 ± 1.6 (Mittelwert±SD) Diagnosen und 4.9 ± 2.4 verschriebenen Arzneistoffen. Von diesen Patienten hatten 190 (6.9%) insgesamt 198 potentiell schwerwiegende Statin-Interaktionen. Interagierende Arzneistoffe waren Fibrate oder Nikotinsäure (9.5% der Patienten mit einer Statin-Interaktion), CYP3A4-Inhibitoren (70.5%), Digoxin (22.6%) oder Cyclosporin (1.6%). Der Anteil der Patienten mit einer Statin-Interaktion war 12.1% für Simvastatin, 10.0% für Atorvastatin, 3.8% für Fluvastatin, und 0.3% für Pravastatin. Das Programm eruierte zusätzlich 393 potentiell kritische nicht-Statin-Interaktionen bei 288 Patienten. Die Studie zeigte, dass die Kombination mit CYP3A4 Inhibitoren der häufigste Grund für potentiell schwerwiegende Interaktionen mit Statinen ist. Da Patienten mit einer solchen Interaktion ein erhöhtes Risiko für Rhabdomyolyse haben, sollten die Kliniker die häufigsten Interaktionen mit Statinen kennen und wissen, wie diese vermieden werden können.

In der dritten Studie regte ich an, Dosisempfehlungen für Chemotherapeutika bei Patienten mit Leberleiden auszuarbeiten, basierend auf den pharmakokinetischen Eigenschaften. Dosisadaptationen von Chemotherapeutika sind bei Patienten mit Leberleiden wichtig, einerseits weil Tumorpatienten nicht selten Hepatopathien haben und andrerseits, weil Chemotherapeutika einen engen therapeutischen Bereich aufweisen. Wir klassifizierten die Chemotherapeutika, welche sich ende 2003 in der Schweiz auf dem Markt befanden, nach Bioverfügbarkeit/hepatischer Extraktion und Ausscheidungsmuster, um Voraussagen zur Dosisadapatation bei Patienten mit Leberleiden machen zu können. Diese Voraussagen wurden mit kinetischen Studien verglichen, welche in dieser Patientenpopulation durchgeführt worden waren. Von den 69 aufgefundenen Arzneistoffen hatten 52 einen dominierenden extrarenalen Metabolismus oder Elimination (meistens hepatisch). Für 48 Arzneistoffe konnte die hepatische Extraktion aufgefunden oder berechnet werden, weshalb diese Arzneistoffe nach hepatischer

Extraktion klassifiziert werden konnten. Für 17 Arzneistoffe fanden sich kinetische Studien in der Literatur, welche meistens die Grundlage für Dosisempfehlungen bilden. Präzise Empfehlungen gibt es für 13 Arzneistoffe, welche biliär eliminiert werden (z.B. Doxorubicin und Derivate sowie Vinca Alkaloide). Allerdings fanden sich keine Validationsstudien, in welchen diese Dosierungsempfehlungen mit der Kinetik und Dynamik dieser Arzneistoffe bei Patienten mit eingeschränkter Leberfunktion studiert wurden. Die Studie zeigt auf, dass die Datenlage bei den Zytostatika gegenwärtig für einen fundierten Gebrauch dieser Arzneistoffe bei Patienten mit Leberleiden nicht gut genug ist. Die pharmazeutische Industrie sollte deshalb von den Behörden dazu verpflichtet werden, kinetische Daten für die Klassifikation von Arzneistoffen zu liefern (insbesondere die hepatische Extraktion neuer und kritischer alter Arzneistoffe) und kinetische Studien bei Patienten mit Leberleiden durchzuführen, damit quantitative Angaben gemacht werden können.

Diese Studien zeigen deutlich auf, dass Medikationsfehler und UAW bei hospitalisierten Patienten häufig vorkommen. Medikationsfehler sind wichtige Risikofaktoren für vermeidbare UAW. Für 2 Medikationsfehler, nämlich Arzneimittelinteraktionen und fehlende Dosisadaptation bei Patienten mit Leberleiden, führten wir Studien durch, welche auf ihre Prävalenz fokussierten und mittels welchen wir Angaben über ihre Vermeidbarkeit machen können. Spital- und klinische Pharmazeuten nehmen bei der Detektion und Vermeidung von Medikationsfehlern und UAW eine wichtige Rolle ein.

2 Summary

Medication errors and adverse drug reactions are frequent in hospitalized patients. The principle aim of my dissertation was to review the existing data about frequency and risk factors of these findings and to propose measures for their reduction, focusing on the possibilities of hospital pharmacists.

In more detail, the aims were:

- To review the literature published between 1990 and 2003 for studies reporting incidences of medication errors and/or adverse drug effects in hospitals
- To investigate the prevalence of potential drug-drug interactions in ambulatory patients treated with a statin
- To propose dosage guidelines for patients with liver disease being treated with antineoplastic drugs. This study was initiated because questions about dose adaptation of antineoplastic drugs are quite frequent in hospital pharmacies

In the first study, I analyzed the original publications about medication errors and/or adverse drug reactions in hospitalized patients published between 1990 and 2003, with a focus on frequency, risk factors and avoidance of problems associated with pharmacotherapy. I performed a database search (Medline, Embase) for original articles using the terms „medication error“, „adverse drug reaction“, “adverse event”, „hospital“ and supplemented the articles retrieved by searching review articles for additional references. The analysis revealed that medication errors occur with a frequency of approximately 5% of all drug applications, with a high variability among the 29 studies retrieved. This variability is explained by the way medication errors are detected (systematic screening of patients or charts vs. spontaneous reports) and by the way drugs were administered (intravenous drugs have the highest error

frequency). Errors occur along the whole medication process, with application errors accounting for more than 50% of them. Important risk factors are insufficient pharmacological knowledge and work overload of the nursing staff, non-computerized transmission of prescriptions and lack of clinical pharmacists on the wards. Adverse reactions affect approximately 6% of the patients per hospitalization and show a high variability between the 31 studies retrieved. This variability can be explained by different assessment of the frequency of adverse drug reactions and by the wards studied. Risk factors for adverse drug reactions include female sex, age >65 years, polypharmacy and medication errors. These findings allowed me to propose strategies for reducing medication errors, e.g. to improve the knowledge about pharmacology of all persons involved in the medication process, computerization of the entire medication process and the engagement of clinical pharmacists on the wards.

In the second study, we performed a cross-sectional analysis of the prevalence of potentially serious drug-drug interactions of ambulatory dyslipidemic patients treated with a statin. Data of patients with dyslipidemia treated with a statin were collected from 242 practitioners from different parts of Switzerland. The medication was screened for potentially harmful DDIs with statins or other drugs using an interactive electronic drug interaction program. We included 2742 ambulatory statin-treated patients (mean age 65.1 ± 11.1 [SD] years; 61.6% males) with 3.2 ± 1.6 (mean±SD) diagnoses and 4.9 ± 2.4 drugs prescribed. Of those, 190 patients (6.9%) had a total of 198 potentially harmful drug-statin interactions. Interacting drugs were fibrates or nicotinic acid (9.5% of patients with drug-statin interactions), CYP3A4-inhibitors (70.5%), digoxin (22.6%) or cyclosporine (1.6%). The proportion of patients with a potential drug-statin interaction was 12.1% for simvastatin, 10.0% for atorvastatin, 3.8% for fluvastatin, and 0.3% for pravastatin. Additionally, the program identified 393 potentially critical non-statin DDIs in 288 patients. Our study showed that CYP3A4 inhibitors are the most

frequent cause for potential interactions with statins. As the risk for developing rhabdomyolysis is increased in patients having drug-statin interactions, clinicians should be aware of the most frequently observed drug-statin interactions and how these interactions can be avoided.

In the third study, we classified the antineoplastic drugs marketed in Switzerland by the end of 2003 according to their hepatic extraction in order to predict their kinetic behavior in patients with liver disease and to give dose recommendations. Dose adaptation for liver disease is important in patients treated with antineoplastic drugs due to the high prevalence of impaired liver function in this population and the dose-dependent, frequently serious adverse effects of these drugs. We therefore classified the antineoplastic drugs marketed in Switzerland by the end of the year 2004 according to their bioavailability/hepatic extraction in order to predict their kinetic behavior in patients with decreased liver function. This prediction was compared with kinetic studies carried out with these drugs in patients with liver disease. Of the 69 drugs identified, 52 had a predominant extrarenal (in most cases hepatic) metabolism and/or excretion. For 48 drugs, hepatic extraction could be calculated and/or bioavailability was available, allowing classification according to hepatic extraction. For 17 drugs, kinetic studies have been reported in patients with impaired liver function, with the findings generally resulting in quantitative recommendations for adaptation of the dosage. In particular, recommendations are precise for 13 drugs excreted by the bile (e.g. doxorubicin and derivatives, and vinca alkaloids). Validation studies comparing such recommendations with kinetics and/or dynamics of antineoplastic drugs in patients with decreased liver function have not been published, however. The study shows that there are currently not enough data for safe use of antineoplastic drugs in patients with liver disease. We concluded that pharmaceutical companies should be urged to provide kinetic data (especially hepatic extraction) used for classification of such drugs and to conduct kinetic studies for drugs with primarily hepatic me-

tabolism in patients with impaired liver function allowing to give quantitative advise for dose adaptation.

The studies show that medication errors and adverse drug reactions are frequent in hospitalized patients. Medication errors are an important risk factor for avoidable adverse drug reactions. For two of them, drug-drug interactions and dose adaptation in patients with liver disease, we performed studies focusing on the incidence and guidelines for their avoidance, respectively. Hospital pharmacists have an important role both in the prevention and detection of medication errors and adverse drug reactions.

3 Introduction

3.1 Medication errors and adverse drug reactions

An optimal pharmacotherapy is achieved when the right drug in the correct dosage and quality reaches the right patient at the right time point. In particular for the hospital pharmacist, drug therapy should also be optimized economically and the correct disposal of drug waste should be assured. Despite all the efforts of hospital pharmacists, physicians, nurses and other health professionals involved, most drug therapies have not only the desired and expected beneficial effects, but are associated also with adverse reactions (1).

All circumstances, which potentially or actually impair the optimal result of pharmacotherapies are called „problems associated with pharmacotherapy" or shorter "drug-related problems" (2), consisting mainly of medication errors and adverse drug reactions (see Table 3.1). Medication errors are errors occurring in the medication process (prescription, storage, preparation, handling, application of drugs, see Table 3.2). In the majority of cases, medication errors do not lead to adverse drug reactions (3, 4), but they represent a strong risk factor for adverse drug reactions, which can be avoided. While medication errors are judged from the handling of drugs, for adverse drug reactions, the patient is in the centre. It can be expected that approximately 6% of the hospitalized patients will have at least one adverse drug reaction during the hospitalization (1).

Table 3.1 Definition of problems associated with pharmacotherapy (drug-related problems)

Drug-related problems	All circumstances that involve a patient's drug treatment that actually, or potentially, interfere with the achievement of an optimal outcome (2)
Medication errors	Any error in the medication process (prescribing, dispensing, administering of drugs), whether there are adverse consequences or not (5)
Adverse drug reactions	Any response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological functions (6)
Adverse drug events	Any injury related to the use of a drug, even if the causality of this relationship is not proven (5)

As stated above, medication errors are errors, which occur somewhere in the medication process (see Table 3.2). Their appearance is highly depending on the motivation but also on the formation in pharmacology of the hospital staff involved in pharmacotherapy (physicians, pharmacists, nurses and others) (2). Medication errors can be grouped according to their appearance in the medication process (see Table 3.3). Approximately 5% of all drug applications contain an error (2), with application of specific drugs such as infusions being affected much more often (7).

Table 3.2 Complexity of pharmacotherapy in hospitals

- Drug history
- Drug prescription
- Logistics: Preparation of drugs in the pharmacy, transport on the wards
- Preparation and administration of drugs on the wards
- Monitoring and individualization of drug therapies
  - Identify drug-drug interactions and adverse effects → optimization of therapy
  - Identify non-responders → find out reasons, adapt therapy
  - Find out optimal dosage (optimization of the ration between benefice and damage)
- Explanation of the therapy before the patient leaves the hospital

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As shown in Table 3.4, adverse drug reactions can be grouped into type A and type B reactions (8). Type A reactions are clearly dose-dependent and predictable, and can therefore be prevented in most instances. Many of them may be the result of medication errors, since they could be avoided by using a reduced dosage. Type B reactions are idiosyncratic, meaning that they are rare, cannot be predicted and are not clearly dose-dependent. There may be risk factors such as known drug allergies or certain family diseases. In most cases, however, they cannot be avoided, but their course can be influenced by early recognition and stopping the administration of the offending drugs.

Table 3.3 Most important medication errors in hospitalized patients

1. Prescription errors

- Wrong drug (e.g. drug not suitable for this indication)
- Correct drug, wrong patient (e.g. ignoring contra-indications, drug-drug interactions or drug allergies)
- Wrong galenic form (e.g. tablets in a patient not able to swallow)
- Wrong dose

2. Transcription and/or interpretation errors

- Transcription of prescriptions (e.g. physicians - nurses)
- Usage of abbreviations, hand-written prescriptions (e.g. illegible scripture)
- Oral prescriptions

3. Preparation and dispensing errors (correct prescription)

- Calculation error, preparation error
- Dispensing (e.g. wrong patient, wrong drug)

4. Administration error

- Wrong dose
- Omitting error, additional dose
- Wrong administration time
- Wrong handling of drugs during application (e.g. infusions)
- Wrong infusion rate

Beside adverse drug reactions there are other instances which can be associated with harm to patients treated with drugs, for instance intoxications or consequences of non-compliance. Since adverse drug reactions are defined as reactions occurring at doses “normally used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological functions” (see Table 3.1), such reactions are formally not adverse drug reactions. The term “adverse drug events” has therefore been created, which includes reactions associated with the application of a drug, even if the causality is unclear (see Table

3.1). Adverse drug events cover therefore adverse reactions due to overdose or omitting drug therapy.

Table 3.4 Classification of adverse drug reactions

1. Intrinsic toxicity (predictable or Type A)

- Clearly dose-dependent, most often exaggeration of the pharmacological effect → predictable and most of them also preventable
- Animal models are available
- *Examples: ethanol (fatty liver), methotrexate (liver fibrosis), ACE inhibitors or angiotensin receptor blockers (hyperkalemia)*

2. Idiosyncratic toxicity (unpredictable or Type B)

- *Metabolic toxicity*
  - Mostly after weeks to months within the first year of treatment
  - Slow reappearance after rechallenge
  - *Examples: isoniazid (hepatotoxicity), valproic acid (hepatotoxicity)*
- *Allergic toxicity*
  - Mostly within the first two months of treatment
  - Very rapidly (1 or 2 doses) following rechallenge
  - Often accompanied by systemic reactions, typical histological changes
  - *Examples: diclofenac (hepatotoxicity), phenytoin (hypersensitivity syndrome), penicillins (skin reactions, cholestatic liver injury)*

While it is difficult for hospital pharmacists to influence the incidence of adverse drug reactions, in particular considering type B reactions, they can provide an important contribution for the identification and reduction of medication errors (3, 9-11).

3.2 ***Studies performed***

With my dissertation I want first to give an overview about the incidence of medication errors and adverse drug reactions in University and Community Hospitals. A comprehensive

review and meta-analysis of US studies covering adverse drug reactions has been published almost 10 years ago (1); it was therefore interesting to compare the incidence in this review with the incidences in more recent studies. Furthermore, to the best of my knowledge, such a comprehensive review has so far not been published for medication errors. I therefore performed a search in the existing literature between 1990 and 2003 and reviewed the original articles reporting incidences of medication errors and/or adverse drug reactions in hospitals. This study also allowed me to detect the drugs involved and the underlying risk factors. Knowing these risk factors, I could propose measures to reduce medication errors and/or adverse drug reactions.

Since drug-drug interactions can be considered to be medication errors and I could show in my first study that drug-drug interactions are an important risk factor for adverse drug reactions, I was interested in conducting a study in this field. I got the possibility to collaborate in a large study assessing the prevalence of potential drug-drug interactions in ambulatory patients suffering from dyslipidemia and being treated with a statin. My contribution was in the design of the study and in judging medication profiles from patients and reporting potential drug-drug interactions to physicians recruiting patients for the study. The study demonstrates that approximately 16% of dyslipidemic patients treated with a statin have potentially severe drug-drug interactions, approximately 7% a drug-drug interaction involving a statin. While the study provides the prevalence of drug-drug interactions, it does not provide the incidence of adverse drug reactions resulting from such interactions. Further studies are therefore necessary in this field.

A further field of interest is the adaptation of the dosage of antineoplastic drugs in patients with liver disease. Antineoplastic drugs are used frequently also in smaller hospitals and questions regarding dose adaptation of such drugs are not rare in hospital pharmacies. A

problem of antineoplastic drugs which are metabolized and/or excreted by the liver is their potential accumulation in patients with liver disease, possibly leading to type A adverse reactions. Lack of dose adaptation in this situation can therefore also be considered to be a medication error, nicely fitting in my field of interest and in the scope of my dissertation. I therefore decided to review all the antineoplastic agents on the market in Switzerland by the end of the year 2003 and to tabulate them according to their metabolism (in particular according to their hepatic extraction) and excretion (in particular biliary excretion). These parameters allow dose adaptation for such drugs in patients with liver cirrhosis and/or cholestasis, as described in section 6. The study allowed also a comparison of the predicted adaptations with the impairment of metabolism of such drugs in patients with liver disease. The study reveals that reliable data exist only for a minority of these drugs. The drug authorities should systematically demand dose adaptation studies in patients with liver disease, in particular for drugs with a small therapeutic range.

3.3 **References**

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4 Drug related problems in hospitals – a review of the recent literature

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4.1 Summary

Background: Problems associated with pharmacotherapy (in particular medication errors and adverse drug reactions) are frequent and are associated with increased costs.

Aims: To analyze the original publications about medication errors and/or adverse drug reactions in hospitalized patients published between 1990 and 2003, focusing on frequency, risk factors and avoidance of problems associated with pharmacotherapy.

Methods: Data base search (Medline, Embase) for original articles using the terms „medication error“, „adverse drug reaction“, “adverse event”, „hospital“. The original articles retrieved were supplemented by searching review articles for additional references.

Results: Medication errors occur with a frequency of approximately 5% of all drug applications, with a high variability among the 29 studies retrieved. This variability is explained by the way medication errors are detected (systematic screening of patients or charts vs. spontaneous reports) and by the way drugs were administered (intravenous drugs have the highest error frequency). Errors occur along the whole medication process, with application errors accounting for more than 50%. Important risk factors are insufficient pharmacological knowledge and work overload of the nursing staff, non-computerized transmission of prescriptions and lack of clinical pharmacists on the wards. Adverse drug reactions affect approximately 6% of the patients per hospitalization and show a high variability between the 31 studies retrieved. This variability can be explained by different assessment of the frequency of adverse drug reactions and by the wards studied. Risk factors for adverse drug reactions include female sex, age >65 years, polypharmacy and medication errors.

Conclusions: Since medication errors are strong risk factors for avoidable adverse drug reactions, strategies have to be put in place for their reduction. Such strategies include a good pharmacological formation of all persons involved in the medication process (nurses, phar-

macists and physicians), computerization of the entire medication process and the engagement of clinical pharmacists on the wards.

4.2 **Introduction**

Drugs not only have beneficial effects but can also be associated with adverse reactions. During the last decade, several studies have been published highlighting the significance of adverse drug reactions in hospitalized patients in terms of frequency (1-4), consequences for the affected patients (5-7) and costs for the hospitals (8-10). Adverse drug reactions can be regarded as the top of a pyramid, which contains all problems associated with drug therapy or “drug related problems”. Drug related problems include all problems, which can potentially affect the success of pharmacotherapy in a given patient, in particular medication errors, adverse drug events and adverse drug reactions (7). A more precise definition of these terms is given in Table 4.1 and a graphical illustration in Figure 4.1.

Medication errors can occur along the whole medication process and represent risk factors for adverse drug reactions (5, 11, 12). As shown in Table 4.2, the medication process starts with the prescription of a drug, the prescription has to be transmitted usually to a nurse and also into the pharmacy for delivery of the prescribed drugs. Nurses usually prepare the drugs on the ward, and distribute and administer them to the patients. The steps, which have been reported to be particularly afflicted with errors are drug prescription and drug administration (7).

Table 4.1 Definition of problems associated with pharmacotherapy (drug-related problems)

Drug-related problems	All circumstances that involve a patient's drug treatment that actually, or potentially, interfere with the achievement of an optimal outcome (7)
Medication errors	Any error in the medication process (prescribing, dispensing, administering of drugs), whether there are adverse consequences or not (13)
Adverse drug reactions	Any response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological functions (14)
Adverse drug events	Any injury related to the use of a drug, even if the causality of this relationship is not proven (13)

Since medication errors can be a pre-stage of adverse drug reactions, knowledge of their origin and of possible risk factors involved is important for their avoidance. One of the aims of the current investigation was therefore to assess these risk factors in order to be able to propose measures for avoiding medication errors in community and university hospitals. Special emphasis was put on the role of the clinical pharmacists in this setting, since several publications have emphasized the importance of a direct supervision of the medication process by pharmacists (15-17).

We therefore performed a search of the literature published between 1990 and 2003 in order to retrieve the relevant original publications reporting the frequency of medication errors and/or adverse drug reactions in hospitalized patients. From these data, we extracted the frequency and the risk factors of these drug-related problems, in order to be able to propose suitable measures for their reduction.

Table 4.2 Most important medication errors in hospitalized patients

1. Prescription errors

- Wrong drug (e.g. drug not suitable for this indication)
- Correct drug, wrong patient (e.g. ignoring contra-indications, drug-drug interactions or drug allergies)
- Wrong galenic form (e.g. tablets in a patient not able to swallow)
- Wrong dose

2. Transcription and/or interpretation errors

- Transcription of prescriptions (e.g. physicians - nurses)
- Usage of abbreviations, hand-written prescriptions (e.g. illegible scripture)
- Oral prescriptions

3. Preparation and dispension errors (correct prescription)

- Calculation error, preparation error
- Dispension (e.g. wrong patient, wrong drug)

4. Administration error

- Wrong dose
- Omittion error, additional dose
- Wrong administration time
- Wrong handling of drugs during application (e.g. infusions)
- Wrong infusion rate

4.3 **Methods**

We performed a computer search in Medline and Embase using the search terms „medication error“ or “adverse drug reaction” or “adverse drug event” in combination with “hospital” and collected the relevant articles published between 1990 and 2003. The articles

retrieved were searched manually and those reporting original data concerning the frequency of medication errors, adverse drug events and/or adverse drug reactions in hospitalized patients were included in the review. Furthermore, review articles covering these subjects were also searched and used for completing the references reporting original data. As already discussed in a preceding publication (4), studies reporting adverse drug events can pose problems in their classification. Unlike adverse drug reactions, adverse drug events also include medication errors such as overdosing (see definitions in Table 4.1). Such studies were therefore reviewed very carefully and were mostly classified under medication errors. If the available data allowed the calculation of the frequency of adverse drug reactions, they could also be classified under adverse drug reactions or under both medication errors and adverse drug reactions. Using these methods, we detected 29 articles reporting frequencies of medication errors and 31 articles reporting frequencies of adverse drug reactions in hospitalized patients.

The frequencies reported were analyzed according to the type of hospital (University vs. non-University hospitals), the type of ward the data were collected, and the detection system used to collect the data. If not indicated otherwise, data are presented as medians and range, since the frequencies of the medication errors and adverse drug reactions showed no normal distribution. Statistical analysis was performed using the non-parametric Mann-Whitney U test when 2 groups were compared. When more than two groups were compared, the Kruskal-Wallis analysis of ranks was used, followed by the Mann-Whitney U test with Bonferroni correction to localize significant differences. A $p<0.05$ was considered to be statistically significant.

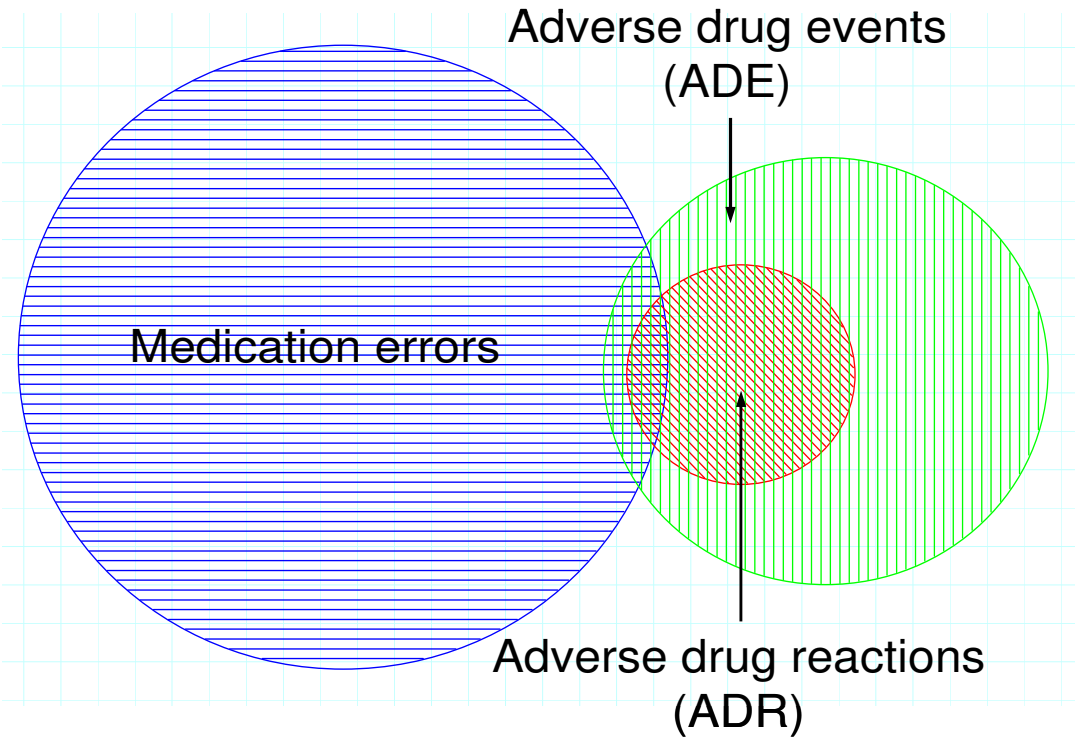

Figure 4.1 Problems associated with pharmacotherapy

Problems associated with pharmacotherapy (drug-related problems) can be illustrated with the intersections of three circles representing medication errors, adverse drug events and adverse drug reactions. Medication errors include every mistake in the medication process (prescribing, dispensing, administering of drugs). Only a minority of the medication errors are resulting in an adverse drug reaction or an adverse drug event. Adverse drug events represent any injury related to the use of a drug, even if the causality of this relationship is not proven. Adverse drug reactions are noxious responses to a drug which are unintended and which occur at normally used doses of this drug. Adverse drug reactions are either predictable (and therefore mostly avoidable, type A reactions), or unpredictable (idiosyncratic or type B reactions).

4.4 **Results**

A total of 60 articles were detected, 29 articles reporting medication errors (Table 4.4) and 31 articles reporting adverse effects of drugs (Table 4.5). Studies, which were not carried

out in hospitals or which did not indicate the frequency of medication errors or adverse drug reactions were not included.

4.4.1 Medication errors

Considering the medication errors, it has to be taken into account that the methods used to measure errors and the way to express error rates differ among studies, rendering the results difficult to compare. As shown in Figure 4.2, medication errors are most often determined as the percentage of errors per administrations. Alternatively, the percentages of the patient days with at least one error or of patients with at least one error during their hospitalization are used. The reported error rates were 5.4 errors per 100 administrations (range 0.038-49, n=22), 1.1 errors per 100 patient days (range 0.35-12, n=6) or 5.8 errors per 100 patients per hospitalization (range 0.15-24, n=9). A close inspection of the data in Figure 4.2 reveals that the variability in the error frequencies is large, even within the groups with the same units for error frequencies. The reasons for this high variability are primarily different drugs the patients studied were treated with, but also different methods used to determine the error rate. Looking at the errors given as a percentage of administrations in Figure 4.2, the two error rates exceeding the 95% percentile originate from studies where a comprehensive monitoring (daily monitoring of patients for a series of predefined events) of the administration of mainly intravenous fluids was performed (18, 19). On the other hand, the error rate below the 5% percentile in the same Figure originates from a large multicentre trial where spontaneous reports were collected (20).

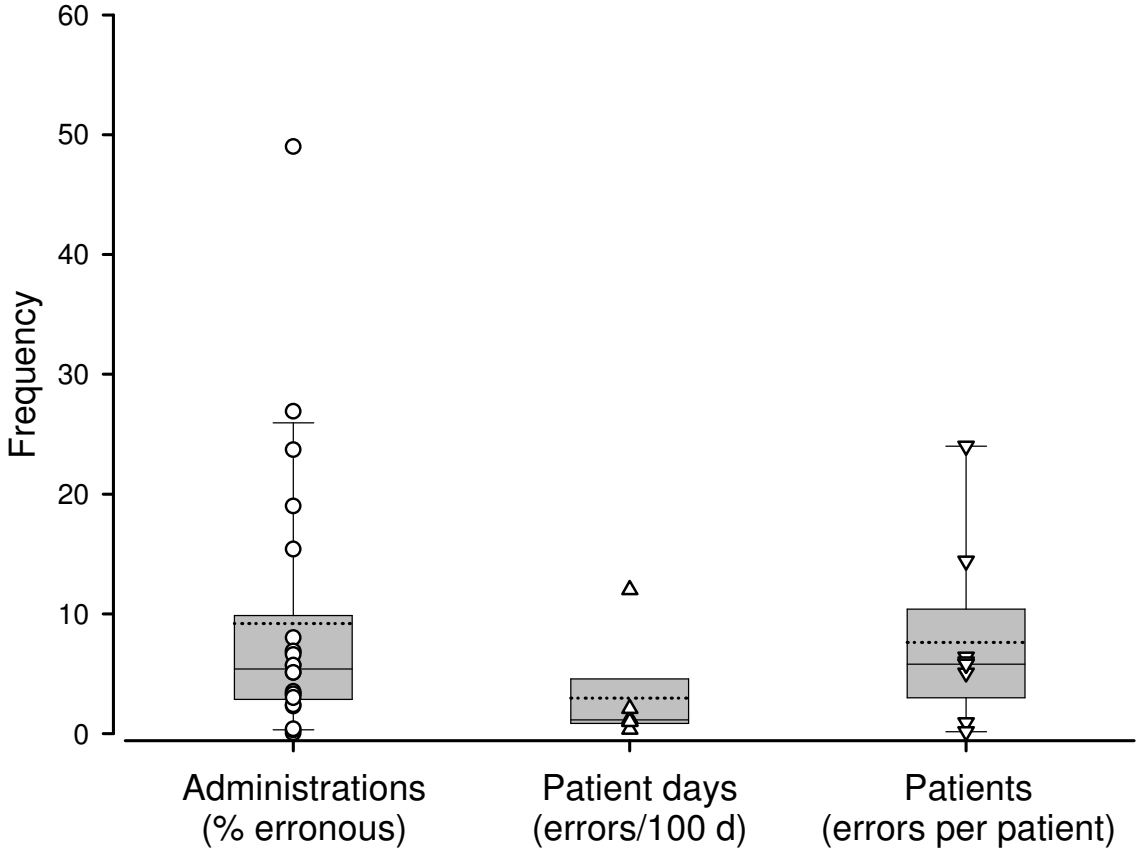

Figure 4.2 Frequency of medication errors

The frequency of medication errors occur is in about 5% of all drug applications, 1.1 errors per 100 patient days or 5.8 errors per 100 patients per hospitalization. The variability in the error frequencies is large, irrespectively how the error rate is determined. The most important reasons for this high variability are different drugs the patients are treated with and different methods used to determine the error rate (see Figure 4.3). In the errors given as a percentage of administrations, the two error rates exceeding the 95% percentile originate from studies where a comprehensive monitoring of the administration of mainly intravenous fluids was performed (18, 19). The error rate below the 5% percentile originates from a large multicentre trial where spontaneous reports were collected (20). Data are represented as box plots (25^{th} to 75^{th} percentile) containing both the median (solid line) and the average (dotted line). T-bars indicate the 5^{th} and 95^{th} percentile.

The influence of the method used for error detection was investigated further for all studies reporting the error rate per administration (Figure 4.3). Although the variability remains large, comprehensive monitoring (median 6.8, range 2.4-49 errors per 100 administrations, n=13) revealed significantly more errors than spontaneous reporting (2.3, range 0.038-3.3, n=3).

In studies reporting the error rate per administration, the type of hospital (University vs. non-University) was not associated with a difference in the error rate. The median error rate was 4.2 (range 0.038 – 26.9, n=17) in University hospitals and 5.95 (range 3.5 – 19%, n=4) in non-University hospitals. Considering the wards, which were investigated, the numbers are too small for meaningful statistical comparisons. A comparison of the medians, which are in the range of 3 – 6.6 errors per 100 administrations (with large ranges), did not reveal substantial differences, however. As stated already above, the ward per se appears to less important than the type of drugs which are administered on this ward.

Drug classes which are prone to errors include in particular antibiotics, cardiovascular drugs, oral anticoagulants, theophyllin and antineoplastic drugs (compare Table 4.4). Errors occur at all stages of the medication process, most often at the administration stage (median 57.5% of all errors, range 28-90%, n=22 studies), unauthorized administration of drugs (25%, range 4-28%, n=3 studies), drug prescription (18.5%, range 6-78%, n=8 studies), transcription (15%, range 11-21%, n=4 studies) and drug preparation (13.5%, range 7-23%, n=4 studies). Considering drug administration, frequent errors are omission of a dose (range 36-74%), wrong application time (14-25%), wrong dose (12-56%) and wrong administration rate (5.5-40%).

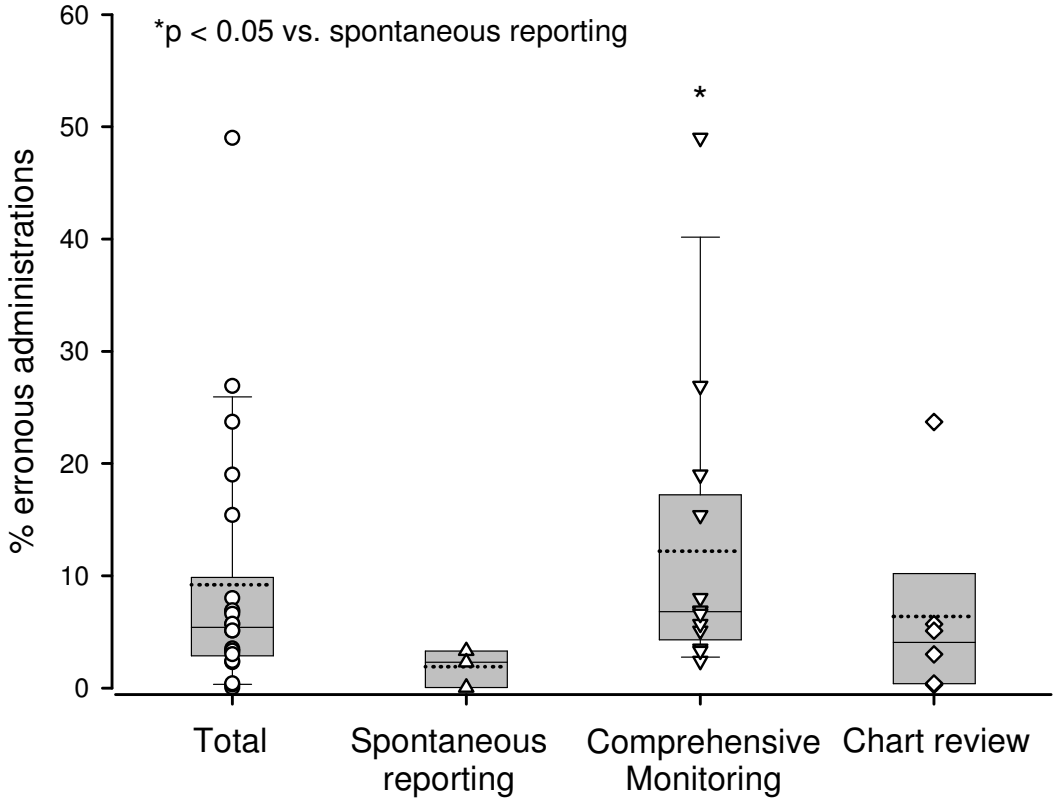

Figure 4.3 Dependence of the medication error frequency on the mode of detection
The influence of the method used for error detection was investigated further for all studies reporting the error rate per administration (first plot in Figure 4.2). Comprehensive monitoring (daily monitoring of patients for a series of predefined events) reveals significantly more errors than spontaneous reporting (median 6.8 vs 2.3 errors per 100 administrations, $p<0.05$). Data are represented as box plots (25^{th} to 75^{th} percentile) containing both the median (solid line) and the average (dotted line). T-bars indicate the 5^{th} and 95^{th} percentile.

The most important risk factors for medication errors include lack of information about drugs or about the patients to be treated, errors in the patient charts and/or in the documentation of the nurses and lacking or decentralized pharmacy services. Recommendations for reducing medication errors include the installation of a decentralized clinical pharmacy service (the clinical pharmacists must be present on the wards) (5), an improved education in pharmacotherapy for the first year residents (21), an electronic ordering and patient survey system (1) and

the installation of a “no-blame” error reporting system (22). Regarding the intravenous administration of drugs, preparation of complex solutions in the hospital pharmacy and replacement of bolus applications by short infusions are recommended (19).

4.4.2 Adverse drug reactions

Similar to the studies reporting medication errors, most of the studies about adverse drug reactions were carried out in University Hospitals, mainly on wards of internal medicine. Only 3 reports originate from Community Hospitals, two from wards of internal medicine and one from a geriatric ward (Table 4.5). Due to the small number of the reports from Community Hospitals, a statistical comparison with University Hospitals is not meaningful. In one of these studies, a retrospective review of patient charts revealed a frequency of 0.59% of patients with an adverse drug reaction during hospitalization (23). The two other studies carried out in community hospitals reported higher frequencies, namely 23.1% by chart review of patients on a medical ward (16) and 60.7% by chart review on a geriatric ward (24).

In contrast to the medication errors, the frequency of adverse drug reactions is given with the same units for all of the studies included, namely as the percentage of patients suffering from an adverse drug reaction per hospitalization. While these units are helpful for a comparison of the frequencies between studies, they disregard the fact that an individual patient can suffer from more than one adverse drug reaction during one hospitalization. The true frequency of adverse drug reactions may therefore be higher than reported in Table 4.5 and Figure 4.4.

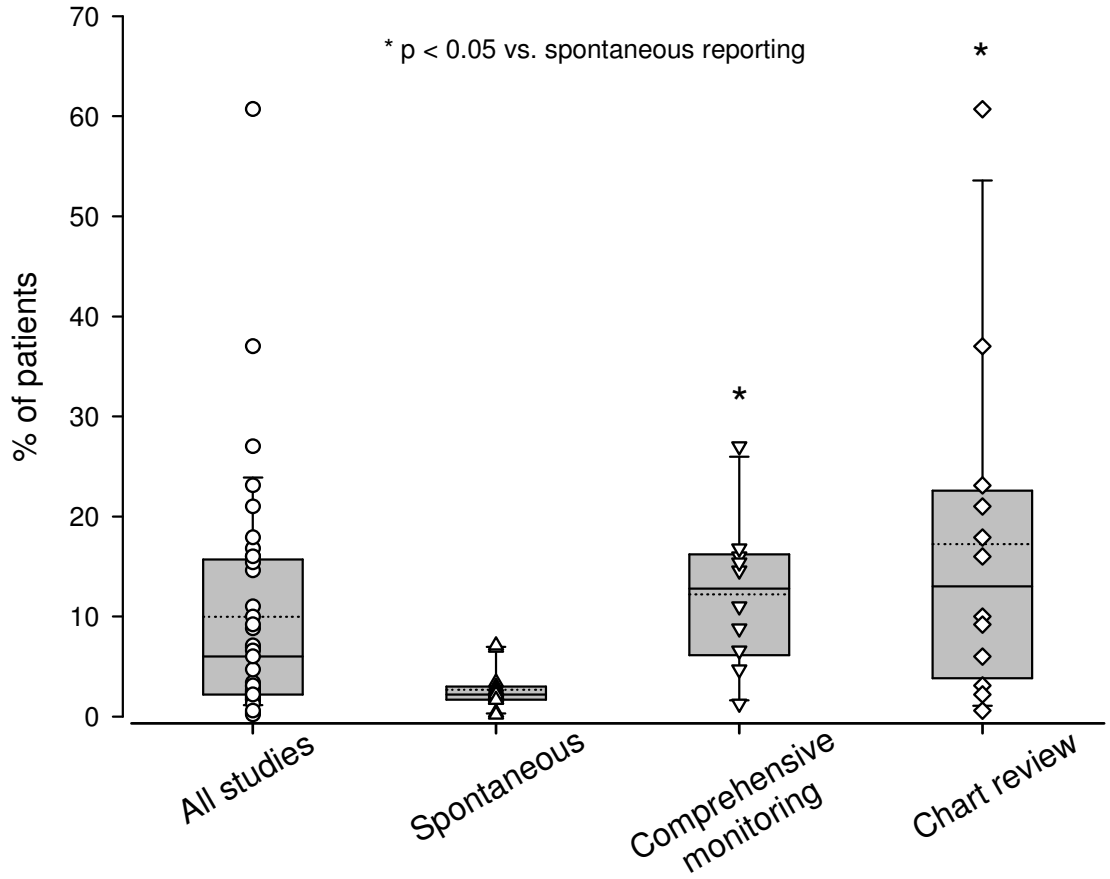

Figure 4.4 Dependence of the incidence of adverse drug reactions on the mode of detection The overall frequency of the adverse drug reactions is 6.0% (median) of the patients during one hospitalization. Similar to the medication errors (Figure 2), the variability between studies is large, possibly originating from different methods used to determine adverse drug reactions and from different wards studied. The frequency of adverse drug reactions detected by spontaneous reporting (median 2.2% of patients) is significantly lower than that obtained by comprehensive monitoring (12.8% of patients) or by chart review (13% of patients). Data are represented as box plots (25^{th} to 75^{th} percentile) containing both the median (solid line) and the average (dotted line). T-bars indicate the 5^{th} and 95^{th} percentile.

The overall frequency of the adverse drug reactions is 6.0% (median) of the patients during one hospitalization (range 0.2 – 60.7%). The large range suggests differences between the studies, possibly regarding the methods used to determine adverse drug reactions

and also regarding the wards the patients were studied. The frequency of adverse drug reactions was either determined by spontaneous reporting (physicians, pharmacists, nurses), by intensive monitoring of the patients (regular review of the chart and visit of the patients and visit of the patients by physicians, pharmacists and/or study nurses), by systematic chart review (either during or after hospitalization), by computerized monitoring of predefined adverse drug events and/or by interviewing the patient at the end of the stay in the hospital. As shown in Figure 4.4, the frequency of adverse drug reactions detected by spontaneous reporting (median 2.2% of patients, range 0.2-7%, n=15 studies), is significantly lower than obtained by comprehensive monitoring (12.8% of patients, 1.3-27%, n=10 studies) or by chart review (13% of patients, 0.59-60.7%, n=12 studies). Since there was only one study using patient interviews (25), this technique was not included in the calculations in Figure 4.4. Computerized monitoring of adverse drug events is a different approach to assess adverse drug reactions as compared to the other techniques. An array of pathological laboratory values and clinical events are predefined and “hits” are created, when the corresponding signs or values of a patient fall into the predefined pathological range (24, 26-28). Since not every hit corresponds to a true adverse drug reaction, such studies were only included, when the frequency of adverse drug reactions was also assessed by one of the conventional methods. The studies using computerized monitoring show, however, that this technique has a sensitivity of 57% (range 47.5 – 73%, n=4) to detect adverse drug reactions. Since computerized monitoring appears to be less time consuming than comprehensive monitoring or systematic review of patient charts, it may be a technique deserving more attention in the future.

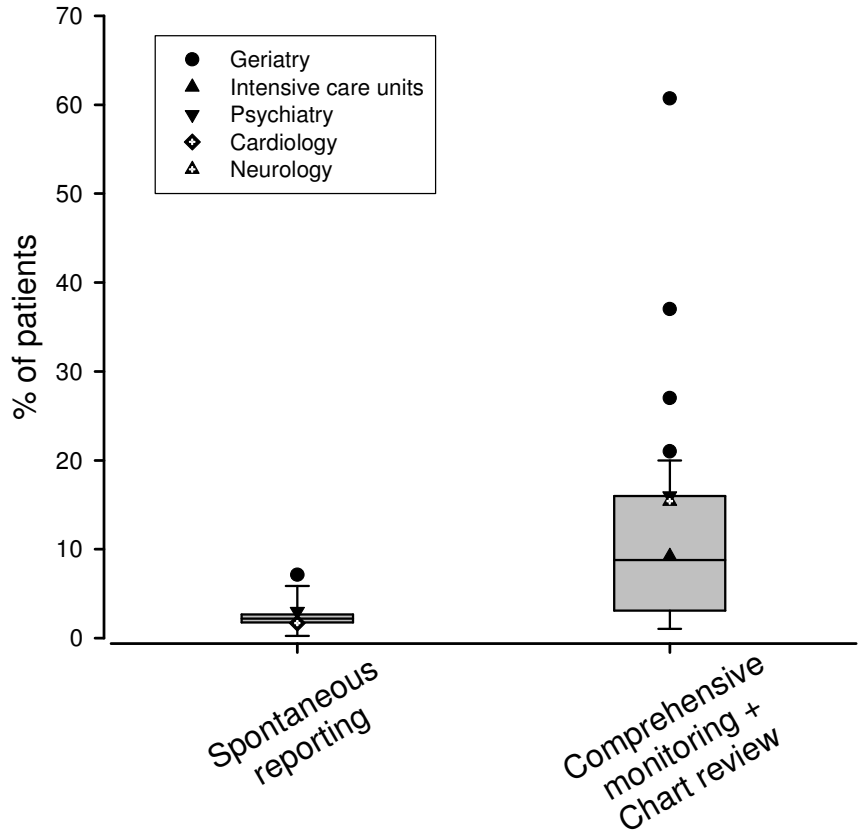

Figure 4.5 Dependence of the incidence of adverse drug reactions on the wards the patients were studied.

The box plots represent all studies performed with patients on wards of internal medicine (n=21 studies). In comparison, in all 5 studies on geriatric wards (circles), the frequency of the adverse drug reactions was higher than the 95% interval obtained for studies on wards of internal medicine, irrespective of the method used. In contrast, the frequency of adverse drug reactions for patients studied in intensive care units (n=1 study), psychiatry (n=2), neurology (n=1) or cardiology (n=1) was similar to patients on wards of internal medicine. Data are represented as box plots (25^{th} to 75^{th} percentile) containing both the median (solid line) and the average (dotted line). T-bars indicate the 5^{th} and 95^{th} percentile.

In addition to the technique how the data are collected, the frequency of adverse drug reactions detected appears also to depend from the ward the study was performed. As shown in Table 4.5, 5 studies were conducted on geriatric wards and in all 5 studies, the fre-

quency of the adverse drug reactions was higher than the 95% interval obtained for studies performed on wards of internal medicine (n=21 studies), irrespectively how the adverse reactions were determined. The frequency of adverse reactions in patients on medical wards was 3.1% of patients (0.2-23.1%, n=21 studies) versus 27% of patients on geriatric wards (7.1-60.7%, n=5 studies), the difference reaching statistical significance ($p<0.05$). On the other hand, the frequency of adverse drug reactions for patients studies in intensive care units (n=1 study), psychiatry (n=2), neurology (n=1) or cardiology (n=1) was similar to patients on wards of internal medicine, but the number of studies and of patients investigated is small.

In 3% of the patients (range 0.51 -7%, n=5), an adverse drug reaction was the reason for the hospitalization, and 2.45% of the patients (range 0.14-3.5%, n=4) of the patients died because of an adverse drug reaction. 62.5% (range 42.3 – 100%, n=8) of the adverse drug reactions detected were type A reactions and thus potentially preventable. In 15% (range 4.8 – 31%, n=5) of the adverse drug reactions, the reason was a drug-drug interaction.

Risk factors for the occurrence of adverse drug reactions were reported in 6 studies (2, 16, 29-32). The most important risk factors appear to be polypharmacy (3/6 studies), female sex (3/6), drugs with a narrow therapeutic range (2/6), drug-drug interactions (2/6), and renal elimination of drugs (1/6), age >65 years (1/6) or a history of allergies (1/6). In patients having an adverse drug reaction, the stay in the intensive care unit was prolonged for 3.4 days or the hospitalization for 3.8 days (range 1.2 – 8.5 days, n=5), leading to an increase in costs per hospitalization.

4.5 **Discussion**

Our study demonstrates that medication errors occur in about 5% of all drug applications and adverse drug reactions in about 6% of all patients per hospitalization. Since, at least

on medical wards, patients are usually treated with 5-10 drugs per day and stay for approximately 8 days in the hospital (2), they may have about 50 drug applications per hospitalization, suggesting that most patients will be affected by one or more medication errors. On the other hand, approximately 6% of the patients have an adverse drug reaction, indicating that only a minority of medication errors will lead to a clinical manifestation. In agreement with these considerations, it has been estimated in clinical studies that approximately 3-5% of all medication errors result in adverse drug reactions (5, 33, 34). The importance of medication errors is therefore primarily given by the facts that they represent risk factors for adverse drug reactions and that they are avoidable.

About 59% (median) of the adverse drug reactions are judged to be preventable (range 50-87%, n=7 studies) (3, 30, 35-39) and can therefore be considered to be primarily the result of medication errors. Looking at the risk factors for adverse drug reactions (polypharmacy, female sex, drugs with a narrow therapeutic range, drug-drug interactions, renal elimination of drugs, age >65 years, ignored allergies; see result section) it becomes evident that drug-drug interactions, failure of dose adaptation in patients with impaired renal function and failure to recognize previous drug allergies are in fact medication errors.

Drug-drug interactions can therefore be considered as medication errors, representing risk factors for adverse drug reactions. In the studies analyzed, drug-drug interactions were estimated to account for a median of 5% (range 4.8-17%) of all adverse drug reactions (23, 24, 40, 41), affecting approximately 0.3% of the patients per hospitalization. Since the prevalence of potentially severe drug-drug interactions is in the range of 60% in hospitalized patients (42), only a small fraction (<1%) of the potential drug-drug interactions appear to cause adverse drug reactions. The fraction of the patients with a potentially serious drug-drug interaction being affected by an adverse drug reaction depends on the drugs involved. While the

incidence of severe hyperkalemia (>6mmol/L) in patients treated with an ACE inhibitor or an angiotensin receptor blocker and low dose (25 mg/day) spironolactone has been reported to be in the range of 6% per year (43), rhabdomyolysis in patients treated with atorvastatin or simvastatin and an inhibitor of CYP3A4 occurs with an at least 50 times lower incidence (44).

Medication errors occur along the entire medication process, from drug prescription to administration (7). Drug administration was found to be affected most often, followed by unauthorized drug administration, prescription, transcription and drug preparation. Regarding drug administration, in particular intravenously administered drugs are prone to errors (18, 19). To increase drug safety, intravenous bolus administrations should be replaced by short infusions and complex infusions should be prepared in the local pharmacy (19). While unauthorized drug administration and transcription errors can be reduced by organizational measures and/or computerized prescription (45), reduction of prescription errors is more complex. Important risk factors for prescription errors include high workload, prescribing for a foreign patient, communication deficits within the team and lack of knowledge in pharmacotherapy (46). Real-time electronic prescription aids may be helpful to reduce such errors (1, 17, 34, 47).

A list of possibilities to reduce medication errors is given in Table 4.3. Several studies have shown that improved pharmacological knowledge of physicians and nurses is an efficient measure for error reduction (48-51). Considering nurses, a single short instruction is not sufficient (52), repetitive instructions are necessary. Furthermore, as discussed above, prescription and transcription errors can be reduced by computerizing the medication process, e.g. by introduction of electronic patient charts and electronic alert systems (1, 17, 34, 47). Regarding prescription, real time information containing important drug data such as dosage (with suggestions for dose adaptation in the case of impaired renal or hepatic function), ad-

verse drug reactions, contra-indications and drug-drug interactions customized for individual patients would be most helpful. As discussed above, complex intravenous administrations should be prepared in the pharmacy and not on the ward and short infusions should be used instead of boli (19). A couple of studies have shown that clinical pharmacists on the ward can help to reduce medication errors (5, 17, 21, 34, 53, 54). Taking into account the costs caused by adverse drug reactions (8, 10, 26, 55), employment of clinical pharmacists on medical and surgical wards may be cost effective for hospitals.

Furthermore, medication errors should be discussed in an open, no-blame, non-punishing atmosphere (22). Voluntary critical incidence reporting systems including regular discussions with all professional groups involved appear to be most suitable for this purpose (56).

Our data show that a median of 6% of the patients will suffer from an adverse drug reaction during their hospitalization. This figure is close to the incidence of 6.7% reported in a meta-analysis from publications between 1966 and 1996 (4), suggesting that the incidence of adverse drug reactions has remained constant over the last 3 to 4 decades. In approximately 60% of the patients, the adverse drug reactions were considered to be potentially preventable, thus to originate from a medication error. In comparison, in a recent report from a Swiss University Hospital where patients on a medical ward are monitored comprehensively for adverse drug events, the fraction of adverse events due to medication errors was much lower, namely in the range of 6% (57). Possible explanations for this discrepancy include differences in the definition of preventability of adverse drug events and differences in the wards studied. Risk factors for adverse drug reactions reported were polypharmacy, female sex, administration of

Table 4.3 Prevention of problems associated with pharmacotherapy

1. Medication errors

- Improved pharmacological education of health professionals (nurses, pharmacists, physicians)
- "Computerization" of the medication process
  - Prescribing aids
  - Improved transcription
  - Improved monitoring of patients
- Clinical pharmacists on the ward
  - Identification of reporting of medication errors/adverse events
  - Control for drug-drug interactions
  - Dose adaptation in patients with impaired renal and/or liver function
  - Monitoring of complex therapies
- Critical incident reporting systems

2. Adverse drug reactions

Type A (dose-dependent, predictable)

- Limit polypharmacy as much as possible
- Consequent dose adaptation according to function of the elimination organs
- Avoidance of drug-drug interactions and of other medication errors

Type B (not predictable, idiosyncratic)

- Difficult to avoid, since not predictable
- Avoid risk factors
  - Prior reactions to drugs
  - Family history of drug reactions
- Limit damage in case of an adverse drug event: Consider to stop all drugs which are not life-saving

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drugs with a narrow therapeutic range, drug-drug interactions, renal elimination of drugs, age > 65 years and ignoring drug allergies. Polypharmacy is a frequent finding particularly in aged, polymorbid patients, but is often difficult to avoid (58, 59). Polypharmacy is associated with an increased risk of adverse drug reactions not only because of the addition of the risk of

the individual drugs, but also because of possible drug-drug interactions (44). Polypharmacy may therefore explain at least partially the higher incidence of adverse reactions observed in geriatric as compared to internal medicine wards (see Table 4.5). As discussed above, drug-drug interactions, missed dose adaptation in patients with impaired renal function and ignored drug allergies are medication errors, which may lead to adverse reactions, depending on the drugs involved and on the individual patient.

As shown in Table 4.3, the preventive strategies for adverse drug reactions differ between type A (predictable and preventable) and type B (not predictable and in most cases not preventable) adverse drug reactions. Considering type A reactions, they can be targeted by reducing polypharmacy and medication errors. For type B reactions, prevention is much more difficult, since these reactions are not predictable. Preventive strategies include avoiding known risk factors and limiting damage to the individual, once an adverse reaction has occurred.

In conclusion, medication errors and adverse drug reactions are frequent findings in hospitalized patients, potentially leading to increased duration of the stay in the hospital or even to fatalities and increased costs for the hospitals. Risk factors are known and should guide the preventive measures.

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Table 4.4 Studies reporting the frequency of medication errors in hospitalized patients

Type of hospital; ward	*Duration, applications*	*Detection methods*	*Error frequency*	*Most frequent medication errors*	*Remarks*	*Reference*
University hospital; all units	12 months; 279'818 applications per month	Spontaneous reporting	0.038% of all applications (107 errors per month)	Errors: 37% omission, 28% unauthorized drugs, 14.8% wrong time, 11.6% wrong dose, 5.5% wrong rate	Frequency increased with duration of study (suggesting learning effect)	(20)
University hospital; all units	37 days; 2967 patient days	Systematic review of patient charts and spontaneous reporting	10 per 1000 pd (33 in coronary care units, 13 on medical wards)	Drugs: antibiotics 25%, cardiac drugs 15%, anticoagulants 10%	72% of the errors performed by physicians, 10% by pharmacists, 8% by nurses	(60)
University hospital; internal medicine	294 discharge medications	Actual verification of prescriptions (clinical pharmacists)	5.8% (17 errors in 294 prescriptions)	Errors: 41% wrong dosage. 11 errors were potentially harmful Risk factors: 24% lacking information	Most errors by first year residents. Clinical pharmacists detected 2 thirds of errors	(21)
Community hospital; outpatient clinics	Year 1: 691 prescriptions (baseline) Year 2: 921 prescriptions (post-intervention)	Actual verification of prescriptions (clinical pharmacists); comparison pre-/post-intervention	Baseline: 14.4% of prescriptions Post-intervention: 6% of prescriptions	Intervention was feedback to baseline errors	Prescribing errors can be reduced by teaching	(48)
University hospital; internal medicine including ICU	8 months; 1484 patient days	Systematic review of patient charts (research nurses)	315 adverse occurrences (0.2 per pd), among them 178 medication errors (0.12 per pd)	Errors: 74% missed dose	Medication errors most frequent. Nurses administration records are best source for detection	(61)
University hospitals; surgical and medical units including ICUs	6 months; 21'412 patient days (pd)	Systematic review of patient charts (research nurses) and spontaneous reporting	20.6 errors per 1000 pd. ADEs: 11.5 per 1000 pd. Medical ICUs 19.4, surgical ICUs 10.5, medical units	Errors: 49% prescription, 11% transcription, 14% dispensing, 26% administration stage. Drugs: classes most affected were analgesics 30%, antibiotics 24% and sedatives 8%. 28% of ADEs preventable, 12%	Many ADEs are serious and/or preventable. Computerized ordering could prevent most ADEs.	(1)

Type of hospital; ward	*Duration, applications*	*Detection methods*	*Error frequency*	*Most frequent medication errors*	*Remarks*	*Reference*
			10.6, surgical units 8.9. Potential ADEs: 9.1. per 1000 pd	(17%) of the ADEs (potential ADEs) life threatening		
USA: University hospital; general medicine UK: University hospital; general medicine	USA: 1 month; 919 applications UK: 2 months; 2756 applications	USA: actual verification (study nurse) UK: retrospective review of prescription (study nurse)	USA: 6.9% UK: 3.0%	Errors: USA: incorrect dose 30%, unordered drug 25%. UK: omission 58%, incorrect dose 14%. Risk factors: USA: Incorrect selection or preparation by nurse 52%, unclear prescription 37%, incorrect drug supplied by pharmacy 6%. UK: Incorrect selection or preparation 40%, drug unavailable on unit 39%, unclear prescription 13%	English system (clinical pharmacists on ward) better than USA system (single dose unit)	(53)
University hospital; all units including ICUs	9 years; 3'903'433 prescriptions	Systematic review of all prescriptions (clinical pharmacists)	11'186 errors; 6.52 errors per 1000 patient days (2.87 per 1000 orders). 1.22 serious errors/1000 pd.	Errors: overdose 37%, underdose 19%, allergy 14%, duplication 6%, wrong drug 4% Drugs: xanthines 20%, antibiotics 12%, cough 7%	Error frequency increases with complexitiy of therapies and new drugs	(12)[)]
University hospital; all units	1 year; 525'750 prescriptions	Systematic review of all prescriptions (clinical pharmacists). Only clinically relevant errors.	2103 errors; 3.99 errors per 1000 orders. 696 could potentially cause ADR.	Errors: Overdose 42%, underdose 16%, allergy 13%, dosage form 12%, wrong drug 5% Drugs: xanthines 20.6/1000 orders, antibiotics 13.6, cardiovascular 5.01, hormones 3.84 Risk factors: limited knowledge of drug therapy (30%) or of patient factors (29%)	Education in pharmacotherapy must be improved	(49)
District hospital; geriatric unit	14 days; 2335 orders	Systematic review of all patient	5.1% of orders (1.5% if docu-	Error: Documentation (failures in nurses' notes) 67%, dosage	Adverse effects in a third of all medication	(62)

Type of hospital; ward	*Duration, applications*	*Detection methods*	*Error frequency*	*Most frequent medication errors*	*Remarks*	*Reference*
		charts (clinical pharmacists)	mentation errors not counted)	19%, omission 9%	errors possible	
District hospital; all units except intensive care units	1 month, 839 applications. One month, 855 applications after intervention	Systematic investigation of drug orders and applications (study nurses)	6.8% of all applications before and 3.5% after intervention	Errors before intervention: 28% wrong application time, 25% wrong administration, 19% wrong prescription	Intervention included teaching of personnel about medication errors. Effectful in particular in nurses	(50)
University hospital; surgery	23 days; 5515 applications. 31 days, 7391 applications after intervention	No-blame spontaneous reporting	Before intervention 3.3%, after intervention 2.3%	Errors: Omission 36% (28%), wrong documentation 21% (39%), wrong time 25% (19%) and wrong dose 1.7% (2.4%) before and after (parentheses) intervention	No-blame self reporting system better than other self-reporting systems. Intervention was performed according to failure mode effects analysis (FMEA)	(22)
University hospital; all except obstetrical units	6 months; 9306 patients	Computerized registration of 37 predefined risk situations	Risk situation (adverse event or error) in 6.4% of patients (true rate may be higher, only 37 events recorded)	Most frequent events: risk situation for digoxin toxicity, renal failure due to radio contrast media, phenytoin toxicity	28% of all events and 42% of life threatening events may be prevented. Computerized alert system recommended	(47)
University hospital; intensive care unit for children	10 weeks; 275 applications	Actual verification of administration (study nurse)	26.9% of administrations	Errors: Wrong time 32%, wrong administration technique 32%, wrong dose preparation 23%	High frequency because of intensive care unit. Reduction by pharmaceutical monitoring	(18)
University hospital; intensive care unit (general, cardiological, recovery room)	13 months; 385 patients in general ICU, 552 in cardiological ICU, 8429 in recovery room	Spontaneous reports	Total 0.93% (87 per 9366 patients). In the general ICU 13.2% (51 per 385 patients)	Errors: wrong dose or preparation, wrong medication/infusion, wrong administration.	37% of errors had consequences for the patient. Most of the errors reported from ICU. True frequency is higher	(63)
University hospital; intensive care unit (car-	75 patients before and after intervention, 75	Systematic review of all prescriptions (clinical pharma-	Preventable ADE's (errors) decreased from 10.4	Errors: incomplete orders, wrong dose, wrong frequency, duplicate therapy	Clinical pharmacists can prevent two thirds of the ADEs during	(54)

Type of hospital; ward	*Duration, applications*	*Detection methods*	*Error frequency*	*Most frequent medication errors*	*Remarks*	*Reference*
diology)	from control unit	cists)	before to 3.5 after intervention (per 1000 patient days). Control group 10.9 and 12.4 (per 1000 patient days)		prescription	
UK: University hospital; general medicine (Clinical pharmacist) Germany 1: University; surgery (traditional distribution system) Germany 2: University; internal medicine (Unit dose system)	UK: 842 solid oral doses Germany 1: 973 solid oral doses Germany 2: 1318 solid oral doses	Comprehensive monitoring	UK 8% Ger 1: 5.1% Ger 2: 2.4%	Errors: Omission, wrong dose, wrong drug, transcription, ordering administration	Lower medication error rate associated with the unit dose system	(64)
University hospital; medical intensive care unit	2009 administrations	Comprehensive monitoring	6.6% (132 errors)	Errors: Dose 31%, wrong rate 22%, wrong preparation technique 18%, incompatibility 14% 26 errors potentially life-threatening Risk factors: medication track, insufficient staff training		(65)
University hospital; pediatrics	3312 medication orders (669 patient-days)	Daily review of the medical records	23.7% (784 errors in 3312 prescriptions)	Errors: “intercepted” errors 98% (prescribing, dispensing, transcription), 2% administration errors	In pediatrics, the most common medication errors are dosing errors	(66)
University hospital; HIV-infected patients	1618 admissions	Medication orders were reviewed (pharmacist) prior	5.8% (108 prescribing errors in 1618 admissions	Errors: under-dosing 48%, over-dosing 34%, drug-drug interactions 5.6%.	The high frequency of prescribing errors is related to the complex	(67)

Type of hospital; ward	*Duration, applications*	*Detection methods*	*Error frequency*	*Most frequent medication errors*	*Remarks*	*Reference*
		to dispensing	affecting 94 patients)		HIV treatment regimens	
University hospital; pediatrics	112'536 admissions or 335'835 patient-days	Retrospective review of medication errors	0.15% of admissions (195 errors): Medical wards 59%, surgical wards 13%, ICUs 27%	Errors: incorrect iv infusion 15.8%, dose 14.8%, extra dose 13.8%, dose omitted 12.3% Drugs: Antibiotics 44%, parenteral nutrition 16.5%, anticancer drugs 10.1, morphine 4.6%		(68)
1116 Hospitals (university and community); general medicine	8'500'000 patients	Spontaneous reports	5.07% errors. More errors in community than university hospitals	Risk factors: decentralized or lacking clinical pharmacists, high pharmacist workload Medication errors with symptoms: 0.25% of patients	Errors rate may be reduced by installing a decentralized clinical pharmacy service	(5)
5 University hospitals; intensive care units	5744 observations in 851 patients	Monitoring of certain medications	3.3% of all administrations (187 errors)	Errors: wrong infusion rate 40.1%. Drugs: cardiovascular 32.6%, sedative/analgesics 25.7%.	20 errors did not reach patient, 159 reached patient but did not result in harm, 5 required monitoring, 2 required intervention. None of the errors resulted in death	(33)
2 University hospitals; ICU	10'778 administrations, 1120 patients	Comprehensive monitoring (physician)	5.7% of administrations (616 errors)	Errors: physician ordering 74%, dosing 28%, route of administration 18%, transcription 14% Administration: intravenous 55%, oral 21% Drugs: antibiotics 20%, analgesics 16%, electrolytes 26%	115 errors resulting in potential ADR (1.1%), 26 ADR (0.24%). Computerized ordering/clinical pharmacist can prevent >90% of errors	(34)
36 hospitals and nursing facilities	3216 applications	Comprehensive monitoring (research pharmacist)	19% of applications (605 errors in 3216 doses)	Errors: Wrong time 43%, dose omitted 30%, wrong dose 17%, unauthorized drug 4%. No difference between university and community hospitals	7% potentially harmful errors	(69)

Type of hospital; ward	*Duration, applications*	*Detection methods*	*Error frequency*	*Most frequent medication errors*	*Remarks*	*Reference*
2 University hospitals; pediatrics	10778 medication orders for 1020 patients	Chart review (physicians)	5.7% of all orders (616 errors), 120 potentially harmful medication errors	Errors: drug ordering 77.8%, dosing 28.4%, route 17.7%, transcription 15.9%, administration 12.8%	Recommendations: electronic ordering, clinical pharmacists, improved communication	(17)
University hospital; cardiology	24538 patients over 4.5 years	Comprehensive monitoring (clinical pharmacist)	24% of patients (4768 errors). Due to physicians in 63%, pharmacist in 26%, nursing in 5%	Errors: wrong drug 36%, wrong dose 35.3%, dose omitted 10.2% Drugs: cardiovascular 41.2%, antibiotics 14.9%, GI-tract 9.5%	Recommendations: Up-to-date information for physicians and nurses, better education for new interns	(51)
1. University hospital; general medicine 2. Non teaching hospital; general medicine	430 intravenous administrations (106 patients)	Comprehensive monitoring (clinical pharmacists, physician, nurses)	49% of all administrations (212 of 430 applications), 3 rated as serious	Errors: wrong preparation 7%, wrong administration 36%, both wrong 6%. Risk factors: Multiple preparation steps, bolus injection	Recommendations: central preparation of complex products, short infusion instead of bolus	(19)
2 University hospitals; medical and surgical units.	12 weeks in every hospital. 5792 (medication nurses: training of 2 days) and 3661 (general nurses) applications	Comprehensive monitoring (trained nurses or pharmacy technicians)	15.4% of all administrations. General nurses 14.9%, medication nurses 15.7%. Medical units 13.2%, surgical units 11.7% (only hospital A)	Errors: Administration technique 42%, preparation 9%, omitted drug 6%, wrong dosage 5%, wrong route 4% Outcome: no adverse drug reactions observed	Simple education of nurses to become medication nurses has no benefit. Education must be more detailed and deserves more studies	(52)

Table 4.5 Studies reporting the frequency of adverse drug reactions in hospitalized patients

Type of hospital; specialty	*Patients, duration of study*	*Detection method*	*ADR frequency*	*Most frequent ADRs or organs affected (in% of ADRs)*	*Remarks*	*Reference*
University hospital; internal medicine	160 patients; 1 month	Comprehensive assessment (clinical pharmacist) vs. spontaneous reporting	8.8% (14/160) vs. 2.5% (4/160). „True rate“ (combination) 15/160.	Drugs: Antibiotics 40%. Organs: GI-tract 33%, kidney 20%, liver 13%, CNS 13%	Intensive screening (clinical pharmacist) is better than spontaneous reporting. Intensive screening detects 93%, spontaneous reporting 27% of ADRs.	(70)
51 hospitals in the state of New York; general medicine	30'195 patient charts	Retrospective review of charts	0.59% (178/30'195); 18% due to negligence, 14% resulting in permanent disability. Only serious ADRs recorded.	Drugs: Antibiotics 16%, chemotherapy 16%, anticoagulants 11%. Organs: Bone marrow 16%, bleeding 15%, CNS 15%, cutaneous 14%.	Drug-drug interactions accounted for 4.8% of ADRs	(23)
University hospital; geriatrics	416 patients, 10 weeks	Comprehensive assessment (physicians)	27% of patients	Drugs: Diuretics 55%, beta-blockers 8%, antidepressants 4.5%, opiates 4%, NSAIDs 4%	50% of ADRs were due to drugs which considered to be contra-indicated or unnecessary. 240 potential drug-drug interactions in 150 patients, 5% caused ADR.	(40)
University hospital; geriatrics (ambulatory and hospitalized patients)	463 patients	Retrospective review of charts	21% of patients	ACE-inhibitors 17%, diuretics 14%, antidepressants 10%, NSAIDs 10%	31% of patients have potential drug-drug interaction. Risk factors for ADRs: drug-drug interactions, drugs requiring therapeutic drug monitoring	(20)
University hospital; medical wards	30 057 patients, 1 year	Spontaneous reporting vs. chart review (predefined events)	Spontaneous reporting 1.7%, chart review 3.1% of patients	Spontaneous reporting: antibiotics 77%, digoxin 7%, analgesics 3%. Chart review: antibiotics 32%, analgesics 13%, psy-	Chart review of predefined events better than spontaneous reporting	(71)[)]

Type of hospital; specialty	*Patients, duration of study*	*Detection method*	*ADR frequency*	*Most frequent ADRs or organs affected (in% of ADRs)*	*Remarks*	*Reference*
				chotropics 9%		
Community hospital; medical ward	1024 patients; 4 months	Chart review	23.1% of patients (2.6% of all drug exposures)	Drugs: Furosemide 12%, diltiazem 3.6%, enalapril 3%. Organs: metabolic/hematologic 33%, GI-tract 18%, genitourinary 12%	Risk factors: age > 65 years, females > males, number of „drug exposures“	(16)
University hospital; internal medicine	440 patients; 2 months	Spontaneous reporting vs. chart review	Chart: 9.4% (males) and 11.2% (females), total 10% (56 ADRs in 44 patients). Spontaneous: 15 patients (3.4%) with 17 ADRs	Hypokalemia (diuretics), hyperkalemia (ACE inhibitors, potassium), hyponatremia (diuretics)	122 ADRs in 98 patients were present at admission (22.3% of patients). Spontaneous reporting is less efficient than chart review. Only definite and probable ADRs.	(72)
University hospital; internal medicine	12229; 2 years	Spontaneous reports	2.2% of patients	ADRs: hypersensitivity 29.3%, drug intoxications 19.9%, cardiovascular 15.9%. Drugs: antibiotics 29%, cardiovascular agents 21%, anticonvulsants 10%) and psychotropics 9%.	Preventive interventions: development of a clinical pharmacist-run anticoagulation clinic, drug utilization evaluation of phenytoin, dosing algorithm for theophylline.	(73)
Community hospital, internal medicine	10587 patients; 7 months	Spontaneous reports verified by clinical pharmacist	1.9% of patients (19% were considered to be preventable)	Drugs (non-preventable): antibiotics 42% (58), cardiovascular 16% (6), analgesic 13% (10). Organs: Cutaneous 50%(38), bleeding 13% (0.6), cardiac 13% (0.6)	Preventable: 50% type A, 50% allergic. Risk factors: allergy not recognized, oral anticoagulants, drugs with therapeutic drug monitoring, renally eliminated drugs	(30)
University hospi-	105 patients;	Systematic review	37% with certain or	Drugs (during stay):	Risk factors: stay in hospital,	(31)[)]

Type of hospital; specialty	*Patients, duration of study*	*Detection method*	*ADR frequency*	*Most frequent ADRs or organs affected (in% of ADRs)*	*Remarks*	*Reference*
tal; geriatrics	3 months	of charts	probable ADR during admission and stay (during stay age-dependent and higher)	Diuretics 32%, laxatives 21%, antibiotics 21%	but not number of drugs or number of diagnoses	
University hospital; internal medicine	24500 vs 25530 patients; both phases 1 year	Spontaneous reports vs. comprehensive assessment (pharmacists)	Spontaneous: 0.4% of patients. Comprehensive: 1.3% of patients	Organs: Cutaneous 41%, respiratory 14%, neurologic 14%, hematologic 12%	Comprehensive assessment: Standardization of detection system, active participation of hospital pharmacists. Drug-drug interactions 5%, medication errors 7% of all ADRs.	(41)
University hospital; psychiatry	3809 patients; 5 years	Spontaneous reports	3% of patients	Drugs: cyamemazine 24%, carbamazepine 24%, fluvoxamine 20%, fluoxetine 20%	Risk factors: females > males, age no risk factor. Drug-drug interactions in 15%	(32)
University hospital; psychiatry	50 patients; 1 year	Systematic review of charts	16% (8 patients) with at least 1 ADR	Neuroleptics are involved in 9 of twelve ADRs	Of 12 ADRs: 2 certain, 8 probable, 2 possible	(74)
University hospital; internal medicine	666 patients, 9 months	Spontaneous reports	2.7% of patients (certain, probable, possible ADRs)	No information	3.5% of patients had ADR as a reason for hospitalization. 51% of ADRs were preventable. 51% type A, 49% type B reactions. 81% severe or moderate.	(35)
University hospital, internal medicine	20695 patients, 3 years	Spontaneous reporting	6.9 % of all patients	Drugs: NSAIDs, anticoagulants, digoxin Organs: GI-bleeding, impaired renal function	80% of ADRs type A, 20% type B. Drug-drug interactions in 20%. Most of the ADRs were reported by nurses and pharmacists. Only 6.3% of the ADRs to be reported were actually reported to authorities	(36)
University hospital; internal me-	91574 patients, 4 years	Spontaneous reporting. Control	2.4% of patients	Drugs: morphine, digoxin, meperidine,	ADRs are associated with prolongation of hospitalization	(6)

Type of hospital; specialty	*Patients, duration of study*	*Detection method*	*ADR frequency*	*Most frequent ADRs or organs affected (in% of ADRs)*	*Remarks*	*Reference*
dicine		group.		oxycodone	(1.74 days), increased mortality (1.05 vs. 3.5%) and cost (2014 $ per patient)	
University hospital; internal medicine	153 patients; 2 months	Retrospective chart review vs. computerized monitoring	16% vs. 24% (only certain and probable)	Organs: renal impairment 31%, hepatic impairment 19%, eosinophilia 19%.	Computerized system (laboratory data) in combination with clinical signs detects 65% of ADRs	(28)
University hospital; internal medicine	329 patients; 6 months	Comprehensive monitoring (physician). Control group.	6.6% of patients during hospitalization	Organs: allergy 14%, hypotension 12%, dehydration 12%, sleepiness, falls 12%, GI disorders 12%	At admission, 3% of patients had ADR. 66% of ADRs are type A. Excess hospital stay is 8.5 day in patients with ADR.	(3)
University hospital; internal medicine	370 patients; 9 months	Comprehensive monitoring (pharmacist)	16.8% of patients (definite, probable, possible)	Organs: hematological 51%, GI-tract 22%, kidney 7%, liver 3%	7% of patients were admitted due to ADR. 59% of the ADRs type A. Mortality of patients with ADR 2.9%	(37)
University hospital; internal medicine	1959 patients (941 test, 1018 control units); 2 years	Spontaneous reporting vs. comprehensive monitoring (pharmacist)	2.1% of patients (spontaneous) vs. 14.6% (comprehensive) (definite, probable, possible)	Organs: GI-tract 27.2%, CNS 16.1%, cardiovascular 14.3%, metabolic 12.1%, blood 7.1%, skin 5.4%	After stopping comprehensive monitoring, ADR reporting rates go rapidly back to pre-intervention levels	(75)
University hospital; gastrointestinal	98 patients; 17 months	Retrospective chart review vs. computerized monitoring	17.9% of patients (definite and probable)	Organs: Liver 44%, kidney 15%, electrolytes 15%, blood 11%, glucose 11%	Computerized monitoring yielded 82 events, 27 were considered definite/probable, 30 possible ADRs.	(26)
University hospital; internal medicine	379 patients, 7 months	Chart review vs. computer based vs. spontaneous	12% of patients (probable and possible); 6% were severe. Computer-based 34/46 (4.4%) and spontaneous reporting 17/46 (2.2%)	Drugs: antibiotics 28%, cardiovascular 11%, antiretrovirals 11%, neuroleptics 9%	Computer-based monitoring detects 73% of ADRs.	(26)

Type of hospital; specialty	*Patients, duration of study*	*Detection method*	*ADR frequency*	*Most frequent ADRs or organs affected (in% of ADRs)*	*Remarks*	*Reference*
University hospital; internal medicine	4331 patients, 3 years	Comprehensive monitoring	11% clinically relevant ADRs (in 16% clinical event, in 31% abnormal laboratory value). Mortality 0.14%.	Drugs: chemotherapy 30.7, iloprost 14.3%, cyclosporin A 4.6%, antibiotics 2.8%, antivirals 2.6% Organs: GI-tract 131, blood 112, skin 93, CNS 61, cardiovascular 27	RF: female sex, polypharmacy (not age). Prolongation of hospitalization by ADR for 1.2 days.	(2)
University hospital; general medicine	9311 patients, 5 months	Actual review of charts (pharmacists, nurses, physicians). Control group	2.1% of patients	Drugs: antibiotics 17.1%, cardiovascular 16.5%, NSAIDs 14.6%, psychotropics 5.5% Organs: GI-tract 24%, skin 19%, Immunology 15%, CNS 13%	Definite 8%, probable 69%, possible 21%. Severe 17%, 2% lethal. Patients with ADRs have 3.8 days more in hospital, costing approximately 5000$.	(76)
University hospital; internal medicine	444 patients, 4 months	Comprehensive monitoring (physicians, pharmacist)	4.7% of patients during hospitalization. In 7% reason for hospitalization, in 21.4% ADR present at hospitalization.	Drugs: Antibiotics 38%, immunoglobulin 15%, topical steroids 15%. Organs: neurologic 31%, skin 23%, GI-tract 15%, liver 15%	42.3% type A reactions, approximately 50% preventable. Risk factors: polypharmacy during hospitalization. 7.5% of hospital bed days due to ADRs.	(38)
University hospital; cardiology	16916 patients, 18 months	Stimulated spontaneous reporting. Control group.	1.69% of patients during hospitalization. In 0.51% reason for hospitalization (likely, possible, doubtful).	Drugs: Contrast media 20%, antibiotics 14%, anticoagulants 13%, diuretics 6%. Organs: cutaneous 24%, cardiovascular 21%, metabolic 12%, coagulation 10%,	Frequency is age-dependent. 18 (5%) ADRs life-threatening, 18 (5%) lethal. Patients with ADRs stay 4 days longer in hospital.	(9)

Type of hospital; specialty	*Patients, duration of study*	*Detection method*	*ADR frequency*	*Most frequent ADRs or organs affected (in% of ADRs)*	*Remarks*	*Reference*
				neurologic 10%		
University hospital; general medicine	21365 patients; 4 months	Spontaneous reporting	0.2% of patients	Drugs: anticoagulants 18%, cardiovascular 16%, CNS drugs 12%, NSAIDs 6%. Organs: Coagulation 18%, neurologic 16%, cardiovascular 12%, GI-tract 10%	None of the serious or new ADRs was reported to the authorities.	(77)
University hospital; neurology	332 patients; 2 months clinical monitoring. 600 patients; 3 months computerized monitoring	Clinical monitoring vs. computerized monitoring	Clinical monitoring: 15.4% of patients. Computerized monitoring: 18.5% of patients (sensitivity 45%). 2.7% of patients with ADR at entry.	Organs (severe ADRs): CNS 53%, hematology 14%, respiratory 12%, GI-tract 7%, cardiovascular 7%	After combination of both methods, sensitivity of clinical monitoring is 72%, computerized monitoring 45%.	(27)
University hospital; surgical ICU	401 patients; 2 years and 7 months	Actual reviewing of charts. Control group.	9.2% of patients (1.1% of drug exposures)	Drugs: morphine 33%, meperidine 23%, metamizole 18% Organs: vomiting 18%, hypotension 15%, nausea 15%, itchiness 10%	87% of ADRs are type A reactions. Patients with ADR were 3.4 days longer on ICU.	(39)
Community hospital; geriatrics	163 patients; 5 months	Actual reviewing of charts (pharmacist) vs. computerized monitoring	60.7% of patients by chart reviewing. Computerized monitoring detected 47.5% of ADRs.	Drugs: cardiovascular 26%, affecting blood 22%, psychotropics 20%. Organs: GI-tract 26%, liver 18%, metabolic 17%, cardiovascular 9%, cutaneous 7%	Drug-drug interactions cause 17% of ADRs (2198 signals, 1.2% of signals with ADR). Idiosyncrasy 21%, intolerance 7%, „adverse effect“ 40%, „secondary pharmacological effect“ 9%, allergy 5%	(24)

Type of hospital; specialty	*Patients, duration of study*	*Detection method*	*ADR frequency*	*Most frequent ADRs or organs affected (in% of ADRs)*	*Remarks*	*Reference*
University hospital; geriatrics	168 patients; 8 months	Spontaneous reporting vs. interview with patients (pharmacist)	7.1% of patients (spontaneous) or 41% patients by interview.	Drugs (spontaneous): cardiovascular 33%, CNS 33%, antibiotics 8%. Drugs (interview): cardiovascular 31%, respiratory 22%, CNS 16%	All ADRs were type A reactions. For ADRs by interview 72% probable and 28% possible.	(25)

5 Prevalence of potentially severe drug-drug interactions in ambulatory dyslipidemic patients treated with a statin

Short title: Drug interactions in dyslipidemic patients

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5.1 Abstract

Background: Drug-drug interactions (DDIs) are a well known risk factor for adverse drug reactions. Statins are a cornerstone in the treatment of dyslipidemic patients, and patients with dyslipidemia are concomitantly treated with a variety of additional drugs. Since DDIs are associated with adverse reaction, we performed a cross-sectional study to assess the prevalence of potentially critical drug-drug and drug-statin interactions in an outpatient adult population with dyslipidemia.

Methods: Data of patients with dyslipidemia treated with a statin were collected from 242 practitioners from different parts of Switzerland. The medication was screened for potentially harmful DDIs with statins or other drugs using an interactive electronic drug interaction program.

Results: We included 2742 ambulatory statin-treated patients (mean age 65.1 ± 11.1 [SD] years; 61.6% males) with 3.2 ± 1.6 (mean±SD) diagnoses and 4.9 ± 2.4 drugs prescribed. Of those, 190 patients (6.9%) had a total of 198 potentially harmful drug-statin interactions. Interacting drugs were fibrates or nicotinic acid (9.5% of patients with drug-statin interactions), CYP3A4-inhibitors (70.5%), digoxin (22.6%) or cyclosporine (1.6%). The proportion of patients with a potential drug-statin interaction was 12.1% for simva-statin, 10.0% for atorvastatin, 3.8% for fluvastatin, and 0.3% for pravastatin. Additionally, the program identified 393 potentially critical non-statin DDIs in 288 patients.

Conclusions: CYP3A4 inhibitors are the most frequent cause for potential interactions with statins. As the risk for developing rhabdomyolysis is increased in patients having drug-statin interactions, clinicians should be aware of the most frequently observed drug-statin interactions and how these interactions can be avoided.

5.2 Introduction

Drug-drug interactions (DDIs) are an important cause for adverse drug reactions. It has been estimated that approximately 5% of prescribing errors (1) or of adverse drug reactions (2) are due to DDIs in hospitalized patients. In a recent investigation, 2.3% to 7.8% of adverse effects in association with the use of co-trimoxazole, digoxin or ACE-inhibitors were found to be due to interactions with specific concomitant drugs (3). Polypharmacy, which is associated with the number of diagnoses in a given patient (4), has been identified as a major risk factor for DDIs. Additionally, the way a drug is metabolized and/or excreted is a major determinant of potential DDIs (5). Regarding drug metabolism, drugs undergoing degradation by cytochrome P450 isoenzymes (CYPs) carry a particularly high risk for DDIs, because of the large number of drugs inhibiting or inducing CYPs (5, 6). Additionally, clinically relevant DDIs can arise on the level of transport proteins responsible for renal and/or biliary excretion of endogenous and exogenous substances. Examples are interactions involving P-glycoprotein (P-gp), e.g. interactions between statins and digoxin (7) or clarithromycin and digoxin (8, 9).

Interactions with statins can lead to rhabdomyolysis, a severe adverse reaction which may be fatal (10, 11). A recent study in Ireland estimated that approximately 30% of all users of statins have concomitant drugs prescribed which can inhibit statin metabolism, potentially leading to rhabdomyolysis (12). It is known that the interaction potential differs between individual statins (13, 14). Atorvastatin, lovastatin and simvastatin are all biotransformed by CYP3A4, the most abundant CYP isozyme, which metabolizes most drugs undergoing CYP-associated biotransformation (6, 15). Accordingly, the risk for interactions is highest for drugs metabolized by CYP 3A4, particularly, if no other CYP isozymes are involved in their biotransformation. Fluvastatin is primarily metaboli-

zed by CYP2C9, an isozyme which is less abundant than CYP3A4 making the drug less prone to DDIs (16, 17). Pravastatin is more hydrophilic due to a hydroxyl group allowing conjugation of the drug without previous phase I biotransformation (13, 14). Accordingly, the risk for interactions with pravastatin is estimated to be lower than for statins undergoing CYP-dependent metabolism (16, 17). Because data on the prevalence and risk factors for potential DDIs in ambulatory patients are rare and interactions in patients treated with statins can be associated with severe adverse effects (10, 11, 18), we identified potential DDIs in ambulatory, hyperlipidemic patients treated with a statin to assess (1) the prevalence of potential DDIs in association with statin therapy, (2) to assess the prevalence of other potential DDIs not involving statins, and (3) to identify risk factors for potential DDIs in this population.

5.3 **Methods**

5.3.1 Subjects, study design and data collection

Between February to April 2002, practitioners from different parts of Switzerland were recruited to participate in the '**S**wiss **A**nalysis **F**ocused on the **E**valuation of Potential Drug Interactions' (SAFE). The participating practitioners screened all patients attending their practice during five consecutive days and completed a data sheet of each dyslipidemic patient with statin therapy. The form included data on year of birth, sex, the statin prescribed, indication for the statin, main diagnoses and all concomitantly prescribed drugs. Diagnoses were coded according to the International Statistical Classification of Disease and Related Health Problems (ICD-10) and drugs according to the WHO Drug Dictionary (Version 01-3, third quart 2001). All patient data were recorded in an electronic database and all drug profiles were screened by the online version of Drug-

Reax® Interactive Drug Interactions (Micromedex™ Healthcare Series Vol. 111-115 / Exp 03-12/2002) (19), a drug interaction program that was used in several previous studies (20-22). This program has proven to be more sensitive to predict potential DDIs than expert physicians (22).

5.3.2 Database and semiautomatic screening by Drug-Reax®

Drug-Reax®, an interactive electronic drug interaction program with a filter for severity rating (major, moderate, minor) and providing referenced information on the clinical picture caused by a given DDI, was used for screening potential DDIs (19). For this project, a specific software for data management and entry was developed. The software allowed coding of diagnoses according to ICD-10 and of drugs according to the WHO Drug Dictionary. Phenprocoumon and acenocoumarol, the two oral anticoagulants used in Switzerland, were coded as warfarin, because they are not listed in Drug-Reax®. After the entry of all drugs of one single patient, the software prepared data records for all possible drug-drug combinations for the patient (number of drug pairs/patient = (number of drugs x (number of drugs - 1) / 2)). By using the browser object of MS-Access, a semiautomatic search was started in Drug-Reax® and the result was pasted into the database. A systematic parsing procedure analyzed the search results, which consequently had to be assigned to the correct drug-drug pair. With this procedure over 30,000 drug-drug pairs were screened. Drug combinations with the potential of relevant interactions for either compound were separated for further evaluation.

5.3.3 Evaluation of clinical relevance of potential drug interactions

Drug-statin interactions

Each patient and medication profile with a possible drug-statin interaction detected by Drug-Reax®, was evaluated by a pharmacist and a clinical pharmacologist for clinical relevance. A drug-statin combination was considered critical or potentially harmful and therefore clinically relevant if 1) the respective statin was combined with a known inhibitor of its metabolism and/or transport; 2) there was at least one published case report describing this interaction, or 3) the potential adverse effect could have had a serious outcome. Serious outcome was defined as described by the ICH guidelines for clinical safety data management of adverse drug reactions (23). In case of disagreement, the specific interaction was discussed until consensus between both assessors was reached.

Non-statin DDIs

Each drug profile with a possible non-statin DDI of 'major severity' according to Drug-Reax® or with a DDI not recognized by Drug-Reax®, but by manual screening using standard literature (24, 25), an additional online drug interaction database (www.pharmavista.ch) and/or Medline, was evaluated by a pharmacist and a clinical pharmacologist. DDIs were considered as potentially harmful (and therefore clinically relevant), if the potential adverse effect of this interaction could have had a serious outcome. Serious outcome was defined as described by the ICH guidelines for clinical safety data management of adverse drug reactions (23). A DDI of "major severity" according to Drug-Reax® was considered as not being clinically relevant, if the interaction did not correspond to the actual clinical situation (e.g. first-dose hypotension of ACE-

inhibitors in patients having long-term treatment with ACE-inhibitors and diuretics), or if one of the potentially interacting drugs was administered topically (e.g. treatment with topical ketoconazole in a patient treated with a CYP3A4 substrate). In case of disagreement between the two assessors, the specific interaction was discussed until consensus was reached.

5.3.4 Statistical analysis

Possible differences of age, number of diagnoses and number of drugs between the groups of patients treated with the different statins were tested by one-way ANOVA. Categorical variables were tested by Pearson χ^2. The 5%-significance level (α-criterion) was adjusted for multiple testing according to Bonferroni-Holm (26).

Potential drug-statin and non-statin DDIs were analyzed by logistic regression analyses using a backward elimination procedure with Wald statistics and likelihood-ratio statistics. The occurrence of potential drug-statin or non-statin DDIs was used as the response variable. Explanatory variables put in the two models of drug-statin and non-statin DDIs included the dichotomous variables male sex, French speaking part of Switzerland, Italian speaking part of Switzerland, diagnosis of hypertension, diabetes, coronary heart disease, cardiac failure, arrhythmias, depression/psychiatric disorders, cerebrovascular diseases, rheumatic diseases/diseases of the musculoskeletal system, gout/hyperuricemia, epilepsia, and other diagnoses (see Table 5.1) The continuous variables included in the model were age (years), number of diagnoses, number of prescribed drugs, and number of prescribed pharmacologically active compounds. Explanatory variables were included in the final model, if the p-value was < 0.1.

The final model of drug-statin interactions comprised the following explanatory variables: Number of diagnoses, number of prescribed drugs, diagnosis of hypertension, diabetes, cardiac failure, arrhythmias, and French speaking part of Switzerland. The influence of the prescribed statin was assessed by an indicator variable for the use of pravastatin (yes/no), i.e. pravastatin was tested against all other statins. The following parameters were put in the final non-statin DDI model as explanatory variables: Male sex, number of prescribed pharmacologically active compounds, diagnosis of diabetes, cardiac failure, arrhythmias, cerebrovascular diseases, and gout/hyperuricemia. The influence on non-statin DDIs was assessed by an indicator variable for the presence of potential drug-statin DDIs. Relative risk estimates are expressed as odds ratios (ORs) with 95% confidence intervals (95% CI).

Statistical analyses were performed with SPSS for Windows version 10.1.4 (SPSS Inc., Chicago, Illinois 60606).

5.4 **Results**

5.4.1 Drug-statin interactions

From February through April 2002, 242 practitioners (43.0% general practitioners, 41.7% internists, 13.6% cardiologists and 1.7% others), from different parts of Switzerland recorded the medication of 2,753 dyslipidemic patients treated with a statin. Eleven patients were excluded from the analysis: ten patients were not prescribed a statin and one patient was on cerivastatin, a statin withdrawn from the market in 2000. Patients were recruited in the German (49.2%), French (37.9%) or Italian (12.9%) speaking part of Switzerland. Pravastatin was prescribed in 34.1% of all patients, atorvastatin in 32.3%, simvastatin in 27.8%, and fluvastatin in 5.8%. Patient characteristics are sum-

marized in Table 5.1. The 2,742 patients included had a total of 8,943 diagnoses (mean 3.2 ± 1.6 per patient) and were prescribed a total of 12,766 drugs (mean 4.9 ± 2.4 drugs per patient, range 1-21). The most prevalent co-morbidities beside dyslipidemia were arterial hypertension, coronary heart disease, diabetes mellitus, cerebrovascular diseases, psychiatric illnesses, arrhythmias and cardiac failure. In comparison to the other statins, patients treated with simvastatin were significantly older and were prescribed more drugs than other statin users.

The distribution of drugs concomitantly prescribed with statins is shown in Table 5.2. Since arterial hypertension and coronary heart disease were the most prevalent co-morbidities, acetylsalicylic acid, betablockers, ACE-inhibitors, angiotensin receptor blockers, and thiazide or loop diuretics were the drugs most often prescribed concomitantly. Overall, 122 patients (4.4%) had no additional drug prescribed.

Overall, 190 (6.9%) of the 2742 patients with statin therapy had a total of 198 drug combinations with the potential for a critical drug-statin interaction; eight patients had two such drug combinations (see Table 5.3). The prevalence of potentially critical drug-statin interactions was 12.1% (95% CI 9.7 to 14.4%) in patients with simvastatin, 10.0% (95% CI 8.0 to 12.1%) with atorvastatin, 3.8% (95% CI 0.5 to 7.1%) with fluvastatin, and 0.3% (95% CI 0.1 to 0.7%) with pravastatin. The potentially interacting drugs comprised other lipid lowering drugs (fibrates, nicotinic acid), known CYP 3A4 inhibitors (amiodarone, verapamil, fluoxetine / norfluoxetine, diltiazem, nefazodone, clarithromycin and systemic azole antifungal drugs), or known CYP2C9 inhibitors (fluoxetine / norfluoxetine). Forty-three patients (22.6% of the patients with a potential drug-statin interaction) were concomitantly treated with digoxin, a P-gp substrate.

Logistic regression analysis indicated that the following variables were associated with a statistically increased relative risk for potentially critical drug-statin interactions: Number of drugs (adjusted OR 1.3; 95% CI 1.2 to 1.4, $p < 0.001$), diagnosis of cardiac failure (adjusted OR 1.8; 95% CI 1.1 to 3.1, $p = .03$), diagnosis of arrhythmias (adjusted OR 5.6; 95% CI 3.6 to 8.5, $p < 0.001$), and being a patient from the French speaking part of Switzerland (adjusted OR 1.5; 95% CI1.1 to 2.1, $p = 0.018$). The use of pravastatin was associated with a lower risk for potentially critical drug-statin interactions (adjusted OR = 0.02, 95% confidence interval 0.01 to 0.07, $p < 0.001$) compared to use of other statins.

Additional drug-statin combinations were observed, which did not meet the criteria to be classified as potential DDIs with harmful clinical consequences as defined, but which are worth mentioning. Three hundred and twenty patients (11.7% of the study population) were prescribed an oral anticoagulant, either phenprocoumon (CYP3A4 and CYP2C9 substrate; 201 patients or 7.3% of all patients studied) or acenocoumarol (CYP 2C9 substrate; 119 patients or 4.3%). In 200 patients (7.3%) oral anticoagulants were administered in combination with atorvastatin, simvastatin or fluvastatin. Since oral anticoagulants are only CYP substrates but not inhibitors, these potential interactions were not included in our analysis. Fifty-four patients (2.0 % of all patients studied) were treated with a CYP inducer. Thirty-nine of these patients (1.4%) had a combination which might lead to a decreased plasma concentration of the statin (simvastatin or atorvastatin) and a potential loss of its clinical effect (7 with barbiturates, 15 with carbamazepine, 2 with phenytoin, and 15 with St. Johns wort). Since the clinical relevance of these potential interactions is not clear, they were not included in our analysis. The potential interaction between atorvastatin and clopidogrel, which was initially published in early

2003 (27) remains controversial (28, 29) and was therefore not included in our analysis. No patient was reported to have signs or symptoms of myopathy during data collection.

5.4.2 Non-statin DDIs

In 288 patients of 2742 patients studied (10.5%), 393 drug combinations with non-statin DDIs were identified, corresponding to a mean of 1.36 ± 0.8 interactions per affected patient. Of 288 patients with interactions, 219 (76.0%) had one non-statin DDI, 47 patients (16.3%) had two and 22 patients (7.6%) had three or more non-statin DDIs. The non-statin DDIs which were detected most often are listed in Table 5.4. Patients treated with ACE-inhibitors, potassium sparing diuretics, betablockers, oral anticoagulants, amiodarone or digoxin were most likely to have potential non-statin DDIs. The underlying mechanism of potential DDIs was pharmacodynamic in 65% of the 393 drug combinations with non-statin DDIs (predominantly among cardiovascular drugs), 14% were pharmacokinetic, and in 21% the mechanism was unclear.

Logistic regression analysis yielded statistically increased relative risks for the following variables: Male sex (adjusted OR 1.4; 95% CI 1.1 to 1.9), number of prescribed pharmacologically active compounds (adjusted OR 1.6; 95% CI 1.5 to 1.7), diagnosis of cardiac failure (adjusted OR 3.3; 95% CI 2.1 to 5.1), diagnosis of arrhythmias (adjusted OR 3.50; 95% CI 2.4 to 5.2), diagnosis of cerebrovascular diseases (adjusted OR 1.6; 95% CI 1.1 to 2.2), and a diagnosis of gout (adjusted OR 2.9; 95% CI 1.7 to 4.9).

5.5 Discussion

Our study demonstrates that overall, approximately 7% of all patients prescribed a statin have a potentially critical drug-statin interaction. This figure is lower than the one obtained in a recent study in Ireland, where potentially interacting drugs were detected in approximately 30% of patients treated with a statin (12). This discrepancy may be explained by differences in the prescribing pattern between Ireland and Switzerland and also by differences in the definition of drug-statin interactions. Considering the prescribing pattern, only 3.6% of the patients in our study were treated with the CYP3A4 inhibitors verapamil or diltiazem, whereas 13.1% of the patients in the Irish study were concomitantly treated with these drugs (12). In the Irish study, inhibitors, inducers and substrates of CYP3A4 and CYP2C9 were regarded as drugs potentially interacting with statins (12). In contrast, in our study, only CYP inhibitors, P-gp substrates and other drugs for which case reports or drug interaction studies about a clinically relevant interaction could be identified, were considered as drugs potentially interacting with statins. Moreover, CYP3A4 and/or CYP 2C9 substrates, for which no case reports of clinically relevant drug-statin interactions exist, were not included in the analysis. In addition, CYP inducers (e.g. phenytoin, carbamazepin, rifampicin and St. Johns wort) were not considered as drugs with a clinically significant interaction potential with statins in our study, and were therefore not included.

Although the participating physicians had been told to transmit the medication lists of the patients entering the study before performing any changes, we cannot exclude the possibility that some practitioners checked the medication list for drug-drug interactions before transmitting it. The true prevalence of drug-drug interactions may therefore be higher than found in our study.

Approximately 40% of all patients treated with a statin who develop rhabdomyolysis are concomitantly treated with an interacting drug (18). A recent analysis of reports to the FDA revealed that mibefradil, fibrates, cyclosporine, macrolides (erythromycin and clarithromycin), warfarin, digoxin, azole antifungals, nicotinic acid, tacrolimus, chlorzoxazone and nefazodone were the drugs or drug classes considered to be involved in statin-induced rhabdomyolysis. From our data, showing that 7% of patients treated with a statin have a potential drug-statin interaction, it can be estimated that drug-statin interactions increase the risk for rhabdomyolysis by a factor of approximately 6. This figure corresponds well with an estimated 10-fold increase in the risk of rhabdomyolysis reported by Omar et al. (18), confirming our findings and calculations. Statin-induced rhabdomyolysis remains therefore a rare event, occurring in 0.04-0.2% of statin treated patients, even in the presence of an interacting drug (18). This is supported by the observation that none of the 2742 patients studied, including the 190 patients with a potential drug-statin interaction, had signs or symptoms of myopathy in our investigation. Despite being a rare adverse reaction, due to the widespread use of statins and the potentially fatal outcome, statin-associated rhabdomyolysis has become an important clinical problem. This was demonstrated dramatically by the recent withdrawal of cerivastatin from the market (30).

Our study defines several risk factors associated with the presence of a potentially critical drug-statin interaction. The individual statin chosen for treatment of dyslipidemia is the most important one. Similar to other epidemiological studies (12, 31) and published case series of patients with statin-induced rhabdomyolysis (18), our study also demonstrates that CYP3A4 inhibitors concomitantly prescribed with simvastatin or atorvastatin (lovastatin is not marketed in Switzerland), are the most frequent combinations

of potentially critical drug-statin interactions. Potential drug interactions with fluvastatin are rarer, because this drug is primarily metabolized by CYP2C9 (13, 32), CYP2C9 inhibitors are less often used in dyslipidemic patients than CYP3A4 inhibitors (12). For pravastatin, potential interactions seem to be even rarer than for fluvastatin, since this statin is not metabolized by CYP450 enzymes, but is glucuronidated.

Furthermore, the study shows that important additional risk factors for the appearance of potentially critical drug interactions with statins include the number of concomitant drugs a patient is prescribed, and a diagnosis of heart failure and/or arrhythmias; these diagnoses are highly correlated with specific drug therapies known to interact with statins. In the case of heart failure, an important interaction is observed between statins and digoxin, which can increase the plasma digoxin level by approximately 30% due to inhibition of P-gp by certain statins. This interaction is observed with P-gp substrates such as simvastatin, lovastatin, and atorvastatin (33). Regarding the narrow therapeutic range of digoxin, this interaction may be clinically relevant for the above mentioned statins, but not with pravastatin (34), which does not inhibit P-gp (33, 35).

The group of patients with the highest risk for potential drug-statin interactions is those with cardiac arrhythmias. In Switzerland, patients with cardiac arrhythmias are often treated with verapamil, digoxin or amiodarone, which can all interact with most statins. Verapamil inhibits both CYP3A4 and P-gp (35, 36), and amiodarone is an efficient inhibitor of several CYPs, among them CYP3A4 and CYP2C9 (37).

The interactions between statins and fibrates or cyclosporine may be mediated by the inhibition of hepatic transporters, which are involved in the hepatic uptake of statins. OATP2/OATP-C-mediated transport has been identified not only for pravastatin (38, 39), but also for simvastatin (38), fluvastatin (38), atorvastatin (40) and cerivastatin (41).

Shatira et al. showed that cyclosporine can inhibit hepatic uptake of cerivastatin, which was at least partly mediated by cyclosporine-induced inhibition of OATP2, suggesting that increased plasma levels of cerivastatin in the presence of cyclopsorine are mainly due to impairment of hepatic uptake than inhibition of CYP3A4 (41). The same mechanism may be responsible for the DDI with cyclosporine and pravastatin (42). Recently, the pharmacokinetic interaction between gemfibrozil and pravastatin has been investigated in more detail. The increase in the pravastatin plasma concentration could be explained by both a decrease in renal clearance and in hepatic uptake (43).

As expected and as shown in previous studies (44, 45), we could identify polypharmacy as a risk factor for DDIs. In agreement with these studies, the current work also demonstrates that the risk for potentially serious DDIs increased with the increasing number of drugs used. This may be critical in particular in patients with cardiac diseases, who are generally treated with more than one drug (46). Accordingly, we identified heart failure as one of the major risk factors associated with potential non-statin DDIs. Regarding the drugs used in heart failure, for instance ACE-inhibitors, digoxin, and potassium-sparing and loop diuretics, they all rank among the drugs with a high prevalence of potentially serious non-statin DDIs.

Potential non-statin interactions frequently detected in patients with heart failure were those between ACE-inhibitors and potassium supplements or potassium-sparing diuretics which is in accordance with a study of the prevalence of DDIs in the medication of medical patients at hospital discharge (20). While the administration of potassium supplements in patients treated with ACE-inhibitors is well known to be associated with hyperkalemia (47, 48), the development of hyperkalemia in patients treated with ACE-inhibitors and low dose spironolactone, i.e. 25-50 mg/day as recommended for the

treatment of heart failure (49), has been reported only recently (50, 51). Renal failure appears to be an additional risk factor for the development of hyperkalemia in patients treated with ACE-inhibitors, in particular when a drug-drug and/or diet-drug interaction is present (50, 52). Concomitant use of loop or thiazide diuretics may diminish the risk of hyperkalemia of ACE inhibitors and potassium supplements or potassium-sparing diuretics, but we still recommend that patients treated with such combinations should be followed carefully, in particular if they also have renal failure.

Another group of patients with a high prevalence of non-statin DDIs identified in our study are those with gout. Our data indicate that this is the case particularly because of a potential interaction between allopurinol and ACE-inhibitors, which may increase the risk of developing an allopurinol-induced hypersensitivity syndrome (53). While examples for this interaction only exist as case reports (54-56), the clinical outcome for the allopurinol-associated hypersensitivity syndrome is potentially so serious (fatalities are reported (53, 57, 58)) that it may be prudent to avoid this drug combination.

Patients with psychiatric disorders, in particular depression, were also identified as risk group for non-statin DDIs. While tri- and tetracyclic antidepressants are generally not relevant inhibitors or inducers of CYPs, this is different for selective serotonin reuptake inhibitors (SSRIs) (59). Significant inhibition of CYPs have been described for fluvoxamine (inhibition of CYP1A2, CYP2C19 and CYP3A4), paroxetine (CYP2D6) and fluoxetine (CYP2D6, CYP1A2, CYP3A4 and CYP2C9) (59-61). For all of these SSRIs, DDIs due to CYP inhibition with clinical relevance have been described. This is important to know for physicians caring for patients with cardiovascular disease, since antidepressants are frequently prescribed in this population (62).

None of the patients included in this study had symptoms or signs of an adverse drug effect due to a statin or non-statin DDI. Regarding other reports in the literature, where approximately 6% of patients with a critical DDI have adverse effects (63, 64), some adverse effects in the 190 patients with statin interactions or the 288 patients identified with a critical non-statin DDI would have been expected. However, the aim of the study was to quantify the prevalence of potential DDIs and not of adverse events. Additionally, we did not have direct access to the patient records to identify adverse clinical outcomes in association with a DDI, potentially favoring underreporting of DDI-associated adverse reaction. Moreover, the medication screened included only those drugs prescribed by the physician taking part in the study. It is possible that patients may have visited other physicians prescribing additional drugs that were unknown to the physician treating the patient for dyslipidemia. Therefore, the prevalence of potential statin or non-statin DDIs in this population may be even higher than the one assessed in this study.

5.6 **Conclusions**

In conclusion, our study shows that CYP3A4 inhibitors are the most frequent cause of potential drug interactions with statins. Although statin-induced rhabdomyolysis is a rare event even in patients having a drug-statin interaction, the possibly severe outcome of rhabdomyolysis favors the concept that potentially interacting drug-statin combinations should be avoided or patients should be monitored more closely. It is therefore important to teach clinicians about the most frequently observed drug-statin interactions and how these interactions can be avoided.

Additionally, serious non-statin DDIs are common in patients with dyslipidemia, mostly due to co-morbidities for which they are treated concomitantly with numerous additional drugs. Further research is necessary to assess the clinical significance of our findings, e.g. the incidence and clinical significance of adverse effects in patients with potentially serious DDIs.

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Table 5.1 Patient characteristics and co-morbidities in 2742 dyslipdemic patients with statin therapy stratified according to individual statins

Patients	**Total (n=2742)**	**Atorvastatin (n=886)**	**Pravastatin (n=934)**	**Simvastatin (n=763)**	**Fluvastatin (n=159)**	**p-value**
Age, yrs (mean ± SD)	65.1 ± 11.2	63.7 ± 11.6	65.3 ± 11.2	66.5 ± 10.8	65.6 ± 10.8	<.05*
Females, n (%)	1052 (38.4)	334 (37.7)	362 (38.8)	296 (38.8)	60 (37.7)	ns
Number of diagnoses (including dyslipidemia) (mean ± SD)	3.2 ± 1.6	3.2 ± 1.6	3.2 ± 1.6	3.4 ± 1.5	3.2 ± 1.3	ns
Number of prescribed drugs inc-luding statin (mean ± SD)	4.9 ± 2.4	4.7 ± 2.4	4.8 ± 2.4	5.1 ± 2.3	5.1 ± 2.2	<.05 †
Hypertension, n (%)	1428 (52.1)	441 (49.8)	479 (51.3)	407 (53.3)	101 (63.5)	ns
Diabetes mellitus, n (%)	520 (19.0)	170 (19.2)	170 (18.2)	151 (19.8)	29 (18.2)	ns
Coronary heart disease, n (%)	1166 (42.5)	372 (42.0)	389 (41.6)	348 (45.6)	57 (35.8)	ns
Cardiac failure, n (%)	130 (4.7)	40 (4.5)	35 (3.7)	49 (6.4)	6 (3.8)	ns
Arrhythmias, n (%)	188 (6.9)	56 (6.3)	63 (6.7)	61 (8.0)	8 (5.0)	ns
Cerebrovascular diseases	461 (16.8)	136 (15.3)	159 (17.0)	139 (18.2)	27 (17.0)	ns

Patients	**Total (n=2742)**	**Atorvastatin (n=886)**	**Pravastatin (n=934)**	**Simvastatin (n=763)**	**Fluvastatin (n=159)**	**p-value**
(including transitory ischemic attacks and peripheral arterial occlusive disease), n (%)						
Depression/psychiatric disorder, n (%)	423 (15.4)	137 (15.5)	133 (14.2)	125 (16.4)	28 (17.6)	ns
Rheumatic diseases / diseases of musculoskeletal system, n (%)	416 (15.2)	124 (14.0)	139 (19.9)	128 (16.8)	25(15.7)	ns
Gout / hyperuricemia, n (%)	103 (3.8)	42 (4.7)	34 (3.6)	21 (2.8)	6 (3.8)	ns
Epilepsy, n (%)	16 (0.6)	4 (0.5)	6 (0.6)	6 (0.8)	0	ns
Other diagnoses, n (%)	244 (8.9)	88 (9.9)	94 (10.1)	54 (7.1)	8 (5.0)	ns

* Age: simvastatin > atorvastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm)

† Number of drugs: simvastatin > atorvastatin, simvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm)

Table 5.2 Comedication prescribed in 2742 statin users stratified according to individual statin

	Total (n=2742)	**Atorvastatin (n=886)**	**Pravastatin (n=934)**	**Simvastatin (n=763)**	**Fluvastatin (n=159)**	**p-value**
Number of concomitant drugs (mean ± SD)	3.9 ± 2.4	3.7 ± 2.4	3.8 ± 2.4	4.1 ± 2.3	4.1 ± 2.2	<0.05 †
Acetylsalicylic acid, n (%)	1258 (45.9)	423 (47.7)	408 (43.7)	366 (48.0)	57 (35.8)	ns
Betablockers, n (%)	1145 (41.8)	373 (42.1)	376 (40.3)	327 (42.9)	69 (43.4)	nt
Thiazide or loop diuretics, n (%)	900 (32.8)	272 (30.7)	320 (34.3)	258 (33.8)	50 (31.4)	ns
ACE-inhibitors, n (%)	778 (28.4)	226 (25.5)	250 (26.8)	252 (33.0)	50 (31.4)	<0.05 &
Angiotensin receptor antagonists, n (%)	551 (20.1)	177 (20.0)	198 (21.2)	147 (19.3)	29 (18.2)	nt
Non-steroidal anti-inflammatory drugs, n (%)	427 (15.6)	122 (13.8)	140 (15.0)	132 (17.3)	33 (20.8)	ns
Calcium antagonists, n (%) (dihydropyridines)	403 (14.7)	129 (14.6)	130 (13.9)	121 (15.9)	23 (14.5)	nt
Antidepressants*, n (%)	340 (12.4)	119 (13.4)	88 (9.4)	103 (13.5)	30 (18.9)	<0.05 $

	Total (n=2742)	**Atorvastatin (n=886)**	**Pravastatin (n=934)**	**Simvastatin (n=763)**	**Fluvastatin (n=159)**	**p-value**
Oral antidiabetics (other than sulfonylureas, n (%)	238 (12.0)	119 (13.4)	111 (11.9)	84 (11.0)	14 (8.8)	nt
Sulfonylureas, n (%)	205 (7.5)	70 (7.9)	67 (7.2)	58 (7.6)	10 (6.3)	nt
Phenprocoumon, n (%)	201 (7.3)	56 (6.3)	76 (8.1)	62 (8.1)	7 (4.4)	ns
Potassium sparing diuretics, n (%)	161 (5.9)	57 (6.4)	53 (5.7)	38 (5.0)	13 (8.2)	nt
Clopidogrel, n (%)	136 (5.0)	43 (4.9)	37 (4.0)	48 (6.3)	8.0 (5.0)	nt
Insulin, n (%)	133 (4.9)	40 (4.5)	40 (4.3)	45 (5.9)	8 (5.0)	nt
Allopurinol, n (%)	122 (4.4)	43 (4.9)	42 (4.5)	27 (3.5)	10 (6.2)	nt
Acenocoumarol, n (%)	119 (4.3)	27 (3.0)	44 (4.7)	41 (5.4)	7 (4.4)	ns
Calcium antagonists (verapamil or diltiazem), n (%)	100 (3.6)	33 (3.7)	30 (3.2)	31 (4.1)	6 (3.8)	nt
Amiodarone, n (%)	82 (3.0)	29 (3.2)	26 (2.8)	23 (3.0)	4 (2.5)	ns
Digoxin, n (%)	67 (2.4)	21 (2.4)	19 (2.0)	23 (3.0)	4 (2.5)	nt
Tramadol , n (%)	24 (0.9)	12 (1.4)	5 (0.5)	7 (0.9)	--	nt

	Total (n=2742)	Atorvastatin (n=886)	Pravastatin (n=934)	Simvastatin (n=763)	Fluvastatin (n=159)	p-value
St. Johns wort, n (%)	23 (0.8)	8 (0.9)	8 (0.9)	5 (0.7)	2 (1.3)	nt
Gingko, n (%)	18 (0.7)	5 (0.5)	9 (1.0)	4 (0.5)	--	nt
Fibrates, n (%)	17 (0.6)	10 (1.1)	3 (0.3)	3 (0.4)	1 (0.6)	nt
Cyclosporine, n (%)	8 (0.3)	--	4 (0.4)	3 (0.4)	1 (0.6)	nt
Methotrexate, n (%)	6 (0.2)	2 (0.2)	2 (0.2)	--	2 (1.3)	nt
Azathioprin, n (%)	4 (0.1)	--	1 (0.1)	3 (0.4)	--	nt
Nicotinic acid, n (%)	3 (0.1)	--	2 (0.2)	1 (0.1)	--	nt
Azole antifungals (systemic), n (%)	2 (0.1)	--	--	2 (0.3)	--	nt

*excluding St. Johns wort extract

nt = not tested to avoid multiple testing on the same sample.

† Number of drugs: simvastatin > atorvastatin, simvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm)

& ACE-inhibitors: simvastatin > atorvastatin; simvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm)

$ Antidepressants: atorvastatin > pravastatin; fluvastatin > pravastatin ($p < 0.05$ by ANOVA/Bonferroni-Holm)

Table 5.3 List of 198 potential drug-statin interactions in 190 dyslipidemic patients treated with a statin; eight patients had two potential interactions (7 in the atorvastatin and 1 in the simvastatin group)

Potential interactions	**Total**	**Atorvastatin**	**Pravastatin**	**Simvastatin**	**Fluvastatin**
Total number of patients with potential interactions, n	190	89	3	92	6
Total number of potential interactions, n (%)	198 (100.0)	96 (100.0)	3 (100.0)	93 (100.0)	6 (100.0)
Other lipid lowering drugs, n (%)	18 (9.1)	10 (10.4)	3 (100.0)	4 (4.3)	1 (16.7)
Fibrates	17 (8.6)	10 (10.4)	3 (100.0)	3 (3.2)	1 (16.7)
Nictotinic Acid	1 (0.5)	--	--	1 (1.1)	--
CYP3A4 inhibitors, n (%)	129 (65.2)	66 (68.8)	NA	63 (67.7)	NA
Amiodarone	52 (26.3)	29 (30.2)	--	23 (24.7)	--
Verapamil	40 (20.2)	21 (21.96)	--	19 (20.4)	--
Diltiazem	5 (2.5)	--	--	5 (5.4	--
Fluoxetin / Norfluoxetin	24 (12.1)	13 (13.5)	--	11 (11.8)	--
Nefazodone	3 (1.5)	3 (3.1)	--	--	--

Potential interactions	**Total**	**Atorvastatin**	**Pravastatin**	**Simvastatin**	**Fluvastatin**
Clarithromycin	3 (1.5)	--	--	3 (3.2)	--
Azole antifungal (systemic)	2 (1.0)	--	--	2 (2.2)	--
CYP2C9 inhibitors, n (%)	5 (2.5)	NA	NA	NA	5 (83.3)
Fluoxetin / Norfluoxetin	5 (2.5)	--	--	--	5 (83.3)
P-gp substrates, n (%)	43 (21.7)	20 (20.8)	NA	23 (24.7)	--
Digoxin	43 (21.7)	20 (20.8)	--	23 (24.7)	--
Others, n (%)	3 (1.5)	--	--	3 (3.2)	--
Cyclosporine	3 (1.5)	--	--	3 (3.2)	--

NA = not applicable

Table 5.4 Description of 393 critical non-statin drug-drug interactions in 288 patients with dyslipidemia

Interaction	**n (%)**	**Mechanism and/or potential risk**
ACE-inhibitor – potassium sparing diuretic	51 (13.0)	Hyperkalemia due to increased potassium retention secondary to lowered aldosterone levels caused by ACE-inhibitor
Digoxin – loop / thiazide diuretics	42 (10.7)	Secondary digoxin toxicity due to diuretic-induced hypokalemia and hyomagnesemia, enhancing Na-K-ATPase inhibition by cardiac glycosides
Allopurinol – ACE-inhibitor	40 (10.2)	Unknown mechanism leading to hypersensitivity syndrome
Amiodarone – oral anticogualants (phenprocoumon, acenocoumarol)	33 (8.4)	Increased bleeding risk due to decreased metabolism of oral anticoagulants
Amiodarone – betablocker	31 (7.9)	Additive cardiac effects (AV node refractory period prolonged and sinus node automaticity decreased by amiodarone), potentially leading to bradycardia, hypotension or cardiac arrest
Aspirin – oral anticoagulant (phenprocoumon, acenocoumarol)	27 (6.9)	Combination of thrombocyte aggregation inhibition and anticoagulant is associated with increased risk of bleeding
Betablocker – antidiabetic agents	22 (5.6)	Blockade of β_2-receptors impairs glycogenolysis and peripheral manifestations of hypoglycaemia (described for insulin or sulfonylureas, but not for thiazolidindiones, acar-

Interaction	n (%)	Mechanism and/or potential risk
		bose or metformin)
Digoxin – betablocker	21 (5.3)	Additive prolongation of AV-conduction time. Digoxin toxicity due to competition for intestinal P-gp (described for talinolol)
Diltiazem / verapamil – betablocker	18 (4.6)	Additive negative inotropic effects and impaired AV conduction possibly leading to hypotension, bradycardia and conduction blocks
Gingko – aspirin / oral anticoagulants (phenprocoumon, acenocoumarol)	16 (4.1)	Increased risk of bleeding due to inhibition of thrombocyte aggregation by gingko
NSAID – aspirin	13 (3.3)	Increased risk of gastrointestinal bleeding in patients with NSAID and low dose aspirin
NSAID – oral anticoagulants (phenprocoumon, acenocoumarol)	11 (2.8)	Increased risk of gastrointestinal bleeding due to gastric erosions, inhibition of platelet aggregation and displacement of anticoagulants from plasma albumin by NSAID
Tramadol – CNS-drugs tricyclic anti-depressants, selective serotonine reuptake inhibitors (SSRI), neurolep-tics, monoamine oxidase inhibitors (MAO)	10 (2.5)	Decreased seizure threshold and enhanced risk for seizures in combination with CNS drugs associated with seizures Increased concentration of serotonin in the nervous system and periphery potentially leading to serotonin syndrome Hypertensive crisis in combination with MAO-inhibitors

Interaction	n (%)	Mechanism and/or potential risk
CYP inducers* (phenobarbital, primidone, phenytoin, carbamazepine, hypericum, rifampicin) – critical CYP substrates* (phenprocoumon, acenocoumarol, clonazepam, clozapin, antiepileptics)	9 (2.3)	Clearance of CYP substrates increased
CYP inhibitors* (amiodarone, fluoxetine, fluvoxamine) – critical CYP substrate* (thioridazine, cisaprid, verapamil, alprazolam, amitriptylin)	7 (1.8)	Clearance of CYP substrates decreased
Potassium – ACE-inhibitors	6 (1.5)	Increased potassium retention and risk for hyperkalemia secondary to lowered aldosterone levels caused by ACE-inhibitor
Potassium – potassium sparing diuretics	5 (1.3)	Increased potassium retention and risk for hyperkalemia
Methrotrexate - NSAID	5 (1.3)	Increased MTX toxicity due to decreased renal methrotrexate clearance due to NSAID

Interaction	n (%)	Mechanism and/or potential risk
		induced impairment of renal perfusion and competition of tubular secretion
other	26 (6.6)	NA

* = the drugs listed (CYP inducers, CYP substrates, CYP inhibitors) contain the drugs which were prescribed during the current study. The list does therefore not necessarily contain the typical drugs interacting with CYPs.

NA = not applicable

6 Dose adaptation of antineoplastic drugs in patients with liver disease

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6.1 Summary

Dose adaptation for liver disease is important in patients treated with antineoplastic drugs due to the high prevalence of impaired liver function in this population and the dose-dependent, frequently serious adverse effects of these drugs. We classified the antineoplastic drugs marketed in Switzerland by the end of the year 2003 according to their bioavailability/hepatic extraction in order to predict their kinetic behavior in patients with decreased liver function. This prediction was compared with kinetic studies carried out with these drugs in patients with liver disease. The studies were identified by a structured, computer-based literature search.

Of the 69 drugs identified, 52 had a predominant extrarenal (in most cases hepatic) metabolism and/or excretion. For 48 drugs, hepatic extraction could be calculated and/or bioavailability was available, allowing classification according to hepatic extraction. For 17 drugs, kinetic studies have been reported in patients with impaired liver function, with the findings generally resulting in quantitative recommendations for adaptation of the dosage. In particular, recommendations are precise for 13 drugs excreted by the bile (e.g. doxorubicin and derivatives, and vinca alkaloids). Validation studies comparing such recommendations with kinetics and/or dynamics of antineoplastic drugs in patients with decreased liver function have not been published.

We conclude that there are currently not enough data for safe use of cyctostatics in patients with liver disease. Pharmaceutical companies should be urged to provide kinetic data (especially hepatic extraction) used for classification of such drugs and to conduct kinetic studies for drugs with primarily hepatic metabolism in patients with impaired liver function allowing to give quantitative advise for dose adaptation.

6.2 **Introduction**

Dose adaptation for patients with liver disease is more difficult than for patients with impaired renal function. The main reason for this statement is the fact that, unlike the creatinine clearance for the kidney, for the liver there is no *in vivo* surrogate to predict drug clearance. Due to the lack of such *in vivo* markers, predictions concerning dose adaptation in patients with liver disease can only be made based on the kinetic properties of the drugs to be administered and on kinetic studies of such drugs in patients with liver disease.

Several reviews have covered this subject during the last years (1-5). In these reviews, drugs are listed according to pharmacokinetic variables which are derived from the hepatic clearance of drugs. The hepatic clearance (Cl_{hep}) of a drug is given by:

$$Cl_{hep} = \frac{(f_u \times Cl_i) \times Q}{(f_u \times Cl_i) + Q} \quad (1)$$

where f_u is the unbound fraction and Cl_i the intrinsic clearance of a drug, respectively, and Q the blood flow across the liver. Cl_i represents the maximal capacity of the liver to metabolize a given drug, not taking into account limitations by liver perfusion (6). Cl_i can therefore reach values which are larger than Q, which is important for understanding the special situations discussed below.

Equation (1) can be simplified for the two extremes (f_u x Cl_i) >> Q or Q >> (f_u x Cl_i). For the first case, (f_u x Cl_i) >> Q, the denominator in equation (1) simplifies to (f_u x Cl_i), and Cl_{hep} equals:

$$Cl_{hep} = Q \quad (2)$$

For such drugs, the liver has a very large metabolic capacity, and the blood flow across the liver becomes rate-limiting for hepatic clearance. These drugs are therefore called “flow-limited” or “high capacity” and are usually cleared by the liver to a substantial degree already during the first hepatic passage. Therefore, they have a high hepatic extraction or a low bioavailability. Since portal blood is impaired in patients with liver cirrhosis (7, 8), hepatic clearance of such drugs is decreased, necessitating a reduction of the maintenance dose in this group of patients. A second potential problem of such drugs is an increase in bioavailability when they are administered orally. Since these drugs have a low bioavailability by definition, an increase in bioavailability could lead to toxic blood levels. This can be expected to happen in patients with porto-systemic shunts, which result from portal hypertension due to liver cirrhosis or fibrosis or, of importance in patients with cancer, due to multiple metastases (9, 10). Therefore, when such drugs are administered orally, the initial and the maintenance doses have to be reduced according to the expected increase in bioavailability and to the decrease in hepatic blood flow. For intravenous administration, only the maintenance dose has to be reduced according to the impairment in hepatic blood flow. A list of such drugs is given in a previous publication (1).

For the second type of drugs, $Q >> (f_u \times Cl_i)$, the metabolic capacity of the liver is much lower than blood flow across the liver. Equation (1) therefore simplifies to:

$$Cl_{hep} = (f_u \times Cl_i) \quad (3)$$

These drugs are therefore called “low extraction” or “capacity-limited”. They have not a high extraction during the first passage across the liver and have therefore a high bioavailability, if bioavailability is not limited by other processes than first pass hepatic metabolism and/or biliary excretion. Since Cl_i decreases for most drugs in patients

with liver cirrhosis due to a decrease in the activity of cytochrome P450 isozymes (CYP) (11, 12) and/or glucuronyl transferases (13-15), the maintenance dose of such drugs has generally to be decreased. For drugs with a high binding to albumin (>90%), the situation may be more complex. The free fraction (f_u) and the free concentration of such drugs can increase in patients with a low serum albumin concentration, e.g. patients liver cirrhosis or malnourished patients such as patients with cancer. An increase in the free concentration and/or f_u of such drugs may be associated with increased toxicity, and, as shown in equation 3, also with an increased hepatic clearance (16, 17). The actual hepatic clearance of such drugs is therefore difficult to predict in patients with chronic liver disease.

In between of these two extremes, there are drugs with an “intermediate extraction”, showing characteristics of both groups. The dosage advice for such drugs in patients with liver cirrhosis is to start with a low dose and to up-titrate carefully in order to find the correct maintenance dose.

Regarding dose adaptation in patients with cancer, it has to be recognized, however, that the dosing guidelines discussed above focus on patients with liver cirrhosis or fibrosis, but not on patients with increased transaminases and/or cholestasis which are found frequently among patients treated with antineoplastic drugs. Since the majority of antineoplastic drugs is metabolized by the liver (see Table 6.3) and is associated with severe dose-dependent toxicity, the question whether the dose has to be adapted in a patient with increased transaminases and/or cholestasis appears to be an important one. The most prevalent liver disease in this group of patients is the presence of liver metastases, possibly resulting in cholestasis and/or portal hypertension (10, 18, 19). Since many antineoplastic drugs are potentially hepatotoxic themselves (see Table 6.3), drug-induced liver disease may also be common in patients undergoing repetitive cycles of chemotherapy. On the other hand, with the

exception of hepatocellular carcinoma, liver cirrhosis is probably not more prevalent in patients with cancer as compared to an age-matched population without cancer, but no exact data are available.

The aims of the current study were therefore 1) to categorize the antineoplastic drugs used according to pharmacokinetic criteria as discussed above 2) to compare this categorization with the dose recommendations in patients with liver disease given in the standard literature 3) to create a table with the current recommendations for dose adaptation 4) to localize gaps in the current recommendations.

6.3 **Methods**

We screened Medline and Embase for studies dealing with dose adaptation and hepatic adverse effects for all antineoplastic drugs which were on the market in Switzerland by the end of the year 2003. The data bases were screened using the following MESH terms: antineoplastic agents, drug toxicity, pharmacokinetics, liver diseases. The references detected by the search in the databases were screened for other references dealing with the subjects. In addition to databases, the standard literature was screened for dose adaptation recommendations and adverse effects on the liver, including the “Swiss Compendium of Drugs” (20) (similar to the “Physicians’ Desk Reference” (21)), “Therapeutic drugs” of Dollery et al. (22) and “Hepatotoxicity” of H. J. Zimmerman (23).

The antineoplastic drugs were categorized according to pharmacokinetic principles as outlined in the introduction and based on the reviews of Huet and Villeneuve (16) and Krähenbühl and Reichen (1). The categorization system used is based on the hepatic extraction or bioavailability, and protein binding of the specific drugs (see

Table **6.1**). Values for bioavailability and protein binding could be found either in the original articles (cited in Table 6.3) or in other sources (20-22, 24). For hepatic extraction, data in the literature are rare, making it necessary to estimate extraction from bioavailability (see
Table **6.1**) or by the following equation:

$$E = \frac{Q_0 \times Cl_{sys}}{Q} \quad (4)$$

where Q_0 is the extrarenal dose fraction (the fraction of a drug which is not excreted unchanged by the kidney), Cl_{sys} the systemic clearance and Q the blood flow across the liver. Most of the values for E in Table 6.3 are estimated using this equation. The values for Q_0 and Cl_{sys} were obtained from the literature (20-22, 25), and Q was assumed to be 1.5 L/min.

Dosage recommendations originate either from the original articles or from the manufacturer as published in the PDR (21) and/or the Swiss Compendium of Drugs (20).

Drug-induced liver disease was classified according to Benichou (26) and the severity of liver disease according to Donelli et al. (27) (see
Table **6.2**).

6.4 **Results**

Informations about all antineoplastic drugs on the market in Switzerland by the end of the year 2003 were collected. Using our search strategy, we identified a total of 112 articles which were found to be relevant for our study. In 64 of them, kinetic

data were reported and 48 contained hepatic adverse effects of antineoplastic agents.

Table 6.1 Categorization of antineoplastic drugs screened according to pharmacokinetic variables.

High hepatic extraction (category 1)

- Hepatic extraction > 60% → oral bioavailability < 40% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete)

Intermediate hepatic extraction (category 2)

- Hepatic extraction 30 - 60% → oral bioavailability 40 - 70% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete)

Low hepatic extraction (category 3)

- Hepatic extraction < 30% → oral bioavailability > 70% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete)
- In this category, protein binding may be relevant: for drugs with high binding to albumin (>90%), hepatic clearance may increase

Hepatic extraction is not known (category 4)

The 69 antineoplastic drugs on the Swiss market by the end of the year 2004 are listed in Table 6.3. From these 69 drugs, 10 fell into category 1, 11 into category 2 and 28 in category 3. Twenty drugs could not be classified (category 4), demonstrating a lack of data about hepatic extraction and/or bioavailability.

Fifty-two out of the 69 drugs had a Q_0 value (extrarenal dose fraction, compare Table 6.3) >0.4, indicating that most antineoplastic drugs are heavily metabolized and/or excreted by the bile. Seven drugs had a Q_0 value ≤0.4 and for 10 drugs, the

Q_0 value could not be identified. For 25 drugs, metabolism by the cytochrome P450 system (CYP) is important, and 18 drugs are excreted to a significant extent (> 5%)

Table 6.2 Classification of liver disease and severity of liver dysfunction

Parameter	*Pathophysiological condition and clinical significance*	*Severity*[1]
Alanine amino-transferase (ALT)	Breakdown (necrosis or apoptosis) of hepatocytes. Hepatocellular injury[2] if > 2 x ULN[3]	2-5 x ULN: moderate injury > 5 x ULN: severe injury
Alkaline phosphatase	Cholestasis[4] if > 2 x ULN	2-5 x ULN: moderate cholestasis > 5 x ULN: severe cholestasis
Serum bilirubin concentration	Cholestasis (exclude prehepatic causes)	25 – 50 µmol/L: moderate > 50 µmol/L: severe
Serum albumin concentration	Impaired hepatic protein synthesis	30 – 35 g/L: moderate < 30 g/L: severe
Prothrombin activity	Impaired hepatic protein synthesis	40 – 70%: moderate < 40%: severe

[1]The severity is classified according to Donelli et al. (27) with some modifications
[2]Hepatocellular injury is defined according to Benichou (26)
[3]ULN: upper limit of normal
[4]Cholestasis is defined according to Benichou (26)

by the bile (vinca alkaloids, doxorubicin and derivatives, amsacrine, biculatamide, dactinomycin, estramustine, exemestan, irinotecan, imitanib, mitoxantrone, paclitaxel and topotecan). For 13 of these drugs, dose adaptation recommendations are given according to the serum bilirubin concentration and/or activity of alkaline phosphatase. For biculatamide, estramustine, exemestan and paclitaxel, there is a general statement that the dose should be adapted or stopped in patients with decreased liver function. For topotecan, no dose reduction is recommended in patients with liver disease. For 16 of the 64 drugs studied, recommendations for dose adaptation are based studies in patients with hepatic dysfunction.

For 42 of the drugs, significant adverse effects on the liver have been reported. This is important to realize, rendering drug-induced liver disease an important differential diagnosis in patients with malignant tumors and impaired hepatic function.

6.5 **Discussion**

Our study demonstrates that for antineoplastic drugs, there is a discrepancy between the general recommendations of how drugs should be dosed in patients with liver disease and the available kinetic data for these drugs. The most important gaps are a lack of information regarding hepatic extraction and of kinetic studies for critical drugs in patients with impaired liver function.

As explained in the introduction, data about hepatic extraction are important for classification of a specific drug regarding hepatic elimination in patients with chronic liver disease, in particular liver cirrhosis. It is evident that such data are difficult to obtain, especially the determination of hepatic extraction of a drug, necessitating an invasive procedure which is usually not performed before a drug is marketed. Bioavailability is only a surrogate for hepatic extraction, since a low bioavailability can be explained by both a high hepatic extraction and/or a low intestinal absorption. For drugs with a low bioavailability (<40%), hepatic extraction should therefore be known, since, as explained above, this parameter is critical for rational drug dosing in patients with impaired liver function. In order to circumvent this invasive procedure in humans, a possibility would be to get such data using perfused livers from animals, e.g. pigs. To the best of our knowledge, no data have been published so far comparing hepatic extraction data for critical drugs between animals (such as pigs) and humans. Another possibility is to estimate hepatic extraction using the extrarenal fraction (Q_0), systemic drug clearance and hepatic blood flow (equation 4 and Table 6.3). As

shown in Table 6.3, the values obtained with this technique are in a satisfactory agreement with the bioavailability for most drugs, with some exceptions.

Regarding antineoplastic agents, many of these drugs are used intravenously only, partially explaining the lack of data considering oral bioavailability. Nonetheless, taking into account the high prevalence of patients with impaired hepatic function among those treated with this type of drugs (28), such data should be available for all substances on the market.

Kinetic studies have been conducted in particular in two conditions, namely patients with cholestasis (as suggested by an increased serum bilirubin concentration) and in patients with hepatic metastases. Considering cholestasis, studies exist for most antineoplastic drugs with significant biliary elimination (see Table 6.3). These studies resulted in quantitative recommendations for dose adaptation in jaundiced patients according to their serum bilirubin concentration. To the best of our knowledge, however, these recommendations have not been validated by kinetic and dynamic studies (including the incidence and severity of dose-dependent adverse effects) in a large series of patients with cholestasis. It remains also unclear, whether the serum bilirubin concentration is the best parameter for dose adaptation in cholestatic patients or whether, for instance, the serum bile acid concentration and/or activity of alkaline phosphatase would be more suitable.

Considering hepatic metastases, only few studies exist and they have generally not resulted in clear dose adaptation recommendations. Since hepatic metastases can be associated with portal hypertension and possibly porto-caval shunts (10, 18), the situation resembles patients with liver cirrhosis. Oral administration of drugs with a high hepatic extraction should therefore be performed cautiously and kinetic data for such drugs should be available in this type of patients when such drugs are approved.

As shown in Table 6.3, treatment with antineoplastic agents can lead itself to liver disease or, for drugs metabolized by the liver and/or excreted by the bile, to increased systemic toxicity in patients with liver disease. There is a third type of toxicity which may be relevant. In several patients with chronic hepatitis B, the immunosuppressive effect of antineoplastic agents was associated with a flare up of their hepatitis due to increased replication of the hepatitis B virus (29-35). Since this condition can be treated but is potentially fatal (35), the immune status regarding hepatitis B should be known before treatment with antineoplastic drugs.

In conclusion, there are currently considerable gaps in the data needed for safe administration of antineoplastic drugs in patients with decreased hepatic function. Drug authorities should urge pharmaceutical companies to provide such data before the drugs are approved. Considering kinetics, in particular oral bioavailability and hepatic extraction should be investigated. For drugs with a predominant hepatic metabolism and/or excretion, the kinetics in patients with liver metastases and/or cholestasis should have been studied before marketing authorisation is provided.

6.6 **References**

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Table 6.3 Kinetic data, hepatic adverse effects and dose recommendations in patients with liver disease of the antineoplastic drugs on the market in Switzerland by the end of the year 2004

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Aldesleukin	4	Not known	0.18	1	-	-			*Frequent*: hepatocellular injury, cholestasis, or hyperbilirubinemia (20).	*Recommendation*: Monitor patients for adverse effects, dose may need to be adjusted patients with liver disease (20, 22). Contraindicated in patients with elevated serum bilirubin (20).
Alemtuzumab	4	Not known	0.15	8	-	-				No dose adjustment recommendations available for patients with liver disease
Aminoglutethimide	3	0.50 N-acetylation, N-hydroxylation (CYP) (22)	1.00	12	25	95	4.5	0.03	*Sporadic*: cholestasis, hyperbilirubinemia (23).	No dose adjustment recommendations available for patients with liver disease.
Amsacrine	4	1 Glutathion conjugation, Biliary excretion (20)	1.40	5	97	-			*Sporadic*: cholestasis, hyperbilirubinemia (23).	*Recommendation*: 50% dose reduction if serum bilirubin > 34 µmol/l (36). Dose reduction (70% of normal dose) in patients with severe liver disease (20, 22).
Anastrozole	4	0.95 N-dealkylation, hydroxylation (CYP), glucuronidation (22)	-	50	45	80			*Sporadic*: cholestasis.	No dose adjustment recommendations available for patients with liver disease.

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Bicalutamide	2	≈1 Oxidation (CYP), glucuronidation. Biliary elimination 40% (20)	-	139	98	-	30	0.34	One case of fulminant liver failure (37)	*Recommendation*: Stop treatment if transaminases > 3 x ULN or in patients with hyperbilirubinemia (20)
Bleomycin	3	0.70 Hydrolysis (22)	0.30	3	-	-	5.2	0.04	*Case reports*: steatosis (23, 38)	*Recommendation*: No dose adjustment in patients with liver disease (22).
Buserelin	3	Not known	-	1.6	-	3				No dose adjustment recommendations available for patients with liver disease.
Busulfan	3	1 Oxidation, sulfation	1.0	2.5	30	70	18.9	0.21	*Sporadic*: hepatocellular injury, cholestasis (39, 40). *Rare*: venoocclusive disease (23).	No dose adjustment recommendations available for patients with liver disease.
Capecitabine	1	0.97 Carboxylesterase, Cytidine desaminase, phosphorylation	-	1.3	54	42	251	>1	*Frequent*: hyperbilirubinemia *Sporadic*: cholestasis *Rare*: Hepatocellular injury (41)	*Studies*: Increased bioavailability by 20% in patients with moderate liver disease due to metastases (42). *Recommendation*: No dose adjustment in patients with moderate liver disease (42)
Carboplatin	3	0.25	0.24	3	20	-	4.5	0.01	*Rare*: hepatocellular injury, cholestasis (23)	*Recommendation*: No dose adjustment in patients with liver disease (20)

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Cetuximab	4	Binding to EGFR in hepatocytes and skin (43)	0.05	120	-	-	0.03		*Frequent:* mild elevations of transaminases and alkaline phosphatase (44)	No dose adjustment recommendations available for patients with liver disease
Chlorambucil	3	1 β-oxidation (22)	1.0	1.5	99	87	11	0.12	*Rare*: hepatocellular injury (23) *Case report*: liver failure (45).	*Recommendation*: Monitor patients for adverse effects, dose may need to be adjusted patients with liver disease (20)
Chlormethine (Mechlorthamine)	4	1 ethyleneimmonium ion (22)	-	-	-	-				No dose adjustment recommendations available for patients with liver disease.
Cisplatin	3	0.65 non-enzymatic degradation (46)	0.3-1	0.5	90	-	0.3	0.01	*Rare*: hepatocellular injury (23)	*Recommendation*: No dose adjustment in patients with liver disease (20, 22)
Cladribine	2	Not known	0.4	6	25	55	60			No dose adjustment recommendations available for patients with liver disease.
Cyclophosphamide	3	0.9 Hydroxylation by CYPs 2B6, 2C19, 2C9, 3A4 (47)	0.80	7	15	75	4.4	0.04	*Rare*: Hepatocellular injury, cholestasis, hyperbilirubinemia (23). *Case reports*: venoocclusive disease (48-50)	*Studies*: Decreased clearance of active drug and decreased production of active metabolites in patients with liver metastases (51), severe liver disease in the presence of Hodgkin's disease (52) or liver cirrhosis (36). *Recommendation*: Monitor patients with liver disease for adverse effects. Dose reduction by 25% in patients with serum bilirubin > 50 µmol/L (20)

Drug	***Cat[1]***	***Kinetic parameters***							***Hepatic adverse effects[9]***	***Studies performed and dosage recommendations***
		Q_0[2], metabolism	*V_d[3] (L/kg)*	*$t½$[4] (h)*	*PB[5] (%)*	*F[6] (%)*	*Cl_{sys}[7] (L/h)*	*E[8]*		
Cyproterone	3	1 hydrolysis, hydroxylation, conjugation (22)	19	38	95	88			*Sporadic*: hepatocellular injury, cholestasis, hyperbilirubinemia *Rare*: liver failure (53-57)	*Recommendation*: Monitor liver function. Stop treatment in patients with liver injury (20, 22)
Cytarabine	2	0.90 cytidine deaminase (22)	3.0	2.3	13	<20	55	0.55	*Sporadic to frequent*: dose-dependent hepatocellular injury, cholestasis, hyperbilirubinemia (23)	*Recommendation*: 50% dose reduction if serum bilirubin > 34 µmol/L, gradual increase while monitoring systemic toxicity (36)
Dacarbazine	3	0.30	1.5	0.7	5	-	12	0.04	*Case reports*: venoocclusive disease (58, 59), hepatic vein thrombosis (59)	No dose adjustment recommendations available for patients with liver disease.
Dactinomycin	4	0.70 Biliary excretion 50%-90% (22)	12	36	-	-			*Rare*: hepatocellular injury, steatosis, venoocclusive disease (23)	*Recommendation*: 50% dose reduction in patients with hyperbilirubinemia. Increase gradually while monitoring systemic toxicity (36).
Daunorubicin	4	0.90 Reduction, biliary excretion 40% (22)	40	27	-	-			*Rare*: Venoocclusive disease when combined with radiation (23)	*Recommendation*: If serum bilirubin 20 - 50 µmol/L 25% dose reduction, if serum bilirubin > 50 µmol/L 50% dose reduction (20, 22)
Docetaxel	2	1 Oxidation by	1.6	0.6 (β)	95	-	39	0.43		*Studies*: Population kinetic studies show a 25% reduction of clearance in patients with

Drug	***Cat[1]***	***Kinetic parameters***							***Hepatic adverse effects[9]***	***Studies performed and dosage recommendations***
		Q_0[2], metabolism	*V_d[3] (L/kg)*	*$t½$[4] (h)*	*PB[5] (%)*	*F[6] (%)*	*Cl_{sys}[7] (L/h)*	*E[8]*		
		CYP3A4 (22). Biliary excretion 75%, 10% as intact drug (20, 22)		11 (γ)						transaminases > 1.5 x ULN and alkaline phosphatase > 2.5. In patients with moderate liver injury/cholestasis clearance was reduced by 27% (20, 22). *Recommendation*: If transaminases > 1.5 x ULN or alkaline phosphatase > 2.5 x ULN 25% dose reduction. If serum bilirubin is increased or transaminases > 3.5 x ULN or alkaline phosphatase > 6 x ULN docetaxel should not be adminstered (20, 22)
Doxorubicin	1	0.95 Reduction to doxorubicinol, sulfation, glucuronidation, biliar excretion 50% (22, 27)	17	26	80	5	69	0.73	*Rare*: in combination with cyclophosphamide, etoposide and cisplatin cholestasis and venoocclusive disease (23)	*Studies*: In 5 patients with disseminated sarcoma, bone marrow toxicity and doxorubicin serum levels correlated with hyperbilirubinemia (60). In patients with hepatocellular carcinoma, bone marrow toxicity and serum doxorubicin/doxorubicinol levels correlated with hyperbilirubinemia (61, 62). In 17 patients with liver metastases and moderate liver disease kinetics of doxorubicin was not changed but the half-life of doxorubicinol increased (63). In 4 patients with moderate liver disease the half-life of doxorubicin was doubled (64). In patients with liver metastases and mild increase in transaminases or alkaline phosphatase, kinetics and toxicity of doxorubicin was not changed (61, 62, 65, 66). *Recommendation*: If serum bilirubin 20 - 50 µmol/l: 50% dose reduction. If serum bilirubin > 50 µmol/l: 75% dose reduction (20, 22, 36,

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
										67). Donelli et al. advise dose reduction only if serum bilirubin is > 50 µmol/L (27).
Epirubicin	1	0.90 Reduction Biliar excretion 40% (68)	20	39	85	-	89	0.89		*Studies*: In patients with liver metastases and increased serum bilirubin, the half-life of epirubicin/epirubicinol was increased (69-71). In patients with hepatocellular carcinoma, epirubicin kinetics correlates with liver function and serum bilirubin (72). In patients with liver metastases, epirubicin kinetics correlates better with transaminases than with serum bilirubin (73-75). *Recommendation*: If serum bilirubin 20 - 50 µmol/l: 50% dose reduction. If serum bilirubin > 50 µmol/l: 75% dose reduction (20, 22, 36)
Estramustine	2	0.90 Oxidation, partial biliary excretion (76)	0.04	1.3	99	44			*Sporadic.* Hepatocellular injury, cholestasis (20)	*Recommendation:* Monitor patients for adverse effects, dose may need to be adjusted patients with liver disease (20).
Etoposide	3	0.65 Esterases, glucuronidation. Biliary excretion <10%.	0.30	8.1	95	50	2.9	0.02	*Frequent.* Hepatocellular injury (23). *Case reports*: Reactivation of hepatitis B virus (30), liver failure (77)	*Studies*: In patients with mild to moderate liver disease, etoposide kinetics was not altered (78-80). In patients with severe liver disease elimination and AUC were highly variable and tended to be increased in the case or impaired hepatic protein synthesis or hyperbilirubinemia (78-81). *Recommendation*: Monitor patients with mild to moderate liver disease. If bilirubin 25 – 50 µmol/L or AST > 180 U/L 50% dose reduction (36). Contraindicated in patients with de-

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
										compensated liver disease (20, 22).
Exemestane	1	1 CYP3A, biliary excretion 40% (82)	19	24	90	42	609	>1	*Sporadic* hepatocellular injury, cholestasis (20)	*Recommendation*: Monitor patients for adverse effects, dose may need to be adjusted patients with liver disease (20).
Fludarabine	3	0.35	2.4	10-30	-	70	15.5	0.06		*Recommendation*: No dose adjustment recommended in patients with liver disease (20, 22).
Fluorouracil	1	0.95 Dihydropyrimidine dihydrogenase	0.3	0.25	94	28	67.2	0.71	*Sporadic*: hepatocellular injury when administered i.v. (23)	*Studies*: In patients with liver metastases, a weak correlation with cholestasis was present (83), but no dose adjustment was recommended. *Recommendation*: Start with 50% of normal dose in patients with liver cirrhosis. Increase gradually while monitoring systemic toxicity (27, 36).
Flutamide	4	1 Hydroxylation (84)	-	8	95	-			*Sporadic*: hepatocellular injury, hyperbilirubinemia (20). *Case reports*: liver failure (85-92).	*Recommendation*: Monitor liver function (20).
Formestane	1	Not known	-	120	93	25				No dose adjustment recommendations available for patients with liver disease
Fosfestrol	3	1	-	0.5	-	80				*Recommendation*: Monitor liver function (20, 22).
Gefitinib	2	CYP3A4, CYP2D6 (93)	20	27	90	50			*Frequent:* hepatocellular	No dose adjustment recommendations available for patients with liver disease

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
									injury, cholestasis (21)	*Recommendation*: Reduce dosage by 50% or avoid in patients with liver disease (93)
Gemcitabine	1	0.9 Deamination, phosphorylation (20)	25	1 – 12	10	-	90	0.9	*Frequent*: hepatocellular injury (self-limiting) (20, 22)	No dose adjustment recommendations available for patients with liver disease
Goserelin	3	0.4	-	4.0	25	-	8.2	0.04		*Recommendation*: Dose adjustment not recommended in patients with liver disease (20).
Hydroxycarbamide	3	0.4	0.5	5.0	80	80			*Case report*: fulminant liver failure (94)	No dose adjustment recommendations available for patients with liver disease
Idarubicin	1	≈1 Oxidation, biliary excretion 8 – 17% (95, 96)	-	15.2	96	28	120	≈1	*Frequent*: hepatocellular injury, hyperbilirubinemia (20)	*Studies*: In patients with metastases, kinetics of idarubicin is not changed (97, 98). *Recommendation*: If serum bilirubin 20 - 34 µmol/l: 50% dose reduction. If serum bilirubin > 34 µmol/l: contraindicated (20)
Ifosfamide	3	0.5 CYP3A (activation) (47)	0.5	6.5	-	100	3.6	0.02	*Sporadic*: hepatocellular injury, hyperbilirubinemia (23)	*Recommendation*: Monitor patients with preexisting liver disease (20). Contraindicated in patients with decompensated liver disease (22).
Imatinib	3	0.95 N-demethylation (CYP 3A), 20% biliary elimination (20)	4.9	18	95	98			*Sporadic*: hyperbilirubinemia, hepatocellular injury (20).	*Recommendation:* Stop treatment if serum bilirubin > 3 x ULN or transaminases > 5 x ULN (20)

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Irinotecan	3	0.75 Esterases, glucuronidation, CYP3A4 Biliary excretion 25% (20, 99)	75	10	65	-	26	0.21		*Study:* In patients with gastrointestinal cancer and cholestasis the AUC for SN-38 (active metabolite) was 50% increased (serum bilirubin 1.1-1.5 x ULN) or 100% increased (>1.5 ULN) (100). *Recommendation*: If serum bilirubin > 1.5 x ULN/transaminases > 5 x ULN dose reduction according to adverse events. Contraindicated if serum bilirubin > 5 x ULN (20). According to (100) 350 mg/^{2} in patients with serum bilirubin 1.1-1.5 ULN and 200 mg/m^2 when serum bilirubin >1.5 ULN.
Letrozol	3	0.95 CYP3A4, 2D6 (20)	1.9	45	60	100	2.4	0.03		No dose adjustment recommendations for patients with liver disease available
Leuprorelin	3	Not known	0.5	3	46	-	8.3	0.05		No dose adjustment recommendations available for patients with liver disease
Lomustine	3	1 Cis- and trans-4-hxdroxylation (101)	1.70	10	-	≈100			*Sporadic*: hepatocellular injury (20)	No dose adjustment recommendations available for patients with liver disease
Medroxyprogesteron	1	1 CYP3A4	0.6	36	94	<10	76	0.84	*Rare*: cholestasis, peliosis (20)	No dose adjustment recommendations available for patients with liver disease.
Megestrol	4	1 Glucuronidation (22)	-	18	-	-			*Rare*: hepatocellular injury, hyperbilirubinemia (20)	No dose adjustment recommendations available for patients with liver disease
Melpha-	2	0.9	0.6	1.5	80	70	31	0.31		*Recommendation*: No adjustment recom-

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Ian		Hydroxylation (22)								mended in patients with liver disease (22).
Mercaptopurine	2	0.9 Xanthine oxidase (thiouric acid), thiopurine methyltransferase (22)	0.6	0.9	19	12	46	0.46	*Frequent*: dose-dependent hepatocellular injury, cholestasis, hyperbilirubinemia in 6 – 40% (23). *Case reports*: liver failure (102-105), venoocclusive disease (23). Risk may be higher in patients with reduced activity of thiopurine methyltransferase	*Recommendation*: Monitor liver function. Contraindicated in patients with decompensated liver disease (20)

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
Methotrexate	3	0.05	0.70	7.2	50	70	8.8	0.01	*Sporadic*: Fatty liver, fibrosis, cirrhosis during long-term treatment with immunosuppressive doses (106-112). *Case reports*: hepatocellular injury, acute liver failure during use as an antineoplastic agent (30, 113-116)	*Studies*: No correlation between liver function and methotrexate serum levels (117). *Recommendation*: Close monitoring in patients with decompensated liver disease. Reduce dose in the presence of ascites and/or decreased renal function (20, 22)
Mitomycine	4	0.9	0.3	0.5	-	-			*Rare*: steatosis *Case reports*: venoocclusive disease (23)	No dose adjustment recommendations available for patients with liver disease
Mitoxantrone	2	0.95 mono- or dicarboxylation (inactive), biliary excretion 25% (20)	10 - 15	57	76	-	45	0.48	*Frequent:* hepatocellular injury (23)	*Studies*: Clearance reduced by 50% in patients with moderate liver disease (118). Patients with serum bilirubin < 60 µmol/L tolerate 14 mg/m^2, patients with serum bilirubin > 60 µmol/L and bad performance status have higher mortality with this dosage (119). In patients with liver metastases, half-life of mitoxantrone correlated with serum bilirubin

Drug	***Cat[1]***	***Kinetic parameters***							***Hepatic adverse effects[9]***	***Studies performed and dosage recommendations***
		Q_0[2], metabolism	*V_d[3] (L/kg)*	*$t_{½}$[4] (h)*	*PB[5] (%)*	*F[6] (%)*	*Cl_{sys}[7] (L/h)*	*E[8]*		
										and cholestasis (120). *Recommendation*: Dose adjustment (8 mg/m^2) or contraindicated (bad performance status) in patients with serum bilirubin > 60 µmol/L (119)
Nimustine	4	1	-	0.6	34	-				No dose adjustment recommendations available for patients with liver disease
Oxaliplatin	4	≈0.5, Reduction (non-enzymatic), biliary excretion 5% (121)	-	260	75	-				*Recommendation*: No dose adjustment in patients with liver disease (20).
Paclitaxel	3	0.95 CYP 3A, 2C8. Biliary excretion > 5% (122)	2.0	3	95		23	0.24	*Sporadic*: hepatocellular injury, cholestasis *Rare*: hyperbilirubinemia, liver failure (20)	*Studies*: Liver disease/liver cirrhosis appears to be a risk factor liver for systemic toxicity (123, 124). Increased risk for myelosuppression in patients with increased transaminases and/or serum bilirubin > 25 µmol/L (125). In patients with increased transaminases (3-10 x ULN) and hyperbilirubinemia (1.3 – 2 x ULN) clearance was decreased by ≈ 40% (126) *Recommendation*: Monitor patients with liver disease well for adverse effects. Do not administer in patients with decompensated liver disease (20, 126)
Raltitrexed	4	0.5 Polyglutamate derivative (127)	7.0	2	93	-			*Frequent*: hepatocellular injury *Sporadic*: cho-	*Recommendation*. No dose adjustment in patients with mild to moderate liver disease. Contraindicated in patients with decompen-

Drug	***Cat[1]***	***Kinetic parameters***							***Hepatic adverse effects[9]***	***Studies performed and dosage recommendations***
		Q_0[2], metabolism	*V_d[3] (L/kg)*	*$t_{½}$[4] (h)*	*PB[5] (%)*	*F[6] (%)*	*Cl_{sys}[7] (L/h)*	*E[8]*		
									lestasis, hyperbilirubinemia *Case report*: liver failure (128)	sated liver disease (20).
Rituximab	4	Not known	-	68	-	-				No dose adjustment recommendations available for patients with liver disease
Tamoxifen	4	1 Hydroxylation, N-dealkylation (CYP 2C9, 2D6, 3A4, 2C8) (22)	60	4 – 11 days	99	-			*Sporadic*: hepatocellular injury, cholestasis, fatty liver (23). *Rare*: liver failure (129-131).	*Studies*: In a patient with liver metastases liver function deteriorated one year after start of tamoxifen (132). In a randomized trial in patients with hepatocellular carcinoma, liver function was not affected (133). *Recommendation*: Monitor liver function in patients with preexisting liver disease.
Temozolomide	3	0.9 non-enzymatic	-	1.8	15	≈100				No dose adjustment recommendations available for patients with liver disease
Thiotepa	3	0.5 CYP 2B1, 2C11 (134)	-	2.4	99	-	19	0.11	*Case report*: liver failure (135)	No dose adjustment recommendations available for patients with liver disease
Tioguanine	4	>0.9, Thiopurine methyltransferase	-	5 - 9	-	-			*Rare*: hepatocellular injury, cholestasis (23). *Case reports*: Veno-occlusive disease (136, 137)	*Recommendation*: Monitor liver function after administration of high doses. Contraindicated in patients with decompensated liver disease (20).
Topotecan	2	0.6 Esterases Biliar excretion 20% (138)	1.9	2.4	35	32	49.5	0.33		*Studies*: 14 patients with increased transaminases and/or hyperbilirubinemia (some with cirrhosis) were treated with 1.5 mg/m^2. Topotecan clearance correlated with ICG

Drug	***Cat[1]***	***Kinetic parameters***							***Hepatic adverse effects[9]***	***Studies performed and dosage recommendations***
		Q_0[2], metabolism	*V_d[3] (L/kg)*	*$t½$[4] (h)*	*PB[5] (%)*	*F[6] (%)*	*Cl_{sys}[7] (L/h)*	*E[8]*		
										clearance but no more adverse effects were observed in patients with liver disease (139). On the other hand, two thirds of patients with hepatocellular carcinoma treated with topotecan developed grade IV neutropenia (140). *Recommendation*: No dose adjustment for patients with hepatic dysfunction but monitor patients well for systemic toxicity (139).
Toremifen	3	1, CYP3A4 (N-demethylation, hydroxylation). Enterohepatic circulation (141)	12-15	148	99	≈100	4.5	0.05		*Studies*: In 10 patients with liver cirrhosis or fibrosis the elimination half-life was increased by 75% and clearance decreased by 28% (141). *Recommendation*: Dose reduction in patients with liver cirrhosis by 50%, gradual increase while monitoring adverse effects (20).
Trastuzumab	4	Not known	0.04	140	-	-				No dose adjustment recommendations available for patients with liver disease
Tretinoin	4	CYP2C8, Isotretinoin, 4-oxo-retinoic acid (21)	-	1.25	95	-			*Frequent:* hepatocellular injury (93)	*Recommendation:* Need for dosage adjustments in patients with hepatic impairment has not been shown. A dose reduction to 25 mg/m^2 is recommended as a precautionary measure (21).
Triptorelin	3	0.52	0.5	3	-	-	5	0.03		*Studies:* As compared to 6 healthy young males, 6 patients with normal renal function and hepatic impairment (Child A or B) had decreased total clearance (57 versus 210 mL/min) and prolonged elimination half-life (7.6 versus 2.8 hours) after a single intravenous bolus of 0.5 mg triptorelin. Despite the-

Drug	***Cat***[1]	***Kinetic parameters***							***Hepatic adverse effects***[9]	***Studies performed and dosage recommendations***
		Q_0[2]*, metabolism*	*V_d*[3] *(L/kg)*	*$t½$*[4] *(h)*	*PB*[5] *(%)*	*F*[6] *(%)*	*Cl_{sys}*[7] *(L/h)*	*E*[8]		
										se differences after intravenous dosing, dose reduction of the sustained-release formulation used clinically is judged not necessary, because its release rate is much slower than its elimination rate (142). *Recommendation:* Dosage reduction of sustained-release triptorelin does not appear to be necessary in patients with liver disease (142).
Vinblastine	2	1 CYP3A4 biliary excretion >50% (22)	20	25	75	-	52	0.58		*Recommendation*: If serum bilirubin > 50 µmol/L → 50% dose reduction (20).
Vincristine	3	0.9 CYP3A4 biliary excretion 70% (22)	8.0	23	75	-	8.5	0.09		*Studies*: In the presence of cholestasis/hyperbilirubinemia β-half-life was prolonged (144). In patients with leukemia or lymphoma and cholestasis, AUC and toxicity were increased (145). *Recommendation*: If serum bilirubin > 50 µmol/L → 50% dose reduction (20). Some authors advise 50% dose reduction also if alkaline phosphatase is increased (36).
Vindesine	4	Not known CYP 3A, biliar excretion	8.8	24	-	-	17.5			*Recommendation*: Monitor patients for adverse effects, dose may need to be adjusted patients with hyperbilirubinemia (20).
Vinorelbine	1	0.85 CYP 3A, biliary excretion 50% (22, 146)	75	30	15	≈40				*Studies*: In 19 patients with liver metastases, clearance was reduced by 50% in patients with >75% of the liver replaced by tumor (147).

Drug	***Cat*[1]**	***Kinetic parameters***							***Hepatic adverse effects*[9]**	***Studies performed and dosage recommendations***
		Q_0[2], metabolism	*V_d[3] (L/kg)*	*$t½$[4] (h)*	*PB[5] (%)*	*F[6] (%)*	*Cl_{sys}[7] (L/h)*	*E[8]*		
										Recommendation: 50% dose reduction if more than 75% of liver replaced by tumor (147) or if serum bilirubin > 34 µmol/L (146).

[1]*Cat* = drug category. Drugs were categorized as follows: Category 1: high hepatic extraction (E) (E > 60%, bioavailability < 40%), category 2: intermediate hepatic extraction (E = 30-60%, bioavailability 40-70%), category 3: low hepatic extraction (E < 30%, bioavailability >70%), category 4: hepatic extraction not known
[2]Q_0: extrarenal dose fraction = fraction metabolized or excreted by bile (1 - Q_0: fraction excreted unchanged by the kidney)
[3]V_d = volume of distribution in L per kg. For calculation, body weight was assumed to be 70 kg.
[4] *$t½$:* dominant half-life
[5]*PB*: Fraction bound to proteins (protein binding in %)
[6]*F*: Bioavailability
[7]Cl_{sys}: systemic clearance (L/min)
[8]*E*: hepatic extraction, calculated as described in equation 4
[9]*Frequency of hepatic adverse effects:* frequent > 10% of patients treated, sporadic: 1-10%, rare: < 1%
Abbreviations: CYP = cytochrome P450, ULN = upper limit of normal
Characterization of liver disease and severity of liver dysfunction: compare Table 2

7 Discussion and Conclusions

The dissertation shows that drug safety in hospitals can be improved on different levels: Considering medication errors, we could show that the prevalence of drug-drug interactions is high in ambulatory patients, a finding which has been reported also in hospitalized patients on medical wards (1). In addition, considering dose adaptation in patients with liver disease, we could show that even for such important drugs as antineoplastic agents, much information is lacking.

So far, it is unclear, however, how strong such risk factors are, or in other words, how many patients affected by such risk factors will finally develop an adverse drug reaction. Some information has been published on the risk of patients with potential drug-drug interactions. In patients treated with the combination of an ACE-inhibitor or an angiotensin receptor blocker and low dose (25 mg/day) spironolactone, the incidence of severe hyperkalemia (>6 mmol/L) is in the range of 6% per year (2). It has also been shown that the risk to develop hypoglycemia in patients treated with a sulfonylurea is increased by a factor of 6 in the presence of concomitant treatment with co-trimoxazole (3). In the same study, the risk for severe digoxin toxicity was increased by a factor of approximately 20 in patients treated concomitantly with clarithromycin (3). The absolute risk was not given in these studies, but can be expected to be quite high (affecting more than 1% of the patients treated per year), since the incidence of hypoglycemia in patients treated with oral antidiabetics or of digoxin toxicity is in this range. In contrast, although concomitant treatment of patients ingesting atorvastatin or simvastatin with a CYP3A4-inhibitor increases the relative risk by a factor in the range of 10 (4), the absolute risk is still low (in the range of 1:1000 to 1:10’000 patient years), since the incidence of rhabdomyolysis in patients treated with statins is low. The examples show that that the frequency of adverse drug reactions due to drug-drug interactions depends not only on the type of interaction, but also on the adverse drug reaction itself. In comparison, the literature contains no data about the risk for adver-

se drug reactions in patients with liver disease treated with drugs which should be reduced at a reduced dosage in this situation. In order to find out the benefit of dose adaptation in patients with liver disease, such studies would be necessary.

Regarding adverse drug reactions, it is interesting to make a comparison between the incidence reported by Lazarou et al. (5) and the one found in our study. The mean given by Lazarou et al. (6.7% of patients per hospitalization) and the median found by us (6% of the patients) are almost identical. Since Lazarou et al. included studies between 1966 and 1996 and most studies included by us were published after 1996, the comparison suggests that the incidence of adverse drug reactions in hospitalized patients did not change much over the last 40 years, despite many new drugs on the market. Newer drugs seem therefore not to be associated with fewer adverse effects under hospital conditions. Such conclusions have to be drawn with caution however, since we did not systematically assess the severity of the adverse drug reactions and also regarding the high variability of the frequencies of adverse drug reactions among studies.

The studies open a large field of occupation for clinical pharmacists. Several studies could show that clinical pharmacists on the ward can help to reduce medication errors (6-10). Taking into account the cost of adverse drug reactions or adverse drug events (11-14) and assuming that most adverse drug reactions/events are avoidable (15-21), the occupation of clinical pharmacists on the wards could be cost beneficial. While clinical pharmacists have a long tradition in English speaking countries such as Great Britain and the United States of America, this is not the case in Switzerland. In particular in smaller hospitals (cantonal, regional and district hospitals), hospital pharmacists have to play the role of clinical pharmacists (due to lack of finances to engage a clinical pharmacist). It is therefore essential that hospital pharmacists have a good training in clinical pharmacy during their formation. This would mean that larger hospitals (in particular University Hospitals) should build up clinical pharmacy units, which would not only have to organize the practical work

on the wards and research projects, but would also have to care for the formation of hospital pharmacists in clinical pharmacy. The future will show, whether this will happen in Switzerland, since budget constraints are also operative in University Hospitals. My work demonstrates that there are enough studies in the literature providing evidence that this would be a good strategy to improve hospital drug safety.

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