Fundamental Progress in Investigating Drug Resistance with Electronic Multidrug Compliance Monitoring (e-MCM)

PEER REVIEWED

Background and Purpose
Current definitions of drug resistance are shaped by the pharmacotherapeutic fields they occurred in. They usually mention various contributing factors and refer either to the clinical or the biomarker level. Particular attention has been attracted by antiplatelet resistance, a phenomenon with clinical, cellular and pharmacogenetical contributors. However, the impact of every single factor to antiplatelet resistance in outpatients under prescribed antiplatelet therapy has not been comprehensively evaluated so far, neither has the temporal pattern of drug intake been studied as a possible contributor.

Methods
We propose generally applicable definitions of drug resistance, therapy failure and a classification of contributing factors to drug resistance. We introduce a study design with the use of blisterpacks in a target population (i.e. patients with a prescription of antiplatelet drugs), filled with the entire oral medication regimen, and equipped with electronic multidrug compliance monitoring (e-MCM) allowing thus to evaluate in a stepwise way the impact of the contributing factors (e.g. potential drug-drug interactions, genetic polymorphism) on biomarker outcome (i.e. in vitro platelet aggregation), with proven intake of the polytherapy.

Discussion and Conclusion
Drug resistance should be judged with the knowledge of the contributing factors and in the context of a patient's polytherapy under daily life conditions. The use of electronic multidrug compliance monitoring (e-MCM) allows the ruling out of non-compliance and the evaluation of the impact of potential drug-drug interactions on biomarker outcome. Pharmacogenetic testing may thus be restricted to those patients with a persistent lack of response, and the impact of the genotype may be interpreted within patients' specific clinical context. An evidence-based optimisation of the therapy in case of insufficient biomarker response may thus be given, and the intervention can be stratified according to the identified contributing factors. The debate may then be opened on the clinical benefit and the cost-effectiveness of practices currently used to overcome insufficient effectiveness solely based on biomarker findings.

Keywords
Compliance, drug resistance, electronic multidrug compliance monitoring, pharmacological biomarker.

Background
The term "drug resistance" has emerged from antibiotic and anticancer therapy and has been discussed in many fields of pharmacotherapy, such as antihypertensive drugs[1], antiepileptics[2,3], antidepressants[4], lipid modifying therapy[5] and antiplatelet medication[6-8].

"Drug resistance" was introduced as a Medical Subject Heading (MeSH) in 1972 and refers to a "diminished or failed response of an organism, disease or tissue to the intended effectiveness of a chemical or drug". This circumscription provides a short and global definition of the phenomenon, but does not specify the clinical context under which resistance is observed. Furthermore, the definition omits to mention if the effectiveness is measured on a clinical level (e.g. mortality) or on the surrogate marker level.

The term "drug resistance" has further been shaped by various authors in the context of their specific field of interest. The different proposed definitions have some basic features in common, like the clinical relevance of drug resistance, its multifactorial aspect, and its detection through pharmacological biomarkers[1-8], but no generally accepted concept of drug resistance has emerged.

Antiplatelet Drug Therapy for the Investigation of Drug Resistance
Dual antiplatelet therapy with aspirin and clopidogrel is a well-established regimen in the prevention of stent thrombosis[9], whereas aspirin has proved its efficacy in the primary and secondary prevention of cardiovascular and cerebrovascular events[10]. Up to 20 % of patients experience recurrent cardiovascular events despite dual antiplatelet therapy after percutaneous coronary intervention[11]. These incidence rates have raised the question of antiplatelet drug resistance, which is characterised by persistent in vitro platelet aggregation.

The term "antiplatelet resistance" describes "a phenomenon of measureable, persistent platelet activation that occurs in patients with prescribed therapeutic doses of aspirin"[12]. This definition is restricted to a biochemical phenomenon and includes any factor liable to compromise the biomarker outcome, including clinical factors that reduce drug exposure like non-compliance or poor absorption.

Clopidogrel resistance received special attention and was differently named "nonresponsiveness"[13] or "variability in platelet response"[14]. The phenomenon has been associated with CYP2C19 loss-of-function genotype[15] and with drug-drug interactions affecting CYP2C19 and CYP3A4 metabolic capacity[16-18]. Further factors with possible influence on platelet

activity were described, like tobacco smoking[19], diabetes mellitus[20] and systemic inflammation with increased platelet turnover[21]. None of these factors emerged as the most likely cause for the unmet clinical outcome, but their effects on in vitro platelet aggregation are evident.

Non-compliance must be generally suspected when patients under antiplatelet therapy do not display the expected in vitro platelet inhibition. Non-compliance has been described as a contributor of outstanding impact in aspirin therapy[22], with a prevalence of 22% in a cohort with manifest coronary artery disease and stroke[23]. However, when aggregation is inhibited, this means that an appropriate amount of the prescribed drug has been taken to produce the pharmacological effect, not that the prescribed regimen has been adhered to[24]. The contribution of non-compliant behaviour to antiplatelet resistance in outpatients under prescribed antiplatelet therapy has not been evaluated so far.

Definition of and Contributing Factors to Drug Resistance

"The absence of the expected biomarker response under (adequately) prescribed therapy (in correctly diagnosed patients)" may represent the cornerstone of a general definition of drug resistance. Consequently, we support that an unfavourable clinical outcome should be addressed as "treatment failure"[25] while "drug resistance" should be reserved for therapies whose efficacy can be evaluated with pharmacological biomarkers.

When a patient fails to respond adequately to a prescribed treatment, either on a clinical or on a biomarker level, the physician must distinguish among different causes of variability (pharmacological, behavioural, biological). Often, a combination of factors has produced the suboptimal results. Given the above definition of drug resistance, the contributing factors can be classified into clinical, genetic and cellular factors (Table 1), as already proposed for antiplatelet resistance[26]. Each single factor may negatively influence the biomarker response, and the ensuing impact depends on the taken drug.

In summary, we promote the comprehensive assessment of drug resistance with the evaluation of all contributing factors. To this purpose, we propose a study design with the implementation of a new compliance monitoring technology, using the field of antiplatelet resistance as a model.

Aims of the Study

The aims of the study of which the design is presented in this article are to identify resistance to antiplatelet therapy in outpatients with a prescription of antiplatelet agents, and to assess all factors that compromise the biomarker response, i.e. the platelet aggregation.

Table 1: Contributing factors to drug resistance, with specific examples for antiplatelet drug resistance

Factors contributing to drug resistance	Factors contributing to antiplatelet drug resistance (aspirin and/or clopidogrel)[25, 26]
Clinical factors	
Prescription	Failure to prescribe; Underdosing
Patient non-compliance	Mostly delayed or omitted doses
Poor absorbance	
Drug-drug interactions	Interaction with ibuprofene (aspirin); Interaction with PPIs and statins (clopidogrel)
Lifestyle factors	Tobacco smoking; Elevated body mass index
Comorbidity	Diabetes mellitus;
Genetic factors	Acute coronary syndrome; Systemic inflammation
Pharmacokinetic	Polymorphisms of MDR1 and CYP isoforms
Pharmacodynamic	Polymorphisms of P2Y12 and GPIIb/IIIa
Cellular factors	
Cell turnover	Increased platelet turnover
Adaptive cellular mechanisms	Increased ADP exposure
Up-/down-regulation of cell metabolism	Up-regulation of ADP-mediated pathways

Methods

Blisterpack and Compliance Measurement Technology

We chose a commercially available weekly blisterpack with 7x4 compartments (Pharmis GmbH, Beinwil a.S., Switzerland), filled with the entire oral medication regimen of the patient (Rx and OTC drugs). The back of the blisterpack is covered with a clear, self-adhering polymer foil (provided by ECCT B.V. Eindhoven, NL) with loops of conductive wires and connected to electronic components (Fig. 1). The attached microchip measures the electrical resistance, and records the time of its changes when a loop is broken, i.e. when a cavity is emptied. The data is transferred with a wireless communication device (near field communication) to a web-based database.

This electronic multidrug compliance monitoring (e-MCM) system enables the monitoring of the entire pharmacotherapy, and thus assessment of compliance behaviour and drug-drug interactions.

Recruitment and Inclusion Criteria

Patients are recruited at their local general practitioners (GP) surgeries during a routine consultation. Inclusion criteria are the prescription for aspirin and/or clopidogrel for the prevention of primary or secondary atherothrombotic events (cardiovascular, stent thrombosis or cerebrovascular event),

or for the treatment of peripheral arterial occlusive disease (PAOD), and the patient's agreement to get a weekly blisterpack with electronics (e-MCM) prefilled with all orally administered drugs and to leave all extra drugs at the study centre. Exclusion criteria are acute cardiac symptoms, residence in a care home or receiving home care, and lack of discernment to manage one's own pharmacotherapy. The use of a pill organiser is not an exclusion criterion.

Biomarkers for Antiplatelet Therapy

Historically, platelet aggregation in platelet-rich plasma was the method of choice to assess in vitro platelet activity[27]. In recent years, new assays have become commercially available. Raising evidence supports the introduction of multiple electrode aggregometry (MEA, Dynabyte, Munich, Germany) for the measurement of platelet aggregation and the prediction of the clinical outcome[28]. In the described study design, MEA is applied to measure in vitro platelet aggregation. The MEA instrument allows two ways to express the AUC: as arbitrary aggregation units (AU · min) or as units (U), whereas 10 AU · min correspond to 1 U. The cut-off value was set at 54 U[29].

Study Plan and Stepwise Assessment of Contributing Factors

At visit 1, demographic data including smoking status, educational level and social background is collected; baseline laboratory data including platelet aggregation is measured, and the individualised blisterpack for one week is delivered. Patients are informed that their drug intake will be electronically monitored, and advised to take their drugs as they were instructed in usual care. Patients' extra drugs are stored at the study centre during participation, thus rendering parallel drug consumption impossible.

At visit 2, one week later, in vitro platelet aggregation is measured and serves to dichotomise the study cohort into subjects with a) sufficient and b) insufficient platelet inhibition. The latter group will get another week of compliance-monitored therapy, with an additional direct observation (DOT, directly observed therapy) of the doses containing the antiplatelet drug on five of seven days.

The assessment of drug-drug interactions and pharmacogenetic polymorphisms is performed in all patients.

Sample Size Estimation

The incidence of antiplatelet resistance in patients with a prescription for aspirin and/or clopidogrel varies widely (8 - 45 %)[12]. For circumstances as defined in our study, an incidence of 20-30 % seems reasonable. The presence of main contributing factors in the general population is assumed to be 15 % for the loss-of-function genotype (g), 60 % for drug-drug interactions (d), and 20 % for comorbidities (c). Thus, the codes of the different patient groups and the rates of non-responders would be g0d0c0 (2 %), g0d0c1 (60 %), g0d1c0 (15 %), g0d1c1 (65 %), g1d0c0 (55 %), g1d0c1 (75 %), g1d1c0 (75 %), g1d1c1 (90 %), with 1 if the factor is present, and 0 if the factor is absent. The primary analysis should demonstrate that the main contributing factors have the expected influence on non-response. A Monte Carlo simulation with adjusted sampling for the estimated overall incidence of non-response resulted in a required total of 493 evaluable patients to achieve a power of 80 % as for the primary analysis.

Expected Results

Baseline platelet aggregation at visit 1 mirrors the effectiveness of a patient's polytherapy, i.e. drug efficacy under daily life conditions. We expect the values after one week to show an improved platelet inhibition, independently of the baseline value (and very likely because of the Hawthorne effect), and to draw conclusions on the optimal temporal pattern of drug intake on biomarker outcome with antiplatelet drugs.

With proven compliance by means of e-MCM, we will be able to quantify the clinical, genetic and cellular factors other than non-compliance in patients with insufficient platelet inhibition under aspirin and/or clopidogrel. With the tracking of the entire pharmacotherapy, we will be able to evaluate the impact of drug-drug interaction on the biomarker response, and to make recommendations for action when platelet inhibition is insufficient. We expect differences between both groups (aspirin and clopidogrel) in frequency rates, with a greater importance of pharmacogenetic polymorphisms and drug-drug interactions under clopidogrel therapy. Non-compliance is assumed to have a similar impact on in vitro platelet inhibition for both antiplatelet drugs.

Figure 1

Discussion and Conclusion

The use of electronic multidrug compliance monitoring (e-MCM) for the assessment of drug resistance allows us to rule out non-compliance and to evaluate the impact of potential drug-drug interactions on biomarker outcome. Pharmacogenetic testing may be restricted to those patients with a persistent lack of response. An evidence-based optimisation of the therapy in case of insufficient biomarker response is thus given, and the intervention can be stratified according to the identified contributing factors. The efficacy of the intervention can then be estimated with the biomarker outcome. In essence, the switch to another drug can be proposed only in case of proven inefficacy (genetic polymorphism, comorbidity, inevitable interaction). Our stepwise approach to identify and assess drug resistance in individual patients is applicable to many therapeutic settings, like treatment of dyslipidemia, hypertension, osteoporosis, and congestive heart failure.

To our knowledge, prospective compliance monitoring in patients with antiplatelet drug resistance has not been evaluated so far; neither has the applicability of in vitro platelet monitoring with multiple electrode aggregation (MEA) in a primary care setting. Insufficiently lowered platelet aggregation with MEA is associated with an unfavourable clinical outcome and thus underlines the relevance of the finding. Stratified interventions may optimise safety and effectiveness of drug therapies under daily life conditions, and back up the utility of diagnostic strategies addressing drug resistance. Further studies are needed to evaluate the clinical benefit and cost-effectiveness of identifying and treating drug resistance in different population groups.

Summary Points

- We support a new definition of drug resistance and propose its attribution to an inadequate biomarker response to prescribed drugs.
- Drug resistance is a phenomenon with multiple contributing factors on the clinical, genetic and cellular level.
- Antiplatelet drug resistance can serve as a model for drug resistance.
- The assessment of contributing factors must involve electronic multidrug compliance monitoring (e-MCM) to rule out non-compliance and to measure exposure to drug-drug interactions.
- More studies are needed to evaluate the clinical benefit and cost-effectiveness of identifying and treating drug resistance in different population groups.

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