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Clopidogrel Salts – Pharmacokinetic, Pharmacodynamic and Clinical Aspects

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Abstract: Clopidogrel hydrogen sulfate plays a central role as a platelet inhibitor in acute coronary syndromes, interventional cardiology and in secondary prevention of ischemic events in patients with myocardial infarction, stroke, or peripheral arterial occlusive disease (PAD). Compared to acetylsalicylic acid (as the standard antiplatelet agent), additional benefit has been shown for clopidogrel hydrogen sulfate in PAD. Regulatory authorities such as the „Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM) recently approved another clopidogrel salt (besilate), based on a bioequivalence (pharmaco-kinetic) study of the inactive mother substance (prodrug). The besilate was originally approved only for secondary prevention of atherothrombotic events in monotherapy (without additional ASA administration), but since mid-2009 – as clopidogrel generic – also for dual platelet inhibitor therapy with ASA in patients with acute coronary syndrome and/or coronary stent implantation, i.e., for the full Plavix indication.

Taking the example of the besilate, this article describes which study data for the use of a new salt of the prodrug clopidogrel could be important and available for a pharmacological and clinical review. Additional supportive data might comprise (1) the pharmacokinetic characterization of the metabolite, conveying the pharmacological activity after being activated out of the inactive prodrug, (2) pharmacokinetics in women and elderly patients respectively, as well as in combination with ASA or other concomitant drugs, (3) pharmacodynamic data (effects on platelets), and (4) clinical data (safety and efficacy). Only in the light of these data can it be assessed whether a new salt of clopidogrel hydrogen sulfate has therapeutic equivalence compared to the well documented reference drug clopidogrel hydrogen sulfate.

Kurzfassung: Clopidogrelhydrogensulfat – Pharmakokinetische, pharmakodynamische und klinische Aspekte. Clopidogrelhydrogensulfat spielt eine zentrale Rolle als Thrombozytenfunktionshemmer in der interventionellen Kardiologie und in der Sekundärprävention ischämischer Ereignisse bei Patienten mit Herzinfarkt, Schlaganfall oder peripherer arterieller Verschlusskrankheit (PAVK). Im Vergleich zum Standard Acetylsalicylsäure (ASS) wurde ein zusätzlicher Nutzen für die Monotherapie mit Clopidogrelhydrogensulfat bei Patienten mit PAVK gezeigt. Auf der Basis einer Bioäquivalenz(kinetik)studie zur inaktiven Mutter-substanz (Prodrug) ließen Zulassungsbehörden wie beispielsweise das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) Mitte 2008 ein anderes Clopidogrelsalz (Besilat) zunächst nur zur Sekundärprävention atherothrombotischer Ereignisse in der Monotherapie (ohne zusätzliche ASS-Gabe) zu, seit Kurzem aber für die duale Thrombozyteninhibition in Kombination mit ASS bei Patienten mit akutem Koronarsyndrom und/oder koronarer Stentimplantation, d. h. in der vollständigen Plavix-Indikation.

Am Beispiel des Besilats wird aufgezeigt, welche Studiendaten für den Einsatz einer neuen Salzverbindung der Prodrug Clopidogrel aus pharmakologischer und klinischer Sicht vorliegen sollten. Wesentlich sind (1) die Darstellung der Pharmakokinetik (PK) des Hauptmetaboliten, der nach Bildung aus der inaktiven Ausgangsubstanz die eigentliche pharmakologische Wirkung vermittelt, (2) die PK bei Frauen bzw. älteren Patienten sowie bei Kombination mit ASS bzw. weiteren Medikamenten, (3) die Untersuchung der Pharmako-dynamik (Wirkungen auf Thrombozyten) sowie (4) klinische Daten (Sicherheit und Effektivität). Nur bei Vorliegen dieser Daten ist eine therapeutische Äquivalenz im Vergleich zur sehr gut dokumentierten Ausgangssubstanz Clopidogrelhydrogensulfat nachvollziehbar. **J Kardiol 2009; 16: 412–6.**

Background

The thienopyridine clopidogrel hydrogen sulfate is a platelet inhibitor that has been on the market since 1998 (trade names: Plavix [1], Iscover). Whereas acetylsalicylic acid (ASA) reduces platelet aggregation, capability to aggregate and secrete by irreversible inhibition of thromboxane synthesis, clopidogrel acts in a different way, by irreversibly blocking the adenosine receptor. The substance clopidogrel hydrogen sulfate was examined in a variety of experimental and clinical studies. A recent Medline search revealed nearly 600 published clinical studies on clopidogrel hydrogen sulfate. Among them are comprehensive endpoint studies such as CAPRIE [2], CURE [3], MATCH [4], CHARISMA [5], or PRoFeSS [6], TRITON TIMI-38 [7] and ACTIVE-A [8], being the largest of their kind. A number of experimental results from investigations of platelet function and clinical studies indicate superior efficacy of clopidogrel hydrogen sulfate compared to ASA and for clopidogrel HS plus ASA compared with ASA alone [9].

All the mentioned studies were performed with clopidogrel hydrogen sulfate. This clopidogrel compound is approved for secondary prophylaxis of atherothrombotic events. Clopidogrel hydrogen sulfate in combination with ASA is additionally approved for the treatment of acute coronary syndrome (ACS) with and without ST segment elevation. There is also explicit approval for coronary intervention with stenting for application within thrombolytic therapy during ST-elevation myocardial infarction.

The „Institut für Qualitätssicherung und Wirtschaftlichkeit im Gesundheitswesen", IQWiG (German Institute for Quality and Efficiency in Health Care) in its systemic review found a benefit for the ASA/clopidogrel combination compared to ASA monotherapy in the treatment of ACS without ST segment elevation (NSTEMI, treatment duration 3–12 months), and for in-hospital treatment of myocardial infarction with ST segment elevation (STEMI) by reduction of the rate of recurrent MI [10].

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Table 1: Indications for clopidogrel compounds. (Source: http://www.emea.europa.eu/humandocs/PDFs/EPAR/clopidogrelbms/H-974-PI-en.pdf)

Clopidogrel is indicated in adults for the prevention of atherothrombotic events in patients
- suffering from myocardial infarction (from a few days to less than 35 days),
- ischemic stroke (from 7 days to less than 6 months)
- established peripheral arterial disease.

Patients suffering from acute coronary syndrome:
- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
- ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

New Clopidogrel Salt for Secondary Prophylaxis

In the middle of 2008, a modified clopidogrel compound was approved by the „Bundesinstitut für Arzneimittel und Medizinprodukte“ (BfArM): the active substance bound to the salt of benzene sulfonic acid (besilate). This besilate compound originally had an approval based on the original indication that resulted from the CAPRIE trial in 1998 limited to secondary prevention of atherothrombotic events. Since August 2009, the combined therapy with ASA for acute or post-treatment of ACS and prevention of acute or subacute stent thrombosis is also included in the indication (Tab. 1), based on recommendations of the Committee for Medicinal Products for Human Use (CHMP) for the approval of clopidogrel besilate formulations e.g. Clopidogrel Aciono or Clopidogrel Hexal, as generics for Plavix [11, 12].

Direct comparisons of different clopidogrel salts are either limited or unpublished. As an exception, a Korean randomized cross-over study with healthy young volunteers was recently published, which did not show statistically significant differences in terms of pharmacokinetic or pharmacodynamic differences between a hydrogen sulfate and a besilate compound [13].

Therapeutic exchangeability of different salt forms is discussed, partly controversially, in the scientific literature. Pharmacokinetic, pharmacodynamic, toxicological and clinical aspects should be considered. Based on valid regulatory guidelines, different salts, esters, ethers, isomers, complexes, or derivatives of active substances should be considered as equal active ingredients, if they do not differ significantly regarding safety and efficacy [14]. For comparable safety and efficacy it has to be ensured that pharmacokinetics, pharmacodynamics and/or toxicity of the active substance are not modified.

Changes of Salt Can Imply Change of Drug

Drugs that are available as free base/acid are frequently transformed to their salt form. Thereby better pharmacokinetic qualities are achieved (e.g. better stability), but also better pharmacodynamic qualities [15]. These qualities are influenced in part variably by different salts, and different pharmacokinetic qualities (e.g. modification of imipramine hydrochloride to imipramine pamoate changes normal to prolonged release formulation) can definitively bring about different pharmacokinetic and therefore also different clinical qualities. Some salts may show intrinsic toxicity, which can be significant particularly in higher doses or in vulnerable patients (e.g. tartrate anions or lithium anions can be nephrotoxic, potassium cations or nitrate anions can cause gastrointestinal ulcers when administered orally) [15]. Clopidogrel hydrogen sulfate was given in loading doses up to 2400 mg in clinical experimental studies [16], and the toxicity of salts could be manifested with these high doses. Against this background it is comprehensible that some regulatory authorities demand more extensive investigations before approval of a modified salt form. Often, additional clinical and toxicological studies („bridging studies“) are claimed as well as new stability data in order to prove clearly the safety of the new preparation [17]. Overall, these other regulatory authorities have requirements which extend beyond those of the European authorities [18].

Pharmacokinetic Aspects

Absorption Dependent on Salt and Galenics

With regard to the absorption of drugs the vehicle can play an important part [19, 20]. Both the rate of absorption and the amount absorbed depend on numerous factors. Included are physicochemical characteristics of the drug, such as acidity constant pKa, dissolubility in water and fat, particle size, and many more. Different salts can differ considerably in their absorption characteristics [19].

Relevant differences might even be present if the same salt compound is used in a different galenical formulation [19].

Prodrug and Active Metabolite

Clopidogrel itself is an inactive prodrug, meaning it has no direct pharmacological activity. The active metabolite, a thiol derivative, is formed after an extensive first-pass effect in the liver by oxidation of clopidogrel to 2-oxo-clopidogrel and a subsequent metabolic step [21]. These two steps are cytochrome P450 mediated and therefore are interindividually strongly variable. The active very short-life thiol metabolite of clopidogrel hydrogen sulfate has been characterized meanwhile.

As the conversion rate of clopidogrel hydrogen sulfate into the active metabolite is responsible for biological effects and lies in the order of 5–10 % with underlying interindividual fluctuations, simple measurement of the prodrug, which is not responsible for the biological effects, is not meaningful or predictive for clinical efficacy. Simple bioequivalence studies based on parent prodrug assessment are only considered sufficient by regulatory authorities in such situations if the pharmacokinetics of prodrug and active metabolite are linear.

In the case of clopidogrel, the initial substance is inactive and its pharmacokinetic linearity has not yet been clearly shown, while the active metabolite exhibits an infra-dose proportionality from 75 to 600 mg. A 4-fold increase in dose from 75 to

300 mg leads to a 2.8-fold increase in the AUC of the active metabolite, while doubling the dose from 300 to 600 mg leads to a 1.4-fold increase in the AUC [22]. It is assumed that the different hepatic conversion rates are one of the reasons for the clopidogrel hyporesponder status of patients, who respond only with a restricted inhibition of platelet aggregation. As a result of rapid developments, it is increasingly more feasible today to measure the pharmacokinetics of the active metabolite, which is of high interest for the comparison of a new salt formulation with the originator product.

Based on the prescribing information of one of the currently approved besilate compounds of clopidogrel, so far only a small study on bioavailability appears to have been performed [23]. In this as yet unpublished study, 46 healthy male volunteers aged 18 to 41 years received the reference compound (clopidogrel hydrogen sulfate) or clopidogrel besilate. Pharmacokinetic data on the active metabolite were not published, and such data on clopidogrel besilate with concomitant application of further drugs are also missing.

Also with regard to this aspect a simple bioequivalence test of the inactive pro-drug does not sufficiently fulfill the clinical pharmacological characteristics of clopidogrel compound. It is quite conceivable that the correlation between the C_{max} of the inactive pro-drug and that of the active metabolite in the distinct salt forms could be different, specifically because the pharmacokinetics of the active metabolite are not linear (its formation decreases when the clopidogrel dose increases). If this were to be the case, it could have implications for clinical efficacy in terms of increased or also decreased efficacy. Hence there is need for evaluation of the clinical efficiency of therapy with clopidogrel besilate; whereas a better bioavailability and higher formation of active metabolite with enhanced platelet inhibition could also mean a potential higher bleeding rate, or alternatively decreased bioavailability and decreased formation of active metabolite with insufficient antithrombotic efficacy could result in a higher cardiovascular event rate.

Therefore it must be stated that if metabolites act as the active agent, their detailed pharmacokinetic profile should be characterized before clinical application [24].

Studies in Prospective Drug User Groups

It is open to criticism in general that within the approval procedure, bioequivalence studies are nearly always performed on homogeneous collectives, usually with young, healthy men without concomitant diseases. A simple extrapolation of the data on other populations is not justified. Clopidogrel is mainly used in elderly, comorbid or multimorbid patients, who may differ from healthy probands not only with regard to metabolism and therefore pharmacokinetics, but also significantly with regard to pharmacodynamics. Possible influences of comedication also have to be considered.

According to a review of the published literature, female and elderly probands of comparable age to the treated patient population have not yet been investigated with new salt formulations of clopidogrel. Inclusion of both genders and elderly probands is explicitly recommended in such bioequivalence studies in US-American guidance documents [17]. Also, no data in patients have yet been proclaimed, especially regarding other demographic data such as age, gender or additional diseases such as diabetic gastroparesis or achlorhydria, which are of particular interest. These diseases or age-related physiological changes can essentially influence the absorption of different salt compounds and their conversion into the active metabolite. Many of these considerations have been adopted in the present draft of the Note for Guidance on the investigation of bioavailability and bioequivalence of the Committee for Proprietary Medicinal Products (CPMP) [18].

Pharmacodynamic Aspects

Adenosine diphosphate (ADP) activates, among other things, the Gi-protein-coupled purine receptor P2Y12 on the platelet surface. The clopidogrel metabolite blocks this receptor and thereby prevents the ADP binding as well as the subsequent activation of the glycoprotein (GP) IIb/IIIa complex and the subsequent binding of fibrinogen on the GP IIb/IIIa-receptor. The decrease of platelet aggregability depends on the completeness of receptor blocking. A number of experimental and clinical reports point out the interindividual variability of efficacy of clopidogrel (as with ASA) [25, 26].

Numerous reasons are under discussion , for example compliance problems, insufficient absorption, incomplete metabolism by cytochrome P450 isoenzyme 2B6 and 3A4, and to a lower extent by 1A1, 1A2 and 2C19 to the pharmacologically effective metabolite in the liver [27]. Additionally, the intercurrence of other substances metabolized in the liver, an increased platelet turnover or functional platelet disorders, comorbidities such as diabetes mellitus or polymorphism of ADP receptor gene are mentioned as reasons for varying reaction [27].

Although response to an antiplatelet usually lies in the normal distribution range, there are patients whose response lies at the extremes. These “outliers” appear to have an increased incidence of cardiovascular events, mortality and bleeding [28]. Subsequently, new clopidogrel salts ought to be investigated in detail regarding their pharmacodynamic characteristics and especially their profile with respect to outliers. As appropriate methods, aggregometry as well as determination of vasodilator-stimulated phosphoproteins (VASP) phosphorylation and of thromboxane metabolite are utilized [29–31]. Such investigations are not yet available for alternative clopidogrel formulations, but are highly relevant with regard to clinical aspects and must be carried out.

Toxicological Aspects

Recently, in a letter to pharmaceutical manufacturers the EMEA stated that in medicinal products containing mesilates, isetionates, tosilates or besilates, alkyl or aryl sulfonic ester contaminations might be formed during the production of the active ingredient and remain as impurities in the product. As these have been associated with mutagenic, carcinogenic or teratogenic effects, manufacturers are mandated to provide risk assessment reports to regulatory authorities [32].

Clinical Aspects

As described above, a theoretical possibility of a changed pharmacological activity exists if salts are replaced. In this context the results of the COMET trial, one of the largest and longest studies on the therapy of chronic heart failure are to be pointed out. The beta-blockers carvedilol and metroprolol were compared. For interpretation of the study results the salt form, used in COMET, the dosage and changed pharmacokinetics were discussed as influencing variables [33, 34].

The clinical profile of the new substance can only be crudely characterized from the laboratory data of healthy probands and has to be evaluated in corresponding trials with patients in the designated indication. Clopidogrel hydrogen sulfate was tested by the pharmaceutical manufacturer in a very large study program with more than 100,000 patients in different chronic and acute indications, including patients with very different cardiovascular risk profiles. From this, the admission for various indications followed, in which clopidogrel showed a positive risk-benefit profile, which means high platelet inhibiting activity, with a significant reduction of atherothrombotic clinical events and a concomitant low bleeding incidence. The latter is of particular relevance, as bleeding events can limit the application. A current example of this problem is the TRITON-TIMI-38 trial, in which the new orally available thienopyridine prasugrel showed greater efficacy for preventing acute myocardial infarction in patients with acute coronary syndrome compared with clopidogrel, but also presented an inferior safety profile with a higher number of major and life-threatening bleeds [7].

From that and other trials (e.g. PRINCIPLE-TIMI-44 [35]) the hypothesis has been derived that platelet inhibitors also present a therapeutic window in which the relationship between antithrombotic effect and safety (regarding bleeds) is optimal.

The compliance with this therapeutic window for an efficient and safe platelet inhibition is especially important in patients with percutaneous coronary interventions, as treatment failure in unfavorable cases can lead to fatal stent thrombosis, whereas excessive inhibition can lead to major bleeding.

Also, in the case of clopidogrel, recently published data again show how important pharmacodynamic studies in patients are. Heestermans et al. reported a significantly decreased bioavailability of clopidogrel in patients with ST-elevation infarction compared to healthy probands [36]. A close correlation between inhibition of platelet aggregation and peak level of the active metabolite existed [36].

With regard to the mentioned implications quod vitam and the available extensive evidence regarding the combined application of clopidogrelhydrogen sulfate and ASA, sufficient documentation for new clopidogrel salts has to be claimed. The approval of clopidogrel salts without additional clinical data in patients means that in clinical practice patients will be at risk of being exposed to possibly changed bioavailability, and more or less varying conversion into the active metabolites, respectively.

Conclusions for the Practising Physician

From a clinical or pharmacological viewpoint, for the safe and effective use of new clopidogrel salts additional pharmacokinetic, pharmacodynamic and clinical data may be necessary.

- First, it is important to collect data on the active metabolite with a reliable and validated method for determination of bioequivalence.
- In patients receiving other clopidogrel salts for secondary prevention in monotherapy and potentially for other indications, the pharmacodynamic profile should be characterized by exploration of platelet function.
- Pharmacokinetic data should be generated also for women and elderly patients as well as patients receiving combination therapy with ASA or other drugs; data are also required for the combination of the clopidogrel salt and ASA data on pharmacodynamics.
- Before approval for combined therapeutic application of ASA and clopidogrel salts in acute conditions (acute coronary syndrome with/without ST elevation, or with/without stenting), clinical data on safety and effectiveness are mandatory.

Only after the availability of these additional investigations can therapeutic equivalence of a new salt formulation to clopidogrel hydrogen sulfate, especially for combined application with ASA, be presumed with sufficient certainty.

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