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Review article

Clopidogrel-Statin Interaction: a Missing Links

Zoran M. Todorović[1,2], Nina B. Djukanović[3], Slobodan D. Obradović[4], Dragana D. Protić[1], Miodrag Č. Ostojić[5]

[1] Department of Pharmacology, Clinical Pharacology and Toxicology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2] University Medical Center "Bežanijska kosa", Belgrade, Serbia
[3] High Medical School Milutin Milanković, Belgrade, Serbia
[4] Clinic of Emergency Medicine, Military Medical Academy, Medical Faculty, University of Defense, Belgrade, Serbia
[5] Faculty of Medicine, University of Belgrade, Belgrade, Serbia

SUMMARY

Introduction: The use of clopidogrel is associated with a large variability in the response to this drug, wherein the results of the numerous studies indicate that even one out of three patients can be placed in the category of non responder.
Corresponding section headings: Among the many causes of modified pharmacodynamic effects of clopidogrel, special attention is addressed to the possible clopidogrel-statin interaction. Numerous studies have focused on this problem, but it still seems to be missing the right answer.
Conclusion: This paper reviews some of the most important facts regarding concomitant use of clopidogrel and statins, and specific issues to be addressed for safe treatment of patients.

Keywords: clopidogrel, resistance, statins, interaction

INTRODUCTION

Combined antiplatelet therapy with aspirin and clopidogrel is the main therapy regimen which is applied in patients with acute coronary syndromes and patients undergoing percutaneous coronary intervention [1-6]. Despite the intensive use of combination of these drugs, the occurrence of adverse cardiovascular events is still significant. Clopidogrel resistance, relative to interindividual variability of response to clopidogrel, is one of the possible reasons for that. Clinical trials have demonstrated that the relationship between inadequate response to clopidogrel and increased risk of future thrombotic events may not be ignored.

Unfortunately, the concept of clopidogrel resistance is still not fully understood, although certain potential mechanisms that may be responsible for this have been promoted [7,8]. They mainly include the combination of clinical, biological and genetic influences which are expressed on platelet function (Table 1) [9-11].

Among the possible mechanisms of clopidogrel resistance, drug interactions which occur on pharmacokinetic level de-

Corresponding author:
Prof Zoran M. Todorović, MD, PhD,
Specialist in Clinical Pharmacology
Department of Pharmacology, Clinical Pharmacology and Toxicology, University Medical Center "Bežanijska kosa", Faculty of Medicine, University of Belgrade
E-mail: zoran.todorovic@mfub.bg.ac.rs

Tabele 1. Potential mechanisms of clopidogrel resistance

Clinical Factors	Biological factors	Genetic factors
- Patient non compliance - Underdosing or nonadequate dosing of clopidogrel - Drug-drug interaction - Elevated body mass index	- Increased release of ADP - Up regulation of the P2Y12 pathway - Up regulation of the P2Y1 pathway - Up regulation of P2Y12-independent pathways - Accelerated platelet turnover	- Polymorphism of CYP - Polymorphism of $P2Y_{12}$

serve particular attention. The role of statins in changing the pharmacodynamic effects of clopidogrel, and the level of platelet reactivity, has been reported, but remains quite controversial [9, 12-14].

CORRESPONDING SECTION HEADINGS

Clopidogrel and statin metabolism

Clopidogrel, which is a thienopyridine derivative, binds specifically and irreversibly to the P2Y12 receptor, thus inhibiting ADP mediated platelet aggregation. Clopidogrel is a prodrug requiring activation by the hepatic cytochrome P450 isoenzymes [15,16]. About 85% of the drug is hydrolyzed by esterases to an inactive carboxylic acid derivative [17]. The remaining part of the drug is oxidized to 2-oxo clopidogrel through a cytochrome P 450 – dependent pathway, in which CYP3A4, CYP3A5 and CYP2C19 have a greater role than the CYP2C9, CYP2B6 and CYP1A2 [15,16,18,19]. Hydrolysis of 2-oxo clopidogrel generates the active metabolite which contains a thiol group that binds to a cysteine on the P2Y12 receptor and thus irreversibly block ADP – binding and receptor activation [20].

Any drug which inhibits cytochrome P450 (CYP) enzyme systems, may potentially block the synthesis of the active metabolite of clopidogrel, and hence its effect on platelet function. Among these drugs, a special place takes the inhibitors of hydroxymethylglutaryl CoA reductase (HMG CoA reductase) – statins. The largest number of statins are lipophilic compounds that are subject to the process of extensive metabolism by the CYP isoenzyme systems. Atorvastatin, simvastatin and lovastatin are substrates of CYP3A4, while CYP2C9 is responsible for the metabolism of fluvastatin [21,22]. Rosuvastatin, although not lipophilic compound, is metabolized by CYP2C9 and to a lesser extent by CYP2C19 [23]. In contrast, the pravastatin as a hydrophilic compound, is metabolized by sulfation and not by the family of CYP enzymes (Table 2) [21].

Tabele 2. Enzymes which are involved in clopidogrel and statin metabolism

Drug	Enzymes
Clopidogrel	Main metabolic pathways: CYP3A4, CYP3A5 and CYP2C19 Enzymes which play a less important role: CYP2C9, CYP2B6, CYP1A2
Atorvastatin	CYP3A4
Simvastatin	CYP3A4
Lovastatin	CYP3A4
Fluvastatin	CYP2C9
Rosuvastatin	CYP2C9 and CYP2C19 (minor role)
Pitavastatin	CYP2C9
Pravastatin	Non CYP

Clopidogrel-statin interaction

CYP3A4-metabolized statins (simvastatin and atorvastatin) seems to be more potent lipid-lowering drugs than pravastatin [24-26]. Such a finding could significantly affect the incidence of adverse cardiovascular outcomes.

Lau et al. were the first who have shown that the lipophilic statins are capable to inhibit CYP3A4 system and thereby reduce the formation of the active metabolite of clopidogrel, i.e. lead to a reduction of its antiplatelet effects [12]. They found that atorvastatin, in contrast to pravastatin, reduced the ability of clopidogrel to inhibit the platelet aggregation. Also, in some studies were obtained similar results with other lipophilic statins, such as simvastatin and fluvastatin [13,27]. However, in most trials is not registered that concomitant use of statins reduced clopidogrel responsiveness. Even more interesting, several researches have found that CYP3A4 metabolized statins can actually increase clopidogrel's effect on platelets [28-29]. Also, in our study, CYP3A4 metabolized statin – simvastain, didn't reduce the antiplatelet response to clopidogrel. Such response was even potentiated in comparison with the group that wasn't receiving statin (simvastatin). Only one of seven patients

Study	Population	Treatment, n	Results
Lau et al. [12]	Elective PCI	Atorvastatin = 19 Pravastatin = 9 No statin = 16	Atorvastatin decreases inhibition of platelet aggregation by clopidogrel
Neubauer et al. [13]	Elective PCI	Atorvastatin = 17 Simvastatin = 8 No statin = 22	CYP3A4 statins competitively inhibit the metabolic activation of clopidogrel
Serebruany et al. [31]	Elective PCI	CYP3A4 statins = 37 Non-CYP3A4 statins = 13 No statin = 25	Statins do not affect the ability of clopidogrel to inhibit platelet function
Trenk et al. [32]	Scheduled CA	CYP3A4 statins = 590 Non-CYP3A4 statins = 123 No statin = 682	CYP3A4 statins have no effect on the antiplatelet activity of clopidogrel
Geisler et al. [33]	Elective PCI	CYP3A4 statins = 756 Non-CYP3A4 statins = 257 No statin = 142	Coadministration of statins does not increase residual platelet aggregation and does not worsen the clinical prognosis
Saw et al. [34]	Elective PCI	CYP3A4 statins = 1001 Non-CYP3A4 statins = 158 No statin = 957	Clopidogrel benefit in reducing the primary end point is similar, regardless of the choice of statin
Saw et al. [36]	High CV risk	CYP3A4 statins = 8245 Non-CYP3A4 statins = 1748 No statin = 5496	No differences in outcomes in relation to the type of statin
Lotfi et al. [37]	ACS	Atorvastatin = 2081 Pravastatin = 2081	Beneficial effects of atorvastatin in reducing the primary end point is independent of coadministration with clopidogrel
Brophy et al. [38]	Elective PCI	Atorvastatin = 727 No Atorvastatin = 2200	More adverse events in the group prescribed atorvastatin

Tabele 3. Pharmacodynamic and clinical studies that investigated the potential interaction of the statin and clopidogrel

PCI - percutaneous coronary intervention,
CA - coronary angiography,
CV - cardiovascular risk,
ACS - acute coronary syndrome

treated with both clopidogrel and statin had a bad response to clopidogrel, compared to four out of eight patients from the group that was receiving only clopidogrel [30].

Different results obtained in all of these studies are likely the consequence of the number of factors, such are: lacking of the unique protocol and method for the determination of platelet function, small sample size, noncomparative doses of statins, the time when the measurement is carried out and finally lack of baseline values of platelet aggregation before the introduction of therapy.

In any case, more important than just the results of ex vivo studies, is whether the potential clopidogrel-statin interaction has an impact on clinical outcomes (Table 3). Different studies have presented diverse results, but most of them have reported that the concomitant clopidogrel-statin use isn't associated with a higher incidence of adverse cardiovascular events.

Authors from CREDO, MITRA PLUS, CHARISMA and PROVE IT–TIMI 22 trials [32-35] didn't register that concomitant use of these drugs and clopidogrel affected the clinical end points. Study of Brophy et al. was one of the few studies that showed that the combined use of CYP3A4 metabolized statins and clopidogrel exerts adverse effects and increases the risk associated with clinical outcomes [38].

Recent studies, ACCEL-STATIN and PORTO, again actualized the issue of clopidogrel-statin interaction. Results of the ACCEL-STATIN study have indicated that in clopidogrel-treated patients with high platelet reactivity during concomitant use with atorvastatin, replacing to a non CYP3A4 metabolized statin (rosuvastatin or pravastatin) caused a significant reduction in platelet reactivity and the prevalence of high platelet reactivity [39]. In PORTO trial it was observed that non CYP3A4 metabolized statin (pitavastatin) had no affect on platelet reactivity in patients who are borderline or non responders to dual antiplatelet therapy, in contrast to the atorvastatin [40]. It should be emphasized that the Pelliccia et al. find that the effect of atorvastatin is particularly pronounced in patients with high platelet reactivity, in which leads to an increment of the already increased platelet reactivity.

CONCLUSION

Taking into account all previously disclosed, it is clear that there are many questions which are required to be explained and based on which we could come to some strong and precious conclusion about possible influence of concomitant statin use on the variability in patient response to clopidogrel.

Perhaps the first step might be to clarify doubts regarding the lack of a unique protocol, ie. precise definition and proof method for identification of the clopidogrel resistance. Although there are more available tests for monitoring of clopidogrel therapy [4, 35] their routine use is not come to life yet. Considering the cost of these tests and accompanied economic expenses, maybe at the beginning, the measurement of platelet function should be limited to patients with a high risk for poor response to clopidogrel.

The absence of cleary defined doses of clopidogrel and statins is the next issue should be resolved. When it comes to doses of clopidogrel, the studies have used different doses: loading doses of 300 or 600 mg and 75 mg maintenance dose. Since, it is known that clinical efficacy of clopidogrel behaves in a dose dependant manner, clinical studies that would explained potentially clopidogrel-statin interaction are still missing in the light of these facts. The situation is similar when it comes to doses of statins.

In patients undergoing percutaneous coronary intervention (PCI), time of sampling for analysis is also something that needs to be taken into account. This is not only because of clopidogrel dose (loading or maintenance dose), but also due to the impact of intervention that seems to activate platelets, causing platelet hyperreactivity within 24 hours after PCI.

In any case, it is expected that the future studies (double-blind, randomized, multicenter with a sufficient number of respondents) come up with an answer to the dilemmas that accompany the issue of possible interaction between clopidogrel and statins. Particularly in terms of the opportunities offered to patients in whom it is determines that statins reduced antithrombotic effect of clopidogrel, whether to increase the dose of clopidogrel (some initial results are not in favor of this thesis) or switch to new antiplatelet drugs.

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Interakcija između klopidogrela i statina: karika koja nedostaje

Zoran M. Todorović[1,2], Nina B. Djukanović[3], Slobodan D. Obradović[4], Dragana D. Protić[1], Miodrag Č. Ostojić[5]

[1] Institut za farmakologiju, kliničku farmakologiju i toksikologiju, Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija
[2] Kliničko-bolnički centar "Bežanijska kosa", Beograd, Srbija
[3] Visoka medicinska škola Milutin Milanković, Beograd, Srbija
[4] Klinika za urgentnu internu medicinu, Vojnomedicinska akademija, Medicinski fakultet, Univerzitet odbrane, Beograd, Srbija
[5] Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija

KRATAK SADRŽAJ

Uvod: Primena klopidogrela je povezana sa velikim varijabilnošću u odgovoru na ovaj lek, pri čemu rezultati velikog broja studija ukazuju da čak jedan od tri pacijenta može biti u kategoriji onih koji ne odgovaraju na lek.
Tema: Među brojnim uzrocima koji modifikuju farmakodinamski efekat klopidogrela, posebna pažnja se posvećuje mogućoj klopidogrel - statin interakciji. Brojne studije su bile fokusirane na ovaj problem, ali se ipak čini da još uvek nedostaje pravi odgovor.
Zaključak: U ovom radu iznete su neke od najvažnijih činjenica u vezi sa istovremenom upotrebom klopidogrela i statina, kao i specifična pitanja koja treba rešiti radi bezbednog lečenja pacijenata.

Ključne reči: klopidogrel, resistancija, statini, interakcija

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