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Clinical paper

Clopidogrel pharmacokinetics and pharmacodynamics in out-of-hospital cardiac arrest patients with acute coronary syndrome undergoing target temperature management☆

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ABSTRACT

Background: Target temperature management (TTM) after cardiac arrest (CA) improves outcome in patients with acute coronary syndrome (ACS). Previous data point to an interaction between hypothermia and drug metabolism, potentially impacting on platelet function in patients on antiplatelet therapy.
Purpose: To compare clopidogrel metabolism and platelet function in clopidogrel naïve ACS patients treated with TTM (33 °C, $n = 15$) and in ACS patients (troponin positive) without TTM ($n = 18$).
Methods: Platelet function was measured by multiple electrode platelet aggregometry (MEA), light transmittance aggregometry (LTA) and VASP analysis before and after administration of a 600 mg clopidogrel loading dose. Plasma levels of clopidogrel and its metabolites were measured. All patients were screened for CYP2C19*2 polymorphism and scheduled for PCI. TTM was carried out for 24 h at a target temperature of 33 °C using a computer feedback surface cooling device in cardiac arrest patients.
Results: Plasma concentration of clopidogrel and metabolites was lower in the TTM group after 2 and 4 h, respectively (all $p < 0.005$ vs. controls), and platelet function tests revealed an attenuated response to clopidogrel with respect to baseline platelet activity in the TTM group. This was significant for MEA, LTA and VASP analysis (all $p < 0.05$). Moreover, there was no significant difference in genotype and platelet function determined *ex vivo* at 33 or 37 °C, respectively.
Conclusion: Inhibition of platelet function is significantly lessened in TTM at 33 °C, likely due to reduced clopidogrel absorption. Patients with TTM might thus have a higher risk for further cardiovascular events despite antiplatelet therapy with clopidogrel.

Introduction

Targeted temperature management (TTM) at a target temperature of 32–36 °C for 24 h is currently recommended for cardiopulmonary resuscitation (CPR) to improve neurological outcome.[1] The most common reason for CPR is cardiac arrest (CA) due to acute coronary syndrome (ACS). Under these circumstances, early revascularization with percutaneous coronary intervention (PCI) and attendant antithrombotic therapy is recommended. These strategies lead to a better outcome in non-cardiac-arrest patients with ACS.[2] The highest risk for stent thrombosis occurs within the first 48 h after PCI, so that quick and sufficient inhibition of platelet function is crucial to avoid thromboembolic complications. Notably, recent data point to an increased risk for stent thrombosis after PCI despite administration of antiplatelet drugs in resuscitated patients treated with TTM which might translate into an augmented mortality.[3,4] In this regard several reasons potentially leading to altered pharmacokinetic and/or pharmacodynamic response of platelet inhibitors have been suggested.[5] In particular, alteration of the hepatic cytochrome P (CYP) 450 system was the subject of recent studies investigating changes in drug metabolism in TTM patients.[6] Combined with acetylsalicylic acid the most widely used specific antagonist of the platelet P_2Y_{12} adenosine diphosphate (ADP) receptor is clopidogrel. Clopidogrel

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Table 1
Patient characteristics.

	TTM ($n = 15$)	Control ($n = 18$)	p-Value
Age (years)	65.3 ± 10.7	71.2 ± 15.0	n.s.
Male gender, *n* (%)	13 (87)	14 (78)	n.s.
Hypertension, *n* (%)	12 (80)	16 (89)	n.s.
Diabetes, *n* (%)	5 (33)	7 (39)	n.s.
Hypercholesterolemia, *n* (%)	5 (33)	8 (44)	n.s.
Active smoker, *n* (%)	3 (20)	6 (33)	n.s.
BMI (kg/m^2)	26.6 ± 3.2	28.1 ± 5.9	n.s.
CPR, *n* (%)	15 (100)	0 (0)	
STEMI, *n* (%)	8 (53)	2 (11)	0.040
Cardiogenic shock, *n* (%)	3 (20)	0 (0)	n.s.
LVEF (%)	43.7 ± 13.7	58.6 ± 9.6	0.001
Triple-vessel disease, *n* (%)	8 (53)	9 (50)	n.s.
No. of stents	1.7 ± 1.0	2.0 ± 1.1	n.s.
Min 1 DES, *n* (%)	14 (93)[a]	18 (100)	n.s.
Time loading to PCI (h)	−0.7 ± 0.8	17.7 ± 44.5	<0.001
Time 75 mg MD to 4th blood sample (h)	9.9 ± 5.3	6.9 ± 2.8	n.s.
Troponin (ng/ml)	0.8 ± 1.0	1.0 ± 2.1	n.s.
CK-MB (U/l)	224.0 ± 225.2	41.6 ± 37.3	<0.001
GPT (U/l)	143.5 ± 115.0	31.1 ± 11.4	<0.001
GGT (U/l)	139.2 ± 117.6	57.7 ± 65.8	0.002
Platelet number (/nl)	221.0 ± 77.1	226.2 ± 54.6	n.s.
Creatinine (mg/dl)	1.4 ± 0.3	1.2 ± 0.4	0.012
ASA, *n* (%)	7 (47)	10 (56)	n.s.
rt-PA lysis	1 (7)	0 (0)	
PPI	4 (27)	4 (22)	n.s.
CYP2C19*1/*1, *n* (%)	11 (73)	14 (78)	
CYP2C19*1/*2, *n* (%)	4 (27)	4 (22)	n.s.
CYP2C19*2/*2, *n* (%)	0 (0)	0 (0)	

TTM, target temperature management; BMI, body mass index; CPR, cardiopulmonary resuscitation; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; DES, drug eluting stent; PCI, percutaneous coronary intervention; MD, maintenance dose; CK-MB, creatine kinase-MB; GPT, glutamate pyruvate transaminase; GGT, Gamma-glutamyl transpeptidase; ASA, acetylsalicylic acid; PPI, proton pump inhibitor.

[a] One patient was treated with a drug-eluting balloon.

is a pro-drug from the thienopyridine group whose antithrombotic action after intestinal absorption is determined by its biotransformation to an active thiol metabolite through a two-step hepatic pathway involving cytochrome P450 isoenzymes.[7] Among these isoenzymes CYP2C19 has been shown to contribute toward an estimated 45% of the initial and about 20% of the final pro-drug activation. Beside well reviewed polymorphisms of the CYP2C19 isoenzyme[8] several other factors such as hypothermia related decreased CYP450 enzyme function, diminished drug absorption due to reduced gastrointestinal motility, altered binding properties at the site of the platelet P_2Y_{12} receptor and concomitantly administered drugs might contribute to increased residual platelet reactivity in post-cardiac-arrest patients treated with TTM and clopidogrel. For this purpose this study aims at investigating clopidogrel pharmacokinetics and pharmacodynamics in resuscitated patients with ACS scheduled for PCI and treated with TTM compared with ACS patients without preceding cardiac arrest.

Methods

Study design

A total of 33 consecutive patients with the diagnosis of troponin-positive ACS (NSTEMI or STEMI) were included in this prospective, non-randomized multicenter study. Three centers in Berlin (Germany) enrolled patients from December 2012 to August 2014. The study complied with the Declaration of Helsinki, the protocol was approved by the Institutional Ethics Committee (no. EA2/129/10), and informed consent was obtained from all participants or their legal representatives. For post-cardiac-arrest patients a healthcare proxy was contacted to give written informed consent as all cardiac arrest survivors were unconscious on admission.

All patients enrolled were clopidogrel naïve for at least 4 weeks, scheduled for coronary angiography and received a loading dose (LD) of 600 mg clopidogrel followed by a 75 mg/day maintenance dose. Patients who underwent cardiopulmonary resuscitation (CPR) of presumed cardiac cause followed by endotracheal intubation, mechanical ventilation and deep analgosedation were included in the TTM arm. According to the local hospital standard protocol all CA patients received TTM as described in detail elsewhere.[9] Hemodynamically stable and conscious ACS patients served as control group. Patients' baseline characteristics are listed in Table 1.

Blood samples for platelet function testing (pharmacodynamic analysis) and determination of clopidogrel and its metabolites (pharmacokinetic analysis) were taken before administration of a 600 mg loading dose (LD) clopidogrel and 2, 4 and 24 h following LD.

Exclusion criteria were: inflammatory, infectious or malignant diseases, administration of GPIIbIIIa inhibitors, chronic treatment with anti-inflammatory drugs (except 100 mg acetyl salicylic acid), treatment with strong CYP2C19 inhibitors (e.g. ciprofloxacin, carbamazepine, fluconazole), platelet count <100,000 μl^{-1}, active bleeding or increased risk for bleeding and history of alcohol or drug abuse. A study flow chart is shown in Fig. 1.

Pharmacodynamic analyses

Platelet function testing was performed by multiple electrode platelet aggregometry (MEA), light transmittance aggregometry (LTA) and vasodilator-stimulated phosphoprotein (VASP) phosphorylation analysis. For LTA and VASP analysis blood was drawn into tubes containing 3.8% trisodium citrate (Monovette, Sarstedt, Nümbrecht, Germany), for MEA tubes containing hirudin