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Morphine Decreases Clopidogrel Concentrations and Effects

A Randomized, Double-Blind, Placebo-Controlled Trial

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Objectives This study sought to examine the possible drug–drug interactions between clopidogrel and morphine.

Background Because morphine—the recommended treatment for pain of myocardial infarction—is associated with poor clinical outcome, we hypothesized that morphine lowers the plasma levels of clopidogrel active metabolite as well as its effects on platelets.

Methods Twenty-four healthy subjects received a loading dose of 600 mg clopidogrel together with placebo or 5 mg morphine intravenously in a randomized, double-blind, placebo-controlled, cross-over trial. Pharmacokinetics was determined by liquid chromatography tandem mass spectrometry, and clopidogrel effects were measured by platelet function tests.

Results Morphine injection delayed clopidogrel absorption ($p = 0.025$) and reduced the area under the curve levels of its active metabolite by 34% ($p = 0.001$). Morphine delayed the maximal inhibition of platelet aggregation on average by 2 h ($n = 24$; $p < 0.001$). Residual platelet aggregation was higher 1 to 4 h after morphine injection ($n = 24$; $p < 0.005$). Furthermore, morphine delayed the inhibition of platelet plug formation under high shear rates (P2Y-Innovance; $n = 21$; $p < 0.004$) and abolished the 3-fold prolongation in collagen adenosine diphosphate-induced closure times seen in extensive and rapid metabolizers ($n = 16$; $p = 0.001$).

Conclusions Morphine delays clopidogrel absorption, decreases plasma levels of clopidogrel active metabolite, and retards and diminishes its effects, which can lead to treatment failure in susceptible individuals. (Drug Drug Interactions of Aspirin and P2Y12-inhibitors; NCT01369186) (J Am Coll Cardiol 2014;63:630–5) © 2014 by the American College of Cardiology Foundation

The $P2Y_{12}$-receptor inhibitor clopidogrel blocks adenosine-diphosphate (ADP)-induced platelet function in vivo, and combination of $P2Y_{12}$-inhibitors with aspirin has become a mainstay for the treatment of patients with acute coronary syndromes (1,2).

Clopidogrel is a pro-drug that requires metabolic activation by cytochrome P450 enzymes in 2 steps (3), explaining its relatively slow onset of action.

Although morphine is recommended for pain relief in myocardial infarction (MI) (1), data for its net benefit from randomized controlled trials are lacking. Interestingly, the use of morphine is associated with higher mortality in patients with non–ST-segment elevation acute coronary syndromes (4) and with delayed activity of prasugrel or ticagrelor in ST-segment elevation MI patients (5). Although this is not a causal proof, there might be a biologically plausible cause–effect relationship: opiates inhibit gastric emptying, which delays absorption and might decrease peak plasma levels of oral drugs (6).

Hence, we hypothesized that morphine lowers the plasma levels of clopidogrel active metabolite as well as its antiplatelet effects and examined drug–drug interactions between morphine and clopidogrel.

Methods

Experimental design and blood collection. A double-blind, block-randomized, placebo-controlled, cross-over trial was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki to evaluate the effect of morphine on the intestinal absorption,

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pharmacokinetics, and pharmacodynamics of clopidogrel. The study was approved by the Ethics Committee of the Medical University of Vienna and the Austrian National Competent Authority; written informed consent was obtained from all healthy subjects (n = 24).

Key inclusion criteria were: ≥18 years of age; non-pregnant; and ability to comprehend the full nature and purpose of the study. Key exclusion criteria were: intake of non-steroidal anti-inflammatory drugs or platelet inhibitors; known coagulation disorders; relevant impairment of renal or hepatic function; chronic infectious diseases (human immunodeficiency virus, hepatitis B and C); clinically relevant abnormal laboratory values; and contraindications for clopidogrel or morphine.

Secretaries conducted randomization by using www.randomization.com, and prepared individually sealed opaque envelopes. Morphine (5 mg intravenous bolus; Vendal, G.L. Pharma, Lannach, Austria) or placebo (0.9% sodium chloride) was prepared by unblinded pharmacists and injected by blinded physicians. A minimum wash-out period of 14 days was chosen, because it exceeds platelet survival in vivo and because the effect of $P2Y_{12}$-inhibition diminishes within 5 days (7) (Fig. 1).

After an overnight fast, a loading dose of 600 mg clopidogrel (Plavix, Sanofi-Aventis, Vienna, Austria) was administered with 250 ml tap water immediately after the injection of placebo or morphine. No food, drink, or tobacco was permitted for 4 h.

Blood sampling times for pharmacodynamic and pharmacokinetic evaluations after study drug administration are depicted in Figures 2 to 4. Blood was collected with an intravenous catheter after drawing a waste sample. The analysts were also blinded with regard to the sequence of periods.

Abbreviations and Acronyms

ADP = adenosine-diphosphate
AUC = area under the curve
CADP-CT = collagen/ADP induced closure times
MI = myocardial infarction
VASP = vasodilator-stimulated-phosphoprotein

Assessment of pharmacokinetics and pharmacodynamics. Clopidogrel effects were measured with the following assays: the vasodilator-stimulated-phosphoprotein (VASP) phosphorylation assay (8); multiple electrode aggregometry (9); where the intercept of the individual downslope and the plateau phase was plotted graphically for the area under the curve (AUC) to estimate the onset of the maximum effect; and the platelet function analyzer under high shear rates (10), where the onset of the maximum effect was defined as the first of 3 consecutive measurements of >300 s. Pharmacokinetics were assessed by liquid chromatography tandem mass spectrometry (11), and subjects were genotyped as described previously (12) for CYP2C9 and CYP2C19 polymorphisms for exploratory reasons only, to allow comparisons of the effect size of morphine with genetic determinants of clopidogrel pharmacokinetics.

Statistical analysis. Pharmacokinetic calculations were made with Kinetica 2000 (version 3.0, InnaPhase Corporation, Philadelphia, Pennsylvania). The primary pharmacokinetic outcome variable was the AUC of clopidogrel active metabolite, as usual for drug interaction studies; all other comparisons were considered secondary.

Data are presented as means for demographic data and medians for outcome variables in the text. Changes in

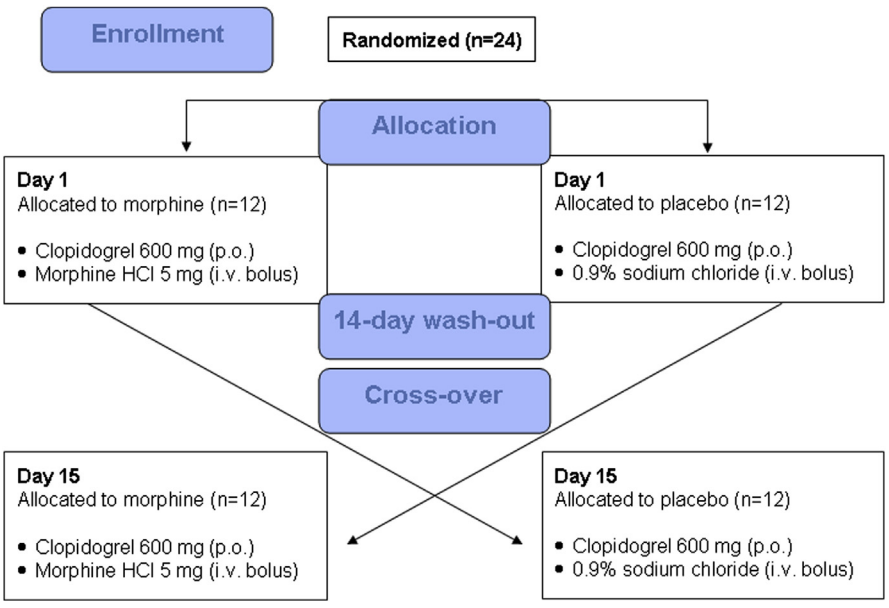

Figure 1 Schematic of Trial Design

HCl = hydrogen chloride.