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
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 P2Y12-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. 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.
all outcome variables were compared by nonparametric Wilcoxon signed rank tests, accounting for the skewed distributions of the measurements. To assess the robustness of results, for the outcome variables showing a significant effect in these analyses, a mixed-model was additionally fitted to test for period and carry-over effects.

The Mann-Whitney U test was used for an exploratory comparison between individuals with different metabolizer status. Statistical calculations were performed with commercially available software (IBM SPSS Statistics, Version 20, IBM, Chicago, Illinois) and SAS (version 9.3, SAS, Cary, North Carolina). In all cases, 2-sided p values ≤0.05 were considered significant.

Results

Demographic characteristics of subjects and adverse events. Healthy volunteers (17 men, 7 women) were 32 ± 9 years of age, had 75 ± 11 kg, and a body mass index of 24 ± 3 kg/m².

Morphine injection caused mild to moderate adverse events in 50% of subjects, including flush (42%), pressure on the chest (25%), nausea (25%), fatigue (17%), headache (8%), and xerostomia (8%).

Pharmacokinetics. Morphine injection delayed maximal plasma concentrations of clopidogrel (T\text{max}: 105 vs. 83 min, p = 0.025) (Table 1) and reduced both the C\text{max} of clopidogrel active metabolite (from 171 to 113 ng/ml, p = 0.025) (Fig. 2) and the total exposure as measured by the AUC\text{0-\infty} by 34% (16,840 vs. 11,103 ng h/ml, p = 0.001).

Pharmacodynamics. Co-administration of morphine delayed the time required to maximally inhibit platelet aggregation 2-fold (3 vs. 1.25 h, p < 0.001) and, in some cases, even up to 5 h. Residual platelet aggregation was higher 1 to 4 h after morphine injection (p < 0.005) (n = 24).

Morphine also delayed the inhibition of platelet plug formation under high shear rates (the median IC100 was observed 75 vs. 45 min with the P2Y-Innovance cartridge: p < 0.004) (Fig. 3) (n = 21). Clopidogrel intake prolonged the conventional collagen/ADP induced closure times.
(CADP-CT) 6 h after intake from a median of 110 to 162 s (p < 0.01) under placebo but not when morphine was co-administered (105 to 106 s, p = 0.97) (n = 23; p = 0.012 between treatments).

Clopidogrel reduced the median platelet reactivity index in the VASP phosphorylation assay from a median of 81% to 41% (p = 0.008; n = 10) and trend-wise less after morphine (87% vs. 59%, p = 0.004; p = 0.30 between treatments) (Fig. 4).

All significant differences between treatments were confirmed in the mixed-model analysis accounting for carry-over and period effects. No significant carry-over and period effects were observed for any of the outcome parameters except for the 90-min time point in the P2Y-assay (p = 0.04) and the change in CADP-CT (p = 0.024), which are expected due to multiple comparisons.

**Genetic polymorphisms.** Subjects with normal and impaired clopidogrel metabolism were compared in an exploratory fashion (Table 2). Median values of Cmax and AUC of clopidogrel active metabolite decreased in the following order: rapid > extensive > intermediate > poor metabolizers. Morphine causes a “poor metabolizer phenotype” in individuals genetically prone to extensively metabolize clopidogrel (Fig. 2).

Clopidogrel increased the median CADP-CT from 108 to 241 s (p = 0.001) in extensive or rapid metabolizers (n = 16) but failed to prolong CADP-CT in intermediate or poor metabolizers (n = 8; 118 to 109 s; p = 0.812; p = 0.035 between groups). In contrast, almost all subjects reached the maximum closure time with the P2Y-cartridge. The only exception was a poor metabolizer in the morphine period.

**Discussion**

This trial identified a novel and potentially relevant drug–drug interaction: morphine slows clopidogrel absorption,

**Table 1** Pharmacokinetic Parameters of Clopidogrel and Its Active Metabolite After a Loading Dose of 600 mg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clopidogrel</th>
<th>p Value</th>
<th>Clopidogrel Active Metabolite</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>5 (2–14)</td>
<td>5 (2–12)</td>
<td>0.753</td>
<td>171 (116–215)</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>83 (68–105)</td>
<td>105 (60–180)</td>
<td>0.025</td>
<td>60 (45–75)</td>
</tr>
<tr>
<td>AUCmax (ng x h/ml)</td>
<td>662 (409–1,467)</td>
<td>704 (333–1,743)</td>
<td>1.000</td>
<td>16,840 (11,719–21,543)</td>
</tr>
</tbody>
</table>

Values are median (interquartile range); n = 24.

AUC – area under the curve.
decreases plasma levels of its active metabolite, and retards and diminishes clopidogrel effects.

The pharmacokinetics in the placebo period was consistent with a 600-mg loading dose, whereas morphine reduced the gastrointestinal absorption of clopidogrel and caused a pharmacokinetic profile similar to a 300-mg loading dose (11). This indicates the comparability of the enrolled population with previous trials and supports the external validity of the trial.

Morphine retarded the absorption of clopidogrel (increased T\text{max}), consequently led to low initial concentrations of its active metabolite, and thereby delayed the pharmacodynamic response on average by 2 h. The residual platelet reactivity was significantly higher after morphine injection. The importance of rapid platelet inhibition in the setting of MI is perhaps best demonstrated by the early reduction of primary outcome events within the first hours by prasugrel versus clopidogrel (13).

Levels of the active metabolite were 2- to 4-fold higher 30 to 90 min after placebo compared with morphine injection, which resulted in higher exposure; this is also reflected by the different platelet function tests (Fig. 3). The lower active metabolite concentrations after morphine correspond to a reduction of the loading dose from 600 to 300 mg (14), which might lead to higher rates of major adverse coronary events, including MI and death (15). Morphine reduced the levels of the active metabolite to concentrations usually observed in intermediate or poor metabolizers (Fig. 2), who are prone to poor clinical outcome (16). Hence, we consider the reduction of the active metabolite to be clinically relevant.

What are possible consequences of our trial? Co-administration of morphine and clopidogrel should likely be avoided, if possible. More potent P2Y\textsubscript{12}-inhibitors might provide greater efficacy when morphine is injected, but their interaction with morphine should be evaluated in further trials.

**Study limitations.** Limitations of the trial include that the VASP phosphorylation assay was only performed in a subset of subjects, because the method was added when the trial was already ongoing and therefore does not allow further subgroup analysis. Also, the trial was not powered to measure differences in effects between different metabolizers. Additionally, the trial was not designed to characterize the well-known half-life or pharmacodynamics for 24 h. However, aggregometry data indicate that differences diminish after 4 h. We observed clopidogrel concentrations and effects for 6 h only, because morphine is injected to treat acute pain due to myocardial necrosis, and because the full effects of a 600-mg loading dose are usually seen within 2 h (17). Finally, the cross-over design required investigation of healthy volunteers rather than ST-segment elevation MI patients, whose gastrointestinal absorption might be further compromised (e.g., by reduced splanchnic blood flow) (18).

**Conclusions**

Concomitant injection of morphine slows clopidogrel absorption, decreases plasma levels of its active metabolite, and retards and diminishes its effects.

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**REFERENCES**


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