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Morphine Interaction with Aspirin: a Double-Blind, Crossover Trial in Healthy Volunteers

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ABSTRACT

Aspirin is a cornerstone in the antiplatelet therapy for acute coronary syndromes. Coadministration of morphine may potentially influence the intestinal absorption, pharmacokinetics, and pharmacodynamics, as seen with $P2Y_{12}$ inhibitors. In this trial, healthy volunteers were randomized to receive morphine (5 mg, i.v. bolus injection) at one of seven different time points before, after, or with aspirin (162 mg, p.o.) in a double-blind, placebo-controlled fashion. After a 14-day washout, subjects received placebo instead of morphine. Pharmacokinetics were determined by liquid chromatography, and aspirin's effects were measured by platelet function tests (whole-blood platelet aggregation: multiplate, platelet plug formation: PFA-100). Morphine increased the total acetylsalicylic acid exposure by 20% compared with placebo when given simultaneously with aspirin, whereas C_{max} and t_{max} were not altered. Morphine had no significant effect on aspirin-induced platelet inhibition. In contrast to coadministration with $P2Y_{12}$ inhibitors, morphine appears to have negligible interaction with aspirin.

Introduction

For more than half a century, morphine has been used for pain relief in the clinical management of myocardial infarction (Bruce and Bing, 1965). Morphine has long been recommended as the drug of choice for chest pain relief in patients with ST-elevation myocardial infarction (Amsterdam et al., 2014) and in patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) refractory to anti-ischemic medication (O'Gara et al., 2013). The rationale of use is based on the strong analgesic-anxiolytic effects and on a veno-dilatational component, thereby reducing heart rate and systolic blood pressure (McCarthy et al., 2016); however, observational studies have challenged the concept that the clinical benefit of morphine outweighs its risks (Meine et al., 2005; de Waha et al., 2015). In a retrospective data analysis of the CRUSADE National Quality Improvement Initiative, morphine use was associated with a higher mortality in 57,039 patients with NSTE ACS (Meine et al., 2005). More recently, a large retrospective study showed that morphine was associated with a longer hospital stay and a larger infarct size in invasively managed NSTE-ACS patients (McCarthy et al., 2017). Since morphine has never been tested in a randomized controlled trial (Parodi, 2016), it is not known whether morphine administration in patients with acute coronary syndromes improves clinical outcome.

With the advent of new therapies, combination of several drugs increases the chance of drug-drug interaction. Morphine and fentanyl can decrease plasma levels and/or antiplatelet effects of oral $P2Y_{12}$ receptor antagonists (Hobl et al., 2014, 2016a,b; Kubica et al., 2016a; McEvoy et al., 2018), which may be explained by an impaired drug absorption, probably as a consequence of delayed gastric emptying, as shown for acetaminophen (Nimmo et al., 1975). This delayed effect may be overcome by intravenous infusion of platelet inhibitors such as abciximab (Siller-Matula et al., 2016) or cangrelor (Bhatt et al., 2013). Although infusion of aspirin rapidly inhibits platelets in patients with myocardial infarction (Fuchs et al., 2010), chewable aspirin is currently recommended in guidelines (Amsterdam et al., 2014). Given that approximately one third of patients with acute coronary syndrome receive intravenous morphine simultaneously with aspirin, it is clinically relevant whether morphine also affects the pharmacokinetics (PK) and pharmacodynamics (PD) of aspirin. We hypothesized that morphine may alter the plasma levels of aspirin and therefore its antiplatelet activity. A randomized, crossover trial in healthy volunteers was performed to investigate the effect of morphine on the PK and PD of aspirin.

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ABBREVIATIONS: AA, arachidonic acid; ASA, acetylsalicylic acid; AUC, area under the concentration-time curve; CEPI, collagen/epinephrine; CEPI-CTs, collagen-/epinephrine-induced closure time; CT, closure time; MEA, multiple electrode aggregometry; NSTE-ACS, non-ST-elevation acute coronary syndromes; PD, pharmacodynamics; PK, pharmacokinetics; SA, salicylic acid; t_{max}, time to reach maximum concentration.

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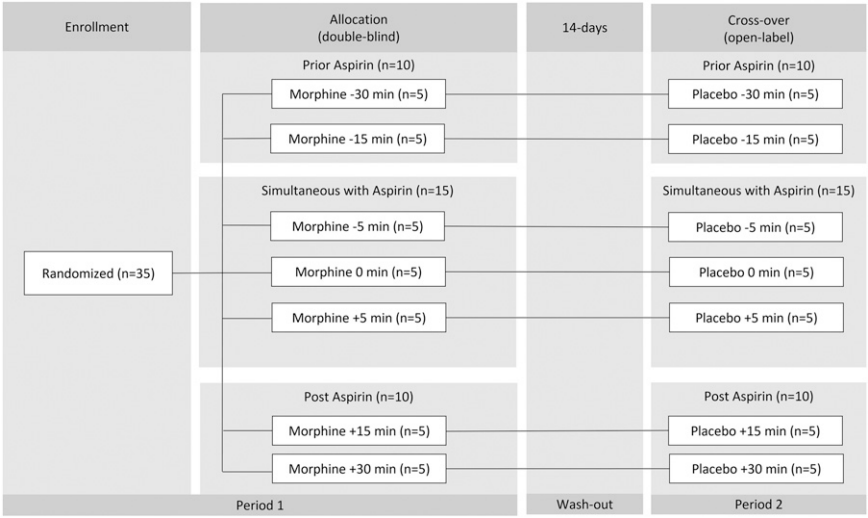

Fig. 1. Schematic of the trial design. To define the optimal time for morphine administration, subjects were randomized to receive 5 mg of i.v. morphine at one of seven different time points coadministered with 162 mg of aspirin. As predefined, within-subjects comparisons between periods were performed for pooled times of morphine injection relative to aspirin: prior [−30, −15 minutes]; simultaneous [−5, 0, +5 minutes]; post [+15, +30 minutes].

Materials and Methods

The trial was conducted at the Department of Clinical Pharmacology, Medical University of Vienna, in accordance with the Declaration of Helsinki and International Conference on Harmonization – Good Clinical Practice (ICH-GCP) (registered at clinicaltrials.gov as NCT01369186). The subjects gave written informed consent before enrollment. After an overnight fast, subjects were randomized to receive a 5-mg i.v. bolus injection of morphine (G.L. Pharma GmbH, Lannach, Austria) at one of seven different time points in the range of 30 minutes before to 30 minutes after chewing 162 mg of enteric coated aspirin (two tablets of 81-mg chewable low-dose "baby" aspirin; Bayer HealthCare, Morristown, NJ). Block randomization was performed by using the open access randomization generator www.randomization.com.

Subjects. Healthy female and male subjects aged ≥18 years were eligible for enrollment. Subjects had to stop any intake of nonsteroidal antirheumatic drugs, including aspirin and $P2Y_{12}$ inhibitors 14 days before study entry.

Trial Design. A randomized, double-blind, and placebo-controlled trial followed by an open-label, fixed-sequence, two-period crossover was conducted in 35 healthy subjects to evaluate the potential effect of morphine (5 mg i.v. bolus injection) on intestinal absorption, PK, and PD of aspirin.

To define the optimal time for morphine administration, subjects were randomized to receive morphine at one of seven different time points in the range of 30 minutes before to 30 minutes after the administration of 162 mg of aspirin. Each group included five subjects (Fig. 1). When the seven different times of morphine administration were compared, no differences in the PK and PD of aspirin between morphine and placebo were found (data not shown). As predefined in the study protocol, the times of morphine injection relative to aspirin were pooled [prior (−30, −15 minutes), simultaneous (−5, 0, +5 minutes), "post" (+15, +30 minutes)] and compared with placebo. PK profiles and PD response were monitored 30 and 0 minutes before and 5, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 360 minutes after oral administration of aspirin during period 1 (morphine) and period 2 (placebo).

Pharmacokinetics. Acetylsalicylic acid (ASA) and salicylic acid (SA) were analyzed by high-performance liquid chromatography as previously described (Hobl et al., 2013). PK variables included the maximum plasma concentration (C_{max}), half-life ($t_{1/2}$), time to reach maximum concentration (t_{max}), area under the concentration-time curve (AUC) from time zero extrapolated to infinity ($AUC_{0-\infty}$) and were derived from plasma ASA and SA concentrations by a non-compartmental analysis using Kinetica 2000, version 3.0 (InnaPhase Corporation, Philadelphia, PA).

Pharmacodynamics. Multiple electrode aggregometry (MEA) (Multiple Platelet Function Analyzer/Multiplate Analyzer; Dynabyte Medical, Munich, Germany) was used to measure inhibition of arachidonic acid (AA) (0.5 nM) induced platelet aggregation (Spiel et al., 2011). MEA data are expressed in arbitrary units (U). Sufficient platelet inhibition was defined by a value of ≤30 U (Spiel et al., 2011; Jakl et al., 2017). Platelet function under high shear rates was measured by the Platelet Function Analyzer-100 system (PFA-100; Siemens Healthcare Diagnostics, Vienna, Austria) using collagen/epinephrine (CEPI) cartridges. Time to formation of a platelet plug (CT, closure times) is expressed in seconds.

Sample Size and Statistical Analysis. Since there was no estimate for the size of the effect (intraindividual differences between periods), it was assumed to be comparable to acetaminophen. In healthy volunteers, the t_{max} of acetaminophen was observed at 22 ± 9 [S.D.] minutes under control conditions and after 114 ± 72 [S.D.] minutes when pethidine was administered before acetaminophen intake. In this study, four subjects were sufficient to demonstrate the negative effect of opiates (Nimmo et al., 1975). To check the assay sensitivity of our experimental model, eight volunteers with the randomization numbers >14 received 1000 mg of acetaminophen in addition to 162 mg aspirin on both occasions.

Data are presented as means for demographic data and medians for outcome variables in the text and descriptively, as appropriate. Outcome variables were compared with the Wilcoxon test.

Results

Demographic Characteristics of Subjects and Adverse Events

Healthy volunteers (10 women, 25 men) were 31 ± 9 years of age, weighed 77 ± 14 kg, and had a body mass index of 24 ± 3 kg/m^2. Morphine injection caused mild to moderate adverse events in 43% of subjects, including head pressure (14%), prickling (11%), and flushing (6%). No adverse effects involving the gastrointestinal tract (e.g., vomiting, nausea) and no clinical signs of an opioid-induced direct histamine release (hemodynamic changes or anaphylactoid reactions) were seen.

Pharmacokinetics

Aspirin. Morphine increased the total ASA exposure (AUC) by ∼20% (median, $P = 0.0084$) when administered simultaneously with aspirin compared with placebo (Fig. 2;

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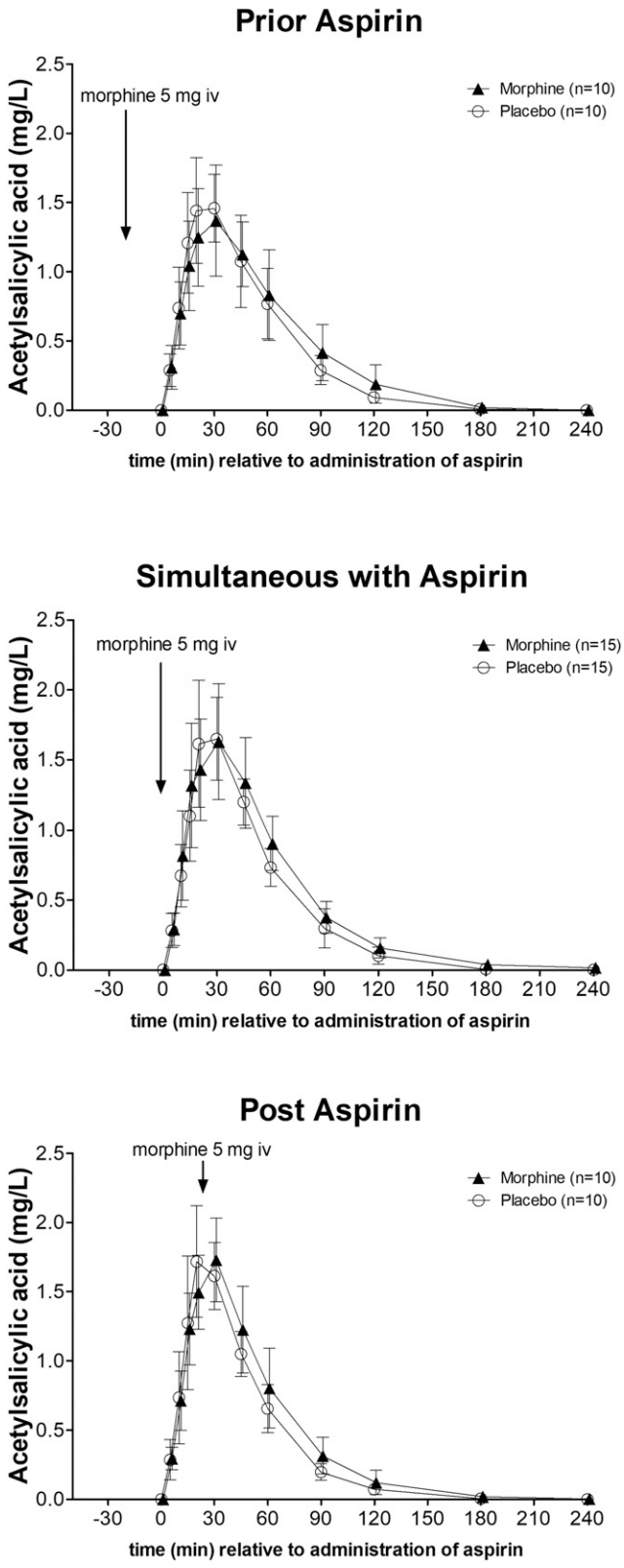

Fig. 2. Morphine interaction with aspirin. Morphine increased total ASA exposure (AUC) by ~20% ($P < 0.01$) when administered simultaneously with aspirin compared with placebo. Healthy subjects received 5 mg of morphine (i.v.) or placebo before (−30, −15 minutes, $n = 10$), simultaneously (−5, 0, +5 minutes, $n = 15$), or post (+15, +30 minutes, $n = 10$) 162 mg of aspirin (p.o.). Data present means (95% CI).

Table 1). No significant differences were detected when morphine was given before or after aspirin. Morphine had no significant effect on C_{max} and t_{max} of ASA or on the PK of salicylic acid (Table 1).

Acetaminophen. Morphine increased the t_{max} 2.3-fold and decreased the C_{max} by 27% compared with placebo (Table 1). Morphine had no significant effect on the total acetaminophen exposure (AUC) (Table 1).

Pharmacodynamics

PFA-100. Baseline (−30 minutes) CEPI closure times (CTs) correlated well between period 1 (morphine) and period 2 (placebo) (median: 171 seconds vs. 176 seconds; Spearman $r = 0.68$, $P < 0.0001$). Morphine (period 1 vs. period 2) and its time of infusion (before vs. simultaneous to vs. after aspirin; period 1) had no significant effect on CEPI-CTs compared with placebo (Fig. 3). Aspirin, coadministered with morphine, increased CEPI-CTs by 46% 20 minutes after administration. Similarly, CEPI-CTs increased by 57% with placebo. Maximal platelet inhibition (i.e., CEPI-CTs >301 seconds) occurred in 27 subjects (77%) receiving morphine and in 31 subjects (86%) receiving placebo within 20 minutes. All subjects receiving placebo and 33 subjects (94%) receiving morphine reached maximal platelet inhibition within 60 minutes after aspirin intake.

Multiple Electrode Aggregometry. Baseline values (−30 minutes) of AA-induced platelet aggregation correlated moderately between period 1 (morphine) and period 2 (placebo) (median: 79 U vs. 83 U; Spearman $r = 0.47$, $P = 0.0042$). Morphine and its time of administration had no significant effect on AA-induced platelet aggregation compared with placebo (Fig. 4). Aspirin, coadministered with morphine, decreased AA-induced platelet aggregation by 69% 20 minutes after administration. Equal in size, AA-induced platelet aggregation decreased by 69% with placebo. Sufficient platelet inhibition (i.e., AUC ≤30 U) occurred (within 20 minutes) in 24 subjects (69%) receiving morphine and in 24 subjects (69%) receiving placebo. Nearly all subjects reached sufficient platelet inhibition within 30 minutes of aspirin administration (placebo: 32/35; morphine: 31/35).

Discussion

The use of aspirin reduces mortality in patients with acute coronary syndrome. Current guidelines recommend chewed ingestion without any delay (Amsterdam et al., 2014). Although there is growing evidence that morphine slows intestinal absorption of oral $P2Y_{12}$ inhibitors, no studies have investigated whether morphine interacts with aspirin. In this study, we investigated the effect of morphine on the PK and PD of aspirin in healthy volunteers. Studies from the mid-1970s demonstrated that opiates inhibit gastric emptying and retard the absorption of orally administered drugs. In healthy volunteers, intramuscular injection of 10 mg of diamorphine (which is twice as potent as morphine) increased the t_{max} of acetaminophen 6.5-fold (Nimmo et al., 1975). Considering that our subjects received 5 mg of morphine (~4-fold lower potency than 10 mg of diamorphine), we observed a comparable 2.3-fold increase in t_{max} in our proof-of-concept study. Other experimental studies, in which the acetaminophen absorption test was used, reported

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TABLE 1
Summary statistics for aspirin pharmacokinetic parameters by treatment time point and acetaminophen (internal control)
Values are represented as median (interquartile range).

	Period 1 (Morphine, 5 mg i.v. Bolus Injection)				Period 2 (Placebo)		
ASA	N	C_{max} (mg/liter)	t_{max} (min)	$AUC_{0-\infty}$ (mg•h/liter)	C_{max} (mg/liter)	t_{max} (min)	$AUC_{0-\infty}$ (mg•h/liter)
Prior aspirin (−30, −15 min)	10	1.5 (1.1–2.0)	30 (28–45)	90 (70–103)	1.8 (1.4–1.9)	30 (20–30)	84 (60–103)
Simultaneous with aspirin (−5, 0, +5 min)	15	1.6 (1.4–2.5)	30 (20–30)	100 (92–120)**	1.6 (1.4–2.0)	30 (20–30)	79 (67–98)
Post aspirin (+15, +30 min)	10	1.8 (1.5–2.1)	25 (20–30)	90 (67–123)	1.9 (1.4–2.3)	20 (20–30)	82 (72–92)
Pooled (−30, −15, −5, 0, +5, +15, +30 min)	35	1.8 (1.4–2.1)	30 (20–30)	98 (73–118)***	1.7 (1.4–1.9)	30 (20–30)	82 (67–94)
Salicylic acid							
Prior aspirin (−30, −15 min)	10	6.6 (5.3–8.4)	90 (60–98)	1682 (1214–2161)	7.2 (5.9–8.6)	90 (56–90)	1863 (1388–1923)
Simultaneous with aspirin (−5, 0, +5 min)	15	6.7 (6.1–9.0)	60 (60–90)	1793 (1429–2478)	7.6 (6.7–8.4)	60 (60–60)	1590 (1378–1958)
Post aspirin (+15, +30 min)	10	7.0 (6.6–9.0)	60 (45–90)	1557 (1373–2451)	7.1 (6.6–9.1)	60 (60–90)	1455 (1397–2553)
Pooled (−30, −15, −5, 0, +5, +15, +30 min)	35	6.7 (6.1–8.3)	60 (60–90)	1700 (1408–2142)*	7.3 (6.5–8.4)	60 (60–90)	1532 (1395–1923)
Acetaminophen							
Prior aspirin (−30, −15 min)	4	13 (8–17)	90 (90–90)	253 (1790–4252)	15 (11–18)	45 (19–83)	2395 (1379–4020)
Simultaneous with aspirin (−5, 0, +5 min)	6	13 (6–14)*	105 (83–150)*	2957 (2713–3835)	17 (14–21)	45 (30–60)	3260 (2785–3482)
Post aspirin (+15, +30 min)	4	53 (23–285)	60 (45–90)	3461 (2853–4353)	53 (34–83)	60 (60–90)	2832 (1831–3975)
Pooled (−30, −15, −5, 0, +5, +15, +30 min)	35	13 (9–16)***	90 (60–120)**	3183 (1988–3482)	18 (14–20)	45 (30–60)	3158 (2708–3961)

AUC, area under the concentration–time curve; C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ vs. placebo.

similar results (Bennett et al., 1994; Yuan et al., 1998). Therefore, our experimental design achieved sufficient assay sensitivity to investigate drug-drug interactions with aspirin. Interestingly, morphine coadministration had no significant effect on aspirin-induced platelet inhibition and virtually no effect on the PK of aspirin. This was an unexpected finding because aspirin, like acetaminophen, is thought to be absorbed mainly by the small intestine (Schrör 2016).

Time to 50% gastric emptying after ingestion of 500–700 ml of technetium-99m labeled solution occurs on average after 12 minutes under physiologic conditions (Chaudhuri, 1974). In healthy volunteers receiving diamorphine, the mean time to 50% gastric emptying of ingested solution was >130 minutes compared with 11.9 minutes in the control group (Nimmo et al., 1975). Because morphine more than doubles the t_{max} of acetaminophen, one would expect a significant delay in reaching maximal plasma concentrations (delayed t_{max}) for aspirin as well; however, this was not the case, suggesting that the concept of the small intestine being the main compartment of aspirin absorption might have some shortcomings.

First, aspirin reached maximal plasma concentrations 15 minutes earlier than acetaminophen (30 minutes vs. 45 minutes, Mann-Whitney test, uncorrected P value 0.0308), indicating a different rate of absorption. Second, morphine did not change the time to peak exposure (t_{max}), showing that delayed gastric emptying was not the rate-limiting step in absorption. Third, sufficient platelet inhibition occurred within 15–20 minutes, whether morphine was given or not.

A study comprising healthy volunteers reported that ~30% of a 0.1 M HCl aspirin solution introduced into the stomach is absorbed by the gastric mucosa within 20 minutes (Hogben et al., 1957). Given that 50 mg of intravenous ASA already completely inhibits AA-induced platelet aggregation (Boger et al., 1993), it is likely that sufficient amounts of aspirin entered the presystemic circulation in our trial.

The antiplatelet effect of aspirin is mediated by the acetyl group of ASA (Roth and Majerus, 1975). Thus, ASA, and not its primary metabolite SA, irreversibly inhibits cyclooxygenase-1 in platelets. Mean ASA exposure and maximal ASA concentrations are ~10-fold higher in the gastric tissue compared with the proximal duodenum in rats (Lichtenberger et al., 2016). This indicates that the stomach mucosa is an effective site of absorption of the nonhydrolyzed, platelet-targeting form of aspirin.

Another important factor is that aspirin can cross the oral mucosa (Schrör, 2016; Mollace et al., 2017), albeit published data on buccal absorption are scarce. Given that ASA and SA were detectable as early as 5 minutes after intake in all the subjects, the oral mucosa was likely a site of absorption. This result is in line with a study in healthy volunteers, in which ASA was already present in plasma 3 minutes after chewing aspirin (Feldman and Cryer, 1999).

According to the ion-trapping hypothesis, aspirin, a weak acid, is available primarily as a unionized, lipid-soluble form at the pH of the gastric juice and therefore passes the gastric mucosa rapidly. The steep pH gradient between gastric mucosa and gastric juice prevents aspirin from back diffusion. Because aspirin's solubility depends on pH (poorly soluble under acidic conditions), however, the stomach is thought to absorb only a minor fraction of aspirin (Schrör, 2016). In our study, aspirin was chewed, and it appears plausible that the high basal pH (~7) of the salivary juice favored the dissolution of aspirin.

Another finding was that morphine increased the total ASA exposure (AUC) by ~20% when administered simultaneously with aspirin compared with placebo (Fig. 2; Table 1). Such a change is of limited consequence because a minimum of a 1.25-fold increase in the AUC is required to be labeled as a "minor" drug-drug interaction (Wiggins et al., 2016); however, visual investigation of the concentration-time profiles revealed that the descending limbs of the concentration-time curve were consistently higher, no matter whether morphine was given

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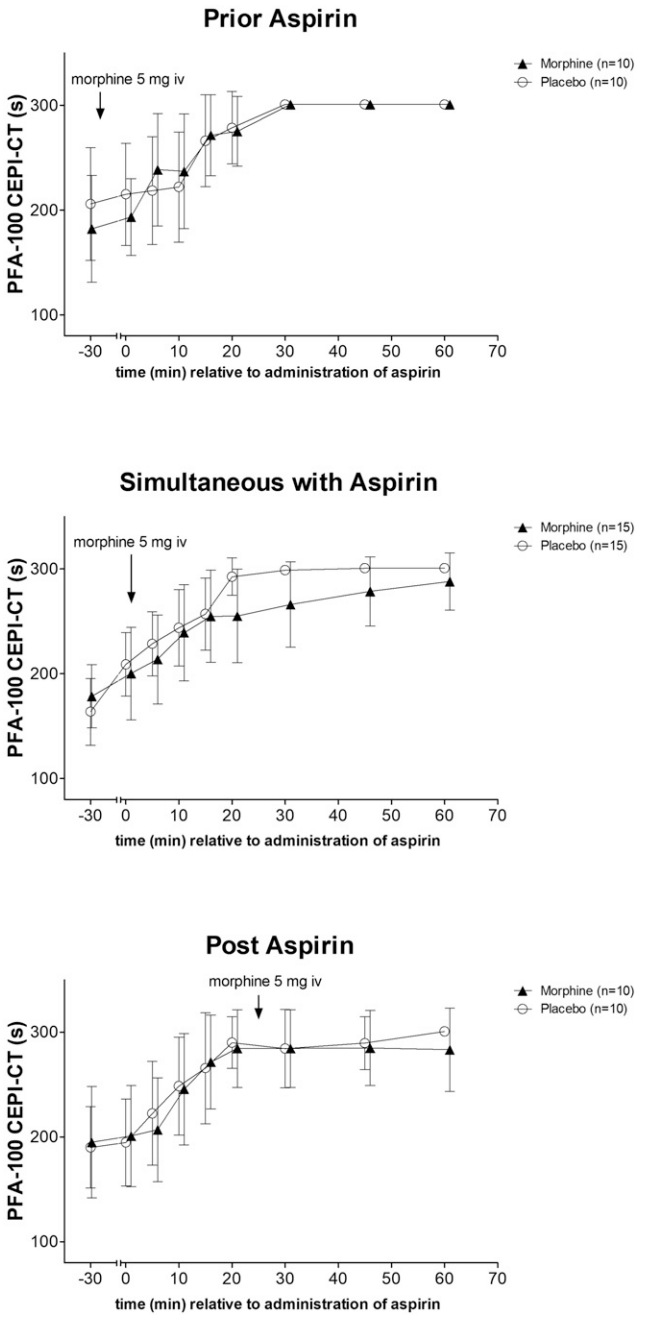

Fig. 3. Morphine interaction with aspirin. Morphine and its time of administration (prior vs. simultaneous vs. post aspirin) had no significant effect on CEPI-CTs compared with placebo. Healthy subjects received 5 mg of morphine (iv) or placebo before (−30, −15 minutes, n = 10), simultaneously (−5, 0, +5 minutes, n = 15), or post (+15, +30 minutes, n = 10) 162 mg of aspirin (p.o.). Data present means (95% CI). CEPI-CT, collagen-/epinephrine-induced closure time.

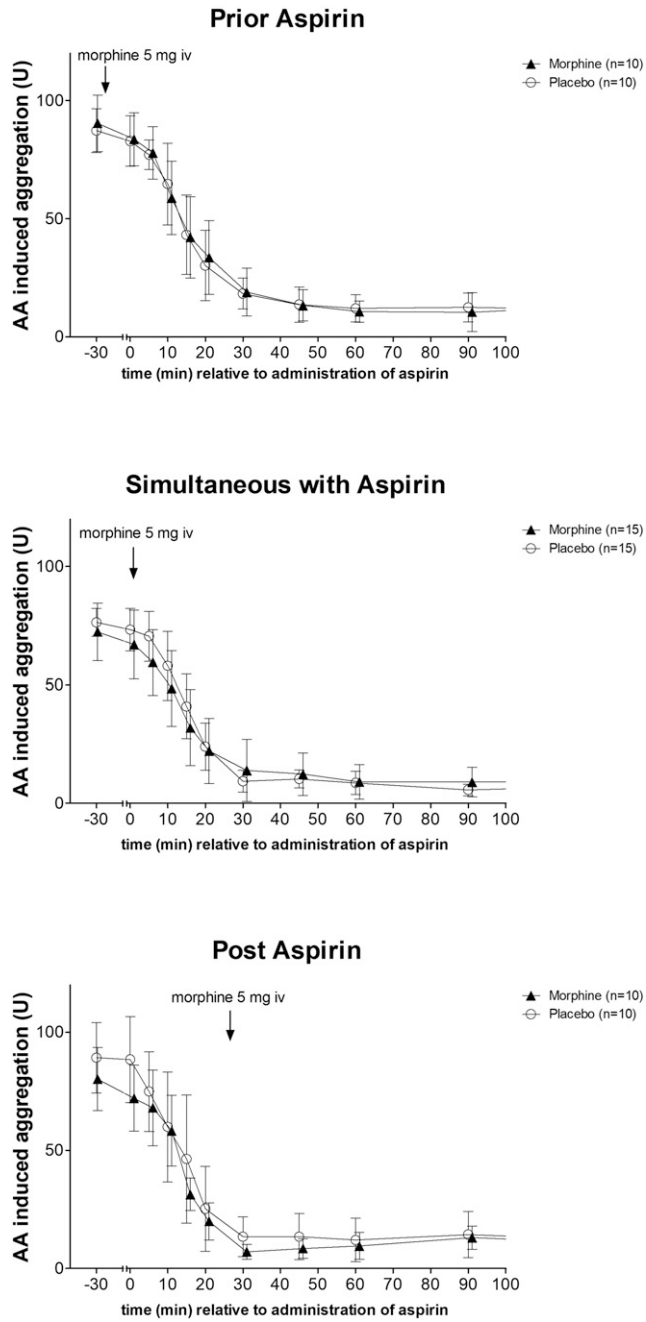

Fig. 4. Morphine interaction with aspirin. Morphine and its time of administration (prior vs. simultaneous vs. post aspirin) had no significant effect on AA (0.5 nM) induced platelet aggregation compared with placebo. Healthy subjects received 5 mg of morphine (i..v) or placebo before (−30, −15 minutes, n = 10), simultaneously (−5, 0, +5 minutes, n = 15), or post (+15, +30 minutes, n = 10) 162 mg of aspirin (p.o.). Data present means (95% CI).

before or after aspirin. Interestingly, the concentration-time curve of acetaminophen showed similar behavior. It is well documented that opioids increase the transit time in the small bowel (Kurz and Sessler, 2003), and therefore the increase in AUC may be caused by the increased contact time with the intestinal mucosa.

The minor effect of morphine on aspirin's PK was also evident in PD responses. Regardless of the time of administration, morphine had no influence on aspirin-induced platelet inhibition. Aspirin alone sufficiently inhibited platelet aggregation within 20 minutes, as measured by impedance aggregometry and the platelet function analyzer. This is in accordance with previous investigations in which chewed enteric coated aspirin inhibited platelet aggregation and thromboxane B2 production at the first measured time point (15 minutes after intake) (Jimenez et al., 1992).

Contemporary ACS guidelines recommend treatment with aspirin as early as possible. The combination of aspirin with a

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P2Y12 receptor inhibitor was proven more effective than aspirin alone (Yusuf et al., 2001). Controversy exists about the timing of the initiation of the P2Y12 receptor blockade (Sibbing et al., 2016). Whether P2Y12 receptor blockade should be initiated early may depend on different factors, such as time to PCI, level of certainty of diagnosis, or bleeding diathesis. A possible contributing cause may be an impaired drug absorption induced by morphine (Kubica et al., 2016b). For example, a multicenter, randomized, double-blind study in 1862 patients with ST elevation myocardial infarction compared prehospital (in the ambulance) versus in-hospital (in the catheterization laboratory) treatment with ticagrelor and found no improvement in coronary reperfusion (Montalescot et al., 2014). As patients who did not receive morphine benefit from prehospital administration of ticagrelor, the investigators suggested that morphine coadministration might delay the action of ticagrelor. In support of this hypothesis, a recent randomized, controlled trial showed that morphine delayed the antiplatelet effects of ticagrelor in patients with acute myocardial infarction (Kubica et al., 2016a). Our trial was designed to investigate the effect of morphine on the PK and PD of aspirin. We could demonstrate that morphine has no significant effect on aspirin-induced platelet inhibition in healthy volunteers. This may be different in ACS patients in which gastrointestinal resorption is impaired (Bochner and Lloyd, 1995), and the used doses of morphine are possibly higher. Accordingly, PK/PD interactions between morphine and aspirin cannot be completely excluded but seem unlikely in ACS patients. The final proof can be determined only by an adequately powered randomized, placebo-controlled trial in the target population, which requires a careful design and planning owing to ethical reasons. In case of uncertainty, an i.v. formulation of ASA is available and has an immediate onset of action in patients with myocardial infarction (Fuchs et al., 2010).

In conclusion, whereas morphine has negative effects on oral P2Y12 inhibitors (Kubica et al., 2016a), it slightly enhances exposure to aspirin, but platelet inhibition is not affected.

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Authorship Contributions

Participated in research design: Jilma, Hobl.

Conducted experiments: Bartko, Schoergenhofer, Schwameis, Jilma, Hobl.

Performed data analysis: Bartko, Jilma, Hobl.

Wrote or contributed to the writing of the manuscript: Bartko, Schoergenhofer, Schwameis, Wadowski, Kubica, Jilma, Hobl.

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