

Title Page

Morphine Interaction with Aspirin: a Double-blind, Cross-over Trial in Healthy Volunteers

Author list:

Johann Bartko, Christian Schoergenhofer, Michael Schwameis, Patricia Wadowski,
Jacek Kubica, Bernd Jilma, Eva-Luise Hobl

Department of Clinical Pharmacology, Medical University of Vienna, Austria (J.B.,
C.S., M.S., P.W., B.J., E. H.)

Ludwig Boltzmann Institute of Osteology, Hanusch Hospital of WGKK, AUVA Trauma
Centre Meidling, Vienna, Austria (J.B.)

Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland (J.K.)

Running Title Page

Running title: Morphine And Aspirin Drug Interaction

Corresponding author:

Bernd Jilma, M.D.

Medical University of Vienna

Department of Clinical Pharmacology

Waehringer Guertel 18-20

1090 Vienna, Austria (Europe)

Telephone +4314040029810

Fax +4314040029980

bernd.jilma@meduniwien.ac.at

Text pages: 13

Tables: 1

Figures: 4

References: 32

Abstract: 144 words

Introduction: 642 words

Discussion: 1507 words

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

Abstract

Aspirin is a cornerstone in the anti-platelet therapy of acute coronary syndromes. Co-administration of morphine may potentially influence the intestinal absorption, pharmacokinetics and pharmacodynamics as seen with P2Y₁₂-inhibitors. In this trial, healthy volunteers were randomized to receive morphine (5 mg, iv bolus injection) at one of 7 different time points before, after or with aspirin (162 mg, po) 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 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 to 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 co-administration with P2Y₁₂-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 (NSTEMI-ACS) if 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 57039 patients with NSTEMI-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 NSTEMI-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 are able to decrease plasma levels and/or anti-platelet effects of oral P2Y₁₂ receptor antagonists (Hobl et al., 2014; Hobl et al., 2016a; Hobl et al., 2016b; Kubica et al., 2016a; McEvoy et al., 2018). This 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 appears 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, cross-over trial in healthy volunteers was performed to investigate the effect of morphine on the PK and PD of aspirin.

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 iv bolus injection of morphine (G.L. Pharma GmbH, Lannach, Austria) at one of 7 different time points in the range of 30 min before to 30 min after chewing 162 mg enteric coated aspirin (two tablets of 81 mg chewable low-dose ‘Baby’ Aspirin, Bayer HealthCare, Morristown, NJ, USA). 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 Non-Steroidal Anti-Rheumatic Drugs, including aspirin and P2Y₁₂-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 iv 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 7 different time points in the range of 30 min prior to 30 min after the administration of 162 mg aspirin. Each group included 5 subjects

(Figure 1). When the 7 different times of morphine administration were compared, there were no differences in PK and PD of aspirin between morphine and placebo (data not shown). As predefined in the study protocol, times of morphine injection relative to aspirin were pooled (“prior” [-30, -15 min]; “simultaneous” [-5, 0, +5 min]; “post” [+15, +30 min]) and compared to placebo. PK profiles and PD response were monitored 30 min, 0 min before and 5, 15, 20, 30, 45, 60, 90, 120, 180, 240 and 360 min after oral administration of aspirin during period 1 (morphine) and period 2 (placebo).

Pharmacokinetics (PK)

Acetylsalicylic acid (ASA) and salicylic acid (SA) were analyzed by high-performance liquid chromatography as previously published (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, USA).

Pharmacodynamics (PD)

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 effect size (intra-individual differences between periods), it was assumed to be comparable to acetaminophen. In healthy volunteers, t_{\max} of acetaminophen was observed at 22 ± 9 [SD] min under control conditions and after 114 ± 72 [SD] min when pethidine was administered before acetaminophen intake. In this study, 4 subjects were sufficient to demonstrate the negative effect of opiates (Nimmo et al., 1975). To check the assay sensitivity of our experimental model, 8 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 females, 25 males) were 31 ± 9 years of age, weighed 77 ± 14 kg, and had a body mass index of 24 ± 3 kg/m². Morphine injection caused mild to moderate adverse events in 43% of subjects, including head pressure (14%), prickling (11%) and flushing (6%). There were 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).

Pharmacokinetics (PK)

Aspirin. Morphine increased the total acetylsalicylic acid exposure (AUC) by ~ 20% (median, $p=0.0084$) when administered simultaneously with aspirin compared to placebo (Table 1, Figure 2). 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 acetylsalicylic acid 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 to placebo (Table 1). Morphine had no significant effect on the total acetaminophen exposure (AUC) (Table 1).

Pharmacodynamics (PD)

PFA-100. Baseline (-30 min) collagen/epinephrine induced closure times (CEPI-CTs) correlated well between period 1 (morphine) and period 2 (placebo) (median: 171 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 to placebo (Figure 3). Aspirin, co-administered with morphine, increased CEPI-CTs by 46% 20 min after administration. Similarly, CEPI-CTs increased by 57% with placebo. Maximal platelet inhibition (i.e. CEPI-CTs >301 s) occurred in 27 subjects (77%) receiving morphine and in 31 subjects (86%) receiving placebo within 20 min. 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 min) of AA-induced platelet aggregation correlated moderately between period 1 (morphine) and period 2 (placebo) (median: 79 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 to placebo (Figure 4). Aspirin, co-administered with morphine, decreased AA-induced platelet aggregation by 69% 20 min 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 min) in 24 subjects (69%) receiving morphine and in 24 subjects (69%) receiving placebo. Nearly all subjects reached sufficient platelet inhibition within 30 min of aspirin administration (placebo: 32/35; morphine: 31/35).

Discussion

The use of aspirin reduces mortality among 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 P2Y₁₂ 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 70s demonstrated that opiates inhibit gastric emptying and retard the absorption of orally administered drugs. In healthy volunteers, intramuscular injection of 10 mg 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 morphine (~4-fold lower potency than 10 mg 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 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 co-administration 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, similar to acetaminophen, is thought to be mainly absorbed by the small intestine (Schrör, 2016).

Time to 50% gastric emptying after ingestion of 500-700 ml Technetium-99m labeled solution occurs on average after 12 min under physiological conditions (Chaudhuri, 1974). In healthy volunteers receiving diamorphine, the mean time to 50% gastric emptying of ingested solution was >130 min compared with 11.9 min 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.

Firstly, aspirin reached maximal plasma concentrations 15 min earlier than acetaminophen (45 vs. 30 min, Mann Whitney test, uncorrected P value 0,0308), indicating a different rate of absorption. Secondly, morphine did not change the time to peak exposure (t_{\max}), showing that delayed gastric emptying was not the rate-limiting step in absorption. Thirdly, sufficient platelet inhibition occurred within 15-20 min, whether morphine was given or not.

A study in 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 min (Hogben et al., 1957). Given that 50 mg of intravenous acetylsalicylic acid already completely inhibits AA-induced platelet aggregation (Boger et al., 1993), it is likely that sufficient amounts of aspirin entered the pre-systemic circulation in our trial.

The anti-platelet 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 non-hydrolyzed, platelet targeting form of aspirin.

Another important factor is that aspirin has the ability to cross the oral mucosa (Schrör, 2016; Mollace et al., 2017), albeit that published data on buccal absorption is scarce. Given that ASA and SA were detectable as early as 5 min after intake in all of the subjects, the oral mucosa was likely a site of absorption. This is in line with a

study in healthy volunteers, in which ASA was already present in plasma 3 min after chewing aspirin (Feldman and Cryer, 1999).

According to the ion trapping hypothesis, aspirin, a weak acid, is primarily available 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. However, because aspirin's solubility depends on pH (poorly soluble under acidic conditions), 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 acetylsalicylic acid exposure (AUC) by ~ 20% when administered simultaneously with aspirin compared to placebo (Table 1, Figure 2). 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 before or after aspirin. Interestingly, the concentration-time curve of acetaminophen showed a 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 min, 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 min after intake) (Jimenez et al., 1992).

Contemporary ACS guidelines recommend treatment with aspirin as early as possible. The combination of aspirin with a 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 pre-hospital (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 pre-hospital administration of ticagrelor, the investigators suggested that morphine co-administration might delay the action of ticagrelor. In support of this hypothesis, a recent randomized controlled trial showed that morphine delayed 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 appear 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 due to ethical reasons. In case of uncertainty, an iv formulation of ASA is available and has an immediate onset of action in patients with myocardial infarction (Fuchs et al., 2010).

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

Acknowledgements

We are indebted to Sabine Schranz, Christa Drucker, Karin Petroczi and Christa Firbas for their technical assistance.

Authorship Contributions

Participated in research design: Jilma and Hobl.

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

Performed data analysis: Bartko, Jilma and Hobl.

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

References

- Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ and Members AATF (2014) 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* **130**:e344-426.
- Bennett MW, Shah MV and Bembridge JL (1994) A comparison of the effect on gastric emptying of alfentanil or morphine given during anaesthesia for minor surgery. *Anaesthesia* **49**:155-156.
- Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, Price MJ, Leonardi S, Gallup D, Bramucci E, Radke PW, Widimsky P, Tousek F, Tauth J, Spriggs D, McLaurin BT, Angiolillo DJ, Genereux P, Liu T, Prats J, Todd M, Skerjanec S, White HD, Harrington RA and Investigators CP (2013) Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* **368**:1303-1313.
- Bochner F and Lloyd JV (1995) Aspirin for myocardial infarction. Clinical pharmacokinetic considerations. *Clin Pharmacokinet* **28**:433-438.
- Boger RH, Bode-Boger SM, Gutzki FM, Tsikas D, Weskott HP and Frolich JC (1993) Rapid and selective inhibition of platelet aggregation and thromboxane formation by intravenous low dose aspirin in man. *Clin Sci (Lond)* **84**:517-524.
- Bruce TA and Bing RJ (1965) Clinical Management of Myocardial Infarction. *JAMA* **191**:124-126.
- Chaudhuri TK (1974) Use of ^{99m}Tc-DTPA for measuring gastric emptying time. *J Nucl Med* **15**:391-395.
- de Waha S, Eitel I, Desch S, Fuernau G, Lurz P, Urban D, Schuler G and Thiele H (2015) Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. *Clin Res Cardiol* **104**:727-734.

- Feldman M and Cryer B (1999) Aspirin absorption rates and platelet inhibition times with 325-mg buffered aspirin tablets (chewed or swallowed intact) and with buffered aspirin solution. *Am J Cardiol* **84**:404-409.
- Fuchs I, Spiel AO, Frossard M, Derhaschnig U, Riedmuller E and Jilma B (2010) Platelet hyperfunction is decreased by additional aspirin loading in patients presenting with myocardial infarction on daily aspirin therapy. *Crit Care Med* **38**:1423-1429.
- Hobl EL, Jilma B, Ebner J and Schmid RW (2013) Simultaneous determination of acetylsalicylic acid and salicylic acid in human plasma by isocratic high-pressure liquid chromatography with post-column hydrolysis and fluorescence detection. *Biomed Chromatogr* **27**:695-698.
- Hobl EL, Reiter B, Schoergenhofer C, Schwameis M, Derhaschnig U, Kubica J, Stimpfl T and Jilma B (2016a) Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. *Eur J Clin Invest* **46**:7-14.
- Hobl EL, Reiter B, Schoergenhofer C, Schwameis M, Derhaschnig U, Lang IM, Stimpfl T and Jilma B (2016b) Morphine interaction with prasugrel: a double-blind, cross-over trial in healthy volunteers. *Clin Res Cardiol* **105**:349-355.
- Hobl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, Jilma-Stohlawetz P, Mannhalter C, Posch M and Jilma B (2014) Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* **63**:630-635.
- Hogben CA, Schanker LS, Tocco DJ and Brodie BB (1957) Absorption of drugs from the stomach. II. The human. *J Pharmacol Exp Ther* **120**:540-545.
- Jakl M, Sevcik R, Fatorova I, Horacek JM and Pudil R (2017) High on-treatment platelet reactivity: risk factors and 5-year outcomes in patients with acute myocardial infarction. *Anatol J Cardiol* **17**:113-118.
- Jimenez AH, Stubbs ME, Tofler GH, Winther K, Williams GH and Muller JE (1992) Rapidity and duration of platelet suppression by enteric-coated aspirin in healthy young men. *Am J Cardiol* **69**:258-262.

- Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, Stankowska K, Buszko K, Navarese EP, Jilma B, Siller-Matula JM, Marszall MP, Rosc D and Kozinski M (2016a) Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J* **37**:245-252.
- Kubica J, Kubica A, Jilma B, Adamski P, Hobl EL, Navarese EP, Siller-Matula JM, Dabrowska A, Fabiszak T, Kozinski M and Gurbel PA (2016b) Impact of morphine on antiplatelet effects of oral P2Y₁₂ receptor inhibitors. *Int J Cardiol* **215**:201-208.
- Kurz A and Sessler DI (2003) Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs* **63**:649-671.
- Lichtenberger LM, Phan T, Fang D, Edler S, Philip J, Li-Geng T and Dial EJ (2016) Bioavailability of aspirin in rats comparing the drug's uptake into gastrointestinal tissue and vascular and lymphatic systems: implications on aspirin's chemopreventive action. *J Physiol Pharmacol* **67**:635-642.
- McCarthy CP, Bhambhani V, Pomerantsev E and Wasfy JH (2017) In-hospital outcomes in invasively managed acute myocardial infarction patients who receive morphine. *J Interv Cardiol*.
- McCarthy CP, Mullins KV, Sidhu SS, Schulman SP and McEvoy JW (2016) The on- and off-target effects of morphine in acute coronary syndrome: A narrative review. *Am Heart J* **176**:114-121.
- McEvoy JW, Ibrahim K, Kickler TS, Clarke WA, Hasan RK, Czarny MJ, Keramati AR, Goli RR, Gratton TP, Brinker JA, Chacko M, Hwang CW, Johnston PV, Miller JM, Trost JC, Herzog WR, Blumenthal RS, Thiemann DR, Resar JR and Schulman SP (2018) Effect of Intravenous Fentanyl on Ticagrelor Absorption and Platelet Inhibition Among Patients Undergoing Percutaneous Coronary Intervention: The PACIFY Randomized Clinical Trial (Platelet Aggregation With Ticagrelor Inhibition and Fentanyl). *Circulation* **137**:307-309.

- Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, Peacock WF, Pollack CV, Jr., Gibler WB, Peterson ED and Investigators C (2005) Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J* **149**:1043-1049.
- Mollace V, Rosano G, Malara N, Di Fabrizio E, Vitale C, Coluccio M, Maiuolo J, Wasti AA, Muscoli C, Gliozzi M, Mollace R, Musolino V, Carresi C, Fini M and Silvestrini B (2017) Aspirin wears smart. *Eur Heart J Cardiovasc Pharmacother*.
- Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chettibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Stibbe O, Ecollan P, Heutz WM, Swahn E, Collet JP, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaut E, Hamm CW and Investigators A (2014) Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* **371**:1016-1027.
- Nimmo WS, Heading RC, Wilson J, Tothill P and Prescott LF (1975) Inhibition of gastric emptying and drug absorption by narcotic analgesics. *Br J Clin Pharmacol* **2**:509-513.
- O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW and American College of Cardiology Foundation/American Heart Association Task Force on Practice G (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* **127**:e362-425.
- Parodi G (2016) Editor's Choice-Chest pain relief in patients with acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care* **5**:277-281.

- Roth GJ and Majerus PW (1975) The mechanism of the effect of aspirin on human platelets. I. Acetylation of a particulate fraction protein. *J Clin Invest* **56**:624-632.
- Schrör K (2016) *Acetylsalicylic acid*. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.
- Sibbing D, Kastrati A and Berger PB (2016) Pre-treatment with P2Y12 inhibitors in ACS patients: who, when, why, and which agent? *Eur Heart J* **37**:1284-1295.
- Siller-Matula JM, Specht S, Kubica J, Alexopoulos D, De Caterina R, Hobl EL, Jilma B, Christ G and Lang IM (2016) Abciximab as a bridging strategy to overcome morphine-prasugrel interaction in STEMI patients. *Br J Clin Pharmacol* **82**:1343-1350.
- Spiel AO, Bartko J, Schwameis M, Firbas C, Siller-Matula J, Schuetz M, Weigl M and Jilma B (2011) Increased platelet aggregation and in vivo platelet activation after granulocyte colony-stimulating factor administration. A randomised controlled trial. *Thromb Haemost* **105**:655-662.
- Wiggins BS, Saseen JJ, Page RL, 2nd, Reed BN, Sneed K, Kostis JB, Lanfear D, Virani S, Morris PB, American Heart Association Clinical Pharmacology Committee of the Council on Clinical C, Council on H, Council on Quality of C, Outcomes R, Council on Functional G and Translational B (2016) Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation* **134**:e468-e495.
- Yuan CS, Foss JF, O'Connor M, Roizen MF and Moss J (1998) Effects of low-dose morphine on gastric emptying in healthy volunteers. *J Clin Pharmacol* **38**:1017-1020.
- Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK and Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial I (2001) Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* **345**:494-502.

Footnote

The Austrian Science Funds (FWF) funded this work [grant SFB54-P04].

LEGENDS FOR FIGURES

Figure 1. Schematic of the trial design. To define the optimal time for morphine administration, subjects were randomized to receive 5 mg iv morphine at one of 7 different points of time co-administered with 162 mg aspirin. As predefined, within-subjects-comparisons between periods were performed for pooled times of morphine injection relative to aspirin: “prior” [-30, -15 min]; “simultaneous” [-5, 0, +5 min]; “post” [+15, +30 min].

Figure 2. Morphine Interaction with Aspirin. Morphine increased total acetylsalicylic acid exposure (AUC) by ~ 20% ($p < 0.01$) when administered simultaneously with aspirin compared to placebo. Healthy subjects received 5 mg morphine (iv) or placebo prior to (-30, -15 min, $n=10$), simultaneously (-5, 0, +5 min, $n=15$) or post (+15, +30 min, $n=10$) 162 mg aspirin (po). Data present means (95%CI).

Figure 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 to placebo. Healthy subjects received 5 mg morphine (iv) or placebo prior to (-30, -15 min, $n=10$), simultaneously (-5, 0, +5 min, $n=15$) or post (+15, +30 min, $n=10$) 162 mg aspirin (po). Data present means (95%CI). CEPI-CT: collagen/epinephrine induced closure time.

Figure 4. Morphine Interaction with Aspirin. Morphine and its time of administration (prior vs. simultaneous vs. post aspirin) had no significant effect on arachidonic acid (AA) (0.5 nM) induced platelet aggregation compared to placebo. Healthy subjects received 5 mg morphine (iv) or placebo prior to (-30, -15 min, $n=10$), simultaneously (-5, 0, +5 min, $n=15$) or post (+15, +30 min, $n=10$) 162 mg aspirin (po). Data present means (95%CI).

Tables

Table 1. Summary statistics for aspirin pharmacokinetic parameters by treatment time point and acetaminophen (internal control).

	Period 1 (Morphine, 5 mg iv bolus injection)				Period 2 (Placebo)		
	<i>N</i>	<i>C</i> _{max} (mg/L)	<i>t</i> _{max} (min)	<i>AUC</i> _{0-∞} (mg•h/L)	<i>C</i> _{max} (mg/L)	<i>t</i> _{max} (min)	<i>AUC</i> _{0-∞} (mg•h/L)
Acetylsalicylic Acid							
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)	2533 (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)

Values are represented as median (interquartile range). *C*_{max}, maximum plasma concentration; *t*_{max}, time to maximum plasma concentration; *AUC*, area under the concentration–time curve. **p*<0.05, ***p*<0.01, ****p*<0.001 vs. placebo.

Figures

Figure 1.

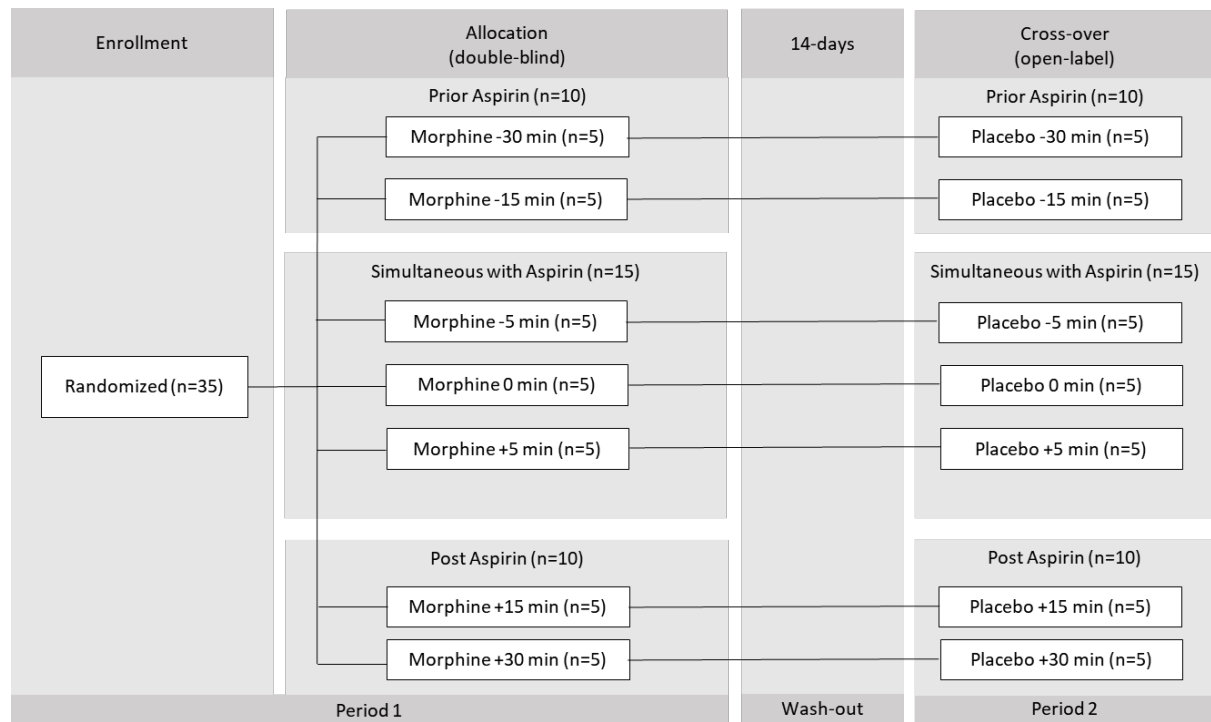


Figure 2.

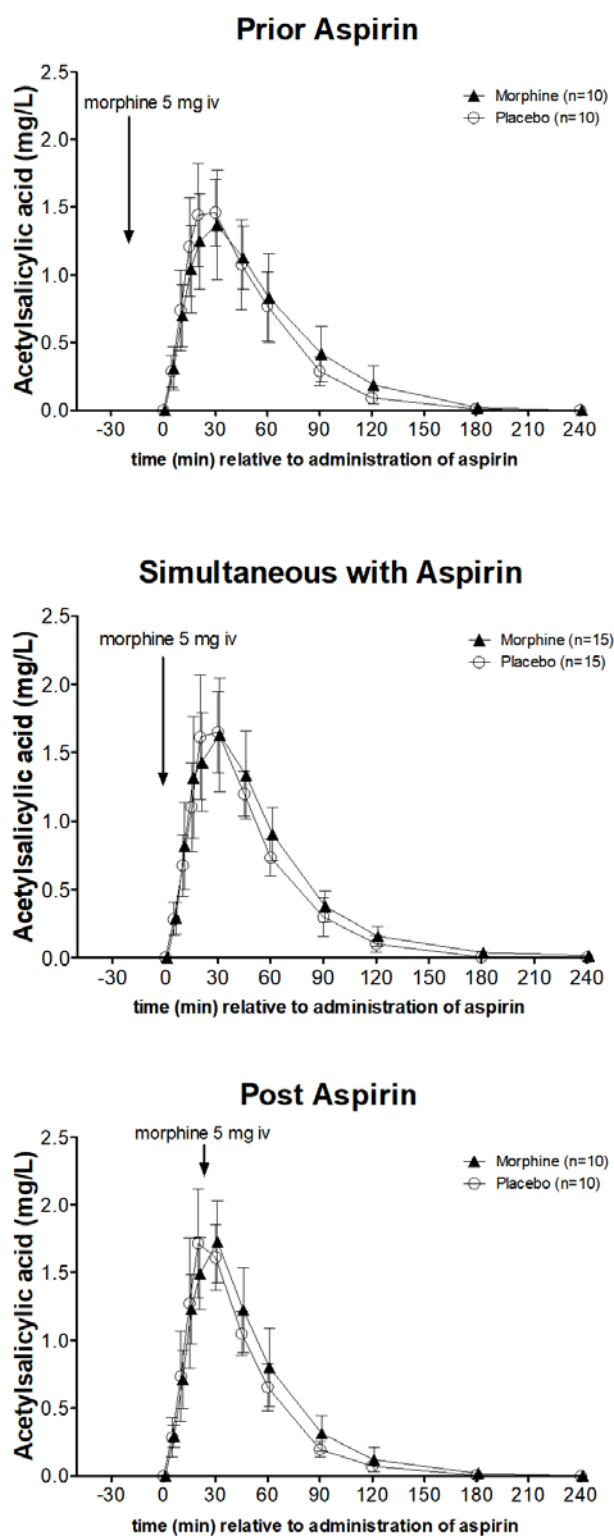


Figure 3.

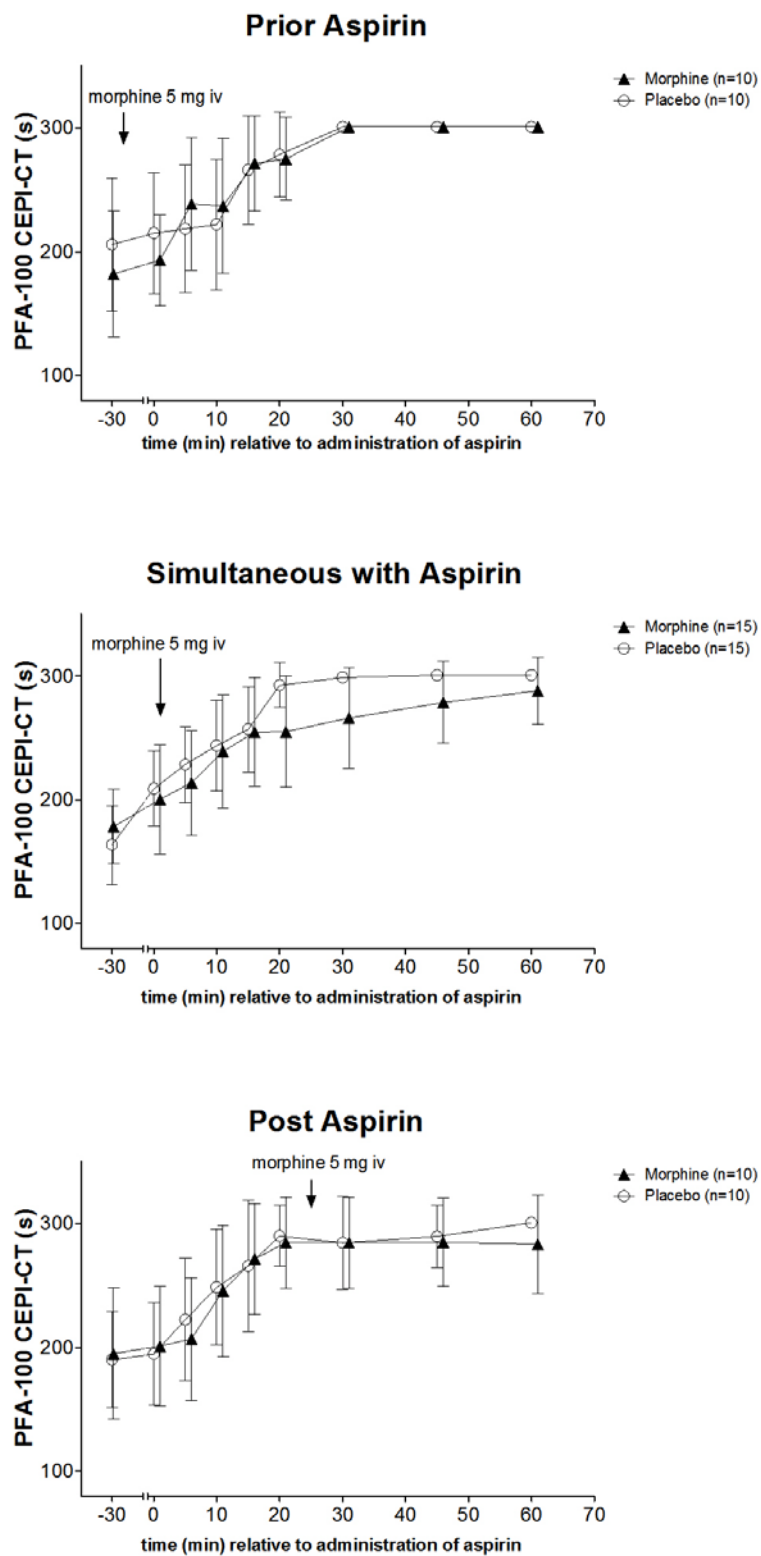


Figure 4.

