Omeprazole, a potent CYP2C19 inhibitor, does not alter the pharmacokinetics or platelet aggregation of aspirin and dipyridamole in combination

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BACKGROUND

- Aspirin in combination with extended-release dipyridamole (ASA+ER-DP) is an established antiplatelet option for the prevention of secondary ischemic stroke.[1]
- Omeprazole (OMEP), a proton pump inhibitor (PPI) indicated for the treatment of gastrointestinal (GI) reflux and duodenal and gastric ulcers, is used to reduce the risk of GI bleeding in patients receiving antiplatelet therapy.[2]
- An elevated gastric pH in patients taking gastric acid suppressing medications such as PPIs may reduce dipyridamole (DP) absorption.[3,4]
- In addition, OMEP is a potent inhibitor of CYP2C19 and has demonstrated clinically important interactions with other antiplatelet agents. Although not a theoretical concern, there is value in ruling out the interaction potential between OMEP and ASA+ER-DP.
- DP shows potent anti-thrombotic activities *in vivo*;[5] however, due to the reversible nature of these effects, maintaining sufficient plasma concentration over time is critical.
- The objective of our study was to show that PPIs do not interfere with maintenance of therapeutic plasma DP levels or the pharmacodynamic effects of ASA.
- This study investigated whether the coadministration of OMEP impacts the pharmacokinetics (PK) and pharmacodynamics (PD) of ASA+ER-DP.

OBJECTIVE

- To determine whether coadministration of OMEP 80 mg once daily (qd) at steady state affects the PK of DP and ASA-induced inhibition of platelet aggregation (IPA) when ASA+ER-DP is administered twice daily (bid) at steady state.

METHODS

Study design and treatment

- Multiple-dose, open-label, randomized, crossover trial involving four 7-day treatments with two treatment sequences (**Figure 1**).
- ASA+ER-DP was administered as Aggrenox® 25 mg/200 mg one capsule bid (Boehringer Ingelheim Pharma GmbH).
- OMEP was administered as Prilosec® 40 mg two capsules qd (AstraZeneca Pharmaceuticals LP).
- Combined treatments were administered after ASA+ER-DP or OMEP reached expected steady state.

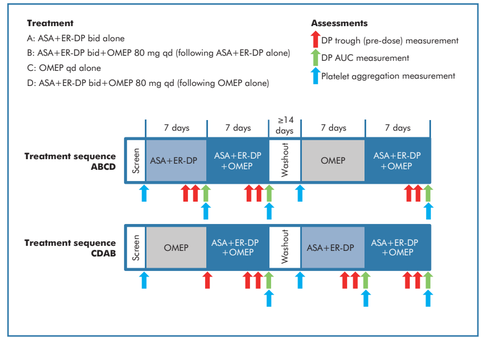
Study population

- 60 healthy volunteers aged 18–50 years.
- Subjects taking medications that might interfere with platelet aggregation within 14 days of, or during the study, were excluded.

Assessments

- Primary comparison: treatment D vs. treatment A.
- Secondary comparison: treatment B vs. treatment A.
- Primary endpoints:
  - Systemic exposure to DP using $AUC_{0\text{-}12,ss}$ and $C_{max,ss}$ of DP in plasma
  - Antiplatelet activity of ASA based on the IPA 4 hours after the last dose of ASA+ER-DP.

Figure 1. Study design



- Secondary endpoints:
  - DP parameters: $C_{min,ss}$ and % peak-trough fluctuation (%PTF)
  - IPA 12 hours after the last dose of ASA+ER-DP.
- Assessment of DP PK:
  - Predose samples obtained within 15 min prior to the morning dose on days 5, 6, and 7 of treatments A, B, and D (**Figure 1**)
  - Blood samples for a full PK time course obtained on day 7 of treatments A, B, and D, at 1, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours post-dose (**Figure 1**)
  - Samples of plasma in EDTA were analyzed for DP by LC-MS/MS with a linear range of 10–3000 ng/mL
  - PK parameters were calculated by non-compartmental analysis using WinNonlin® Version 5.0.1 (Pharsight®).
- Assessment of ASA PD (IPA):
  - Blood samples for platelet aggregation (PA) were drawn at baseline prior to the first day and 4.0 and 12.0 hours after the morning dose on day 7 of treatments A, B, and D (**Figure 1**), and were processed within 4 hours
  - Platelet rich plasma samples were stimulated with 500 µg/mL (1.64 mmol/L) of arachidonic acid and PA was assessed using a Biodata PAP 8E aggregometer
  - IPA (%) was derived from the measurement of PA and calculated using the following formula: IPA=[1–(PAt/PA0)]x100%, in which PAt=PA measured at time t (4 or 12 hours following dosing of ASA+ER-DP), and PA0=PA at baseline
  - Baseline PA values were derived from the sample collected at the beginning of each of the two 14-day confinement periods.
- Adverse events (AEs), treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) were recorded under the appropriate system/organ/class category.

Statistical methods

- DP PK:
  - For primary and secondary comparisons, the $AUC_{0\text{-}12,ss}$, $C_{max,ss}$ (primary endpoint), and $C_{min,ss}$ (secondary endpoint) of the test (T) and reference (R) treatments from the PK set were log-transformed before fitting an analysis of variance (ANOVA) model
  - The difference between the expected means for log(T)–log(R) was estimated by the difference in the corresponding least-squares (LS) means
  - Two-sided 90% confidence intervals (CI) based on the t-distribution were calculated
  - These quantities were back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the intra-subject ratio between response under test and response under reference
  - The statistical model used for the primary and secondary endpoints included the following effects accounting for sources of variation: "subjects within sequence" (random effect) and "sequence", "period", and "treatment" (fixed effects).
- ASA PD:
  - An ANCOVA model was fitted with baseline as a covariate; the difference between the expected means was estimated by the difference in the corresponding LS means (point estimate) and two-sided 90% CI based on the t-distribution
  - The ANCOVA model was used for the analysis of IPA at 4 hours for both the primary and secondary comparisons and applied to untransformed values of platelet aggregation.

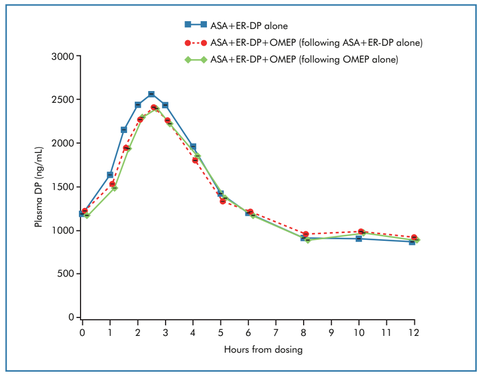
RESULTS

- 51 of 60 initial subjects finished the study.

Pharmacokinetics

- Mean plasma DP concentrations for treatments A, B, and D were plotted against time (**Figure 2**); the curves are nearly superimposable.
- Results for the primary endpoints of PK parameters $C_{max,ss}$ and $AUC_{0\text{-}12,ss}$ are shown in **Table 1**
  - Mean ratios for treatment D vs. A and treatment B vs. A were close to 100% and 90% CIs were fully contained within the "no effect" boundary of 80%–125% for drug-drug interactions.[6]

Figure 2. DP concentration over time with and without OMEP, geometric mean (SD)



- For secondary endpoints of PK parameters $C_{min,ss}$ and %PTF:
  - 90% CIs were likewise fully contained within the "no effect" boundary of 80%–125% for drug-drug interactions in both comparisons (**Table 2**)
  - %PTF did not appear to be affected by treatment (**Table 3**).

Table 1. Plasma DP PK parameters: primary endpoints

	Parameter	% mean ratio	90% CI
Primary comparison (treatment D vs. A)	$C_{max,ss}$ (ng/mL)	92.03	86.95–97.40
	$AUC_{0\text{-}12,ss}$ (ng*hr/mL)	96.38	90.96–102.13
Secondary comparison (treatment B vs. A)	$C_{max,ss}$ (ng/mL)	92.30	87.76–97.08
	$AUC_{0\text{-}12,ss}$ (ng*hr/mL)	97.03	93.26–100.95

Table 2. Plasma DP PK parameters: secondary endpoints

	Parameter	% mean ratio	90% CI
Primary comparison (treatment D vs. A)	$C_{min,ss}$ (ng/mL)	105.55	97.09–114.74
Secondary comparison (treatment B vs. A)	$C_{min,ss}$ (ng/mL)	106.09	98.64–114.09

Table 3. Plasma DP PK parameters: %PTF secondary endpoint

Parameter	Treatment A	Treatment B	Treatment D
%PTF, mean (SD)	144 (31.8)	132 (41.4)	134 (41.2)

PTF = peak-trough fluctuation.

Pharmacodynamics

- All treatments resulted in nearly identical IPA at 4 hours.
- The ratio of means for the IPA at 4 and 12 hours (respective primary and secondary PD endpoints) were nearly identical (**Table 4**).

Table 4. Plasma DP PD parameters: primary (IPA_4) and secondary (IPA_{12}) endpoints

	Parameter	% mean ratio	90% CI
Primary comparison	IPA_4	99.02	98.32–99.72
(treatment D vs. A)	IPA_{12}	99.38	98.80–99.95
Secondary comparison	IPA_4	98.42	97.66–99.18
(treatment B vs. A)	IPA_{12}	99.02	98.46–99.59

IPA = inhibition of platelet aggregation.

Safety

- There were no SAEs.
- 2 subjects were discontinued by the Investigator during ER-DP treatment due to AEs of hypersensitivity and urticaria, both considered drug-related.
- 53 (88%) subjects reported at least 1 TEAE.
- The majority of AEs were mild in severity and were considered drug-related.
- Transient headache and myalgia were the most common AEs, reported by 50 (83%) and 32 (53%) subjects, respectively; AE incidence was not different following combination therapy compared with ASA+ER-DP alone.

CONCLUSIONS

- No drug-drug interaction was observed between OMEP and ASA+ER-DP.
- The PK of the DP component was not affected by OMEP:
  - The 90% CIs for the primary and secondary PK variables for DP in the presence/absence of OMEP were well within the 80%–125% range, indicating no clinically significant differences
  - The concentration vs. time curves for DP in the presence/absence of OMEP were virtually superimposable.
- OMEP did not affect the PD of ASA+ER-DP:
  - The extent of IPA was nearly identical regardless of the presence or absence of OMEP
  - IPA was maintained at 12 hours as indicated by the IPA_{12}
  - This lack of drug-drug interaction was observed regardless of the order in which OMEP and ASA+ER-DP were administered.
- There is no need for an alternative PPI or antiplatelet agent in patients receiving OMEP concurrent with ASA+ER-DP.

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