Pharmacokinetic and Pharmacodynamic Interactions of Sodium Oxybate with Diclofenac: Results from a Randomized, Double-Blind, Placebo-Controlled, Crossover Study
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Purpose
Evaluate drug-drug interactions between sodium oxybate (SXB) and diclofenac with regard to PK, PD, and safety. SXB is the sodium salt of gamma-hydroxybutyrate (GHB), a substrate for the monocarboxylate transporter that may be inhibited by diclofenac, which also binds to GHB receptors in the brain.

Methods
Healthy volunteers were randomized to SXB+diclofenac placebo, SXB+diclofenac, or SXB placebo+diclofenac in a three-period, double-blind, crossover design with a 2-day washout between periods. Diclofenac/placebo (50mg immediate-release) was given qid every 4h on days 1 and 2, and 1h before and 3h after the first SXB dose on day 3; SXB/placebo was given as two 3g doses 4h apart on day 3. Blood and urine were sampled at predefined times for noncompartmental PK analysis. PD testing, performed at the end of each treatment period, included the Karolinska Sleepiness Scale, and several automated tests from CDR System (bracketglobal.com) including Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Tracking, and Numeric Working Memory tasks. Safety was assessed at specified time points, and throughout the study.

Results
Of 22 subjects (77% male/55% white/mean age 34.2±6.6 years), 20 completed the study. SXB PK were similar with and without diclofenac. LS mean percent ratios of SXB PK parameters with and without diclofenac ranged from 94.8-106.7; 90% CIs were within the 80%-125% equivalence range, suggesting no PK drug-drug interaction (Table 1). A similar lack of differences was observed for diclofenac PK. SXB induced sleepiness and attentional impairments. SXB+diclofenac had significantly less impairment compared with SXB alone on accuracy and speed on digit vigilance (Table 2), choice reaction time, and power of attention. SXB effects on self-rated sleepiness and tracking performance were not reduced by diclofenac. The most common adverse events (AEs) (≥2 subjects) are listed in Table 3.

Conclusion
Co-administration of SXB and diclofenac did not significantly change the PK of either drug. Diclofenac co-administration appeared to reduce SXB-associated impairments to attention and information processing relative to SXB alone. AEs with SXB+diclofenac reflect a combined effect of both drugs.

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