Original Research

Gabapentin Enacarbil and Morphine Administered in Combination Versus Alone: A Double-blind, Randomized, Pharmacokinetic, and Tolerability Comparison

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ABSTRACT

Purpose: Coadministration of morphine with oral gabapentin has been shown to increase plasma gabapentin concentrations. This study evaluated whether there was any interaction between gabapentin enacarbil (GEn), which is a prodrug of gabapentin, and morphine in terms of pharmacokinetics, pharmacodynamics, safety, and tolerability.

Methods: This randomized, double-blind, 3-treatment crossover study included nonelderly, healthy male subjects. The study subjects received (in random order and with a minimum 7-day washout between treatments) the following: morphine placebo + GEn 600 mg; morphine 60 mg + GEn 600 mg; and morphine 60 mg + GEn placebo. Morphine/morphine placebo was administered in fasted conditions, and GEn/GEn placebo was administered 2 hours later with food. The primary end points were AUC and C_{max} for gabapentin, morphine, and morphine-6-glucuronide. Pharmacodynamic measures were limited to subject assessment of somnolence, dizziness, and nausea conducted by using a visual analog scale (VAS). Safety monitoring included adverse event reporting, clinical laboratory tests, vital signs, pulse oximetry, and 12-lead ECGs.

Findings: Of the 18 enrolled subjects (mean age, 36 years), 15 (83%) completed the study. Sixteen received GEn, 15 received morphine, and 18 received the combination. Compared with the single treatments, the 90% CIs for the ratio of the geometric means for both AUC and C_{max} were all within 0.8 to 1.25, the accepted range for bioequivalence. Ratios of geometric mean (90% CIs) values were as follows: gabapentin, AUC of 1.10 (1.035–1.162) and C_{max} of 1.02 (0.920–1.126); morphine, AUC of 1.06 (1.014–1.098) and C_{max} of 1.05 (0.967–1.134); and morphine-6-glucuronide, AUC of 0.992 (0.929–1.058) and C_{max} of 0.953 (0.855–1.062). Mean changes from predose VAS scores were generally small and suggested a slight increase in dizziness after GEn and slight increases in dizziness, somnolence, and nausea after morphine. Trends were noted suggesting slightly greater score changes from predose with the combination treatment than with either drug given alone for somnolence and dizziness. Adverse events were generally mild; there were no serious adverse events or subject withdrawals due to adverse events. Headache and nausea were among the most commonly reported events for the combination and morphine treatments (headache, 27% and 28%; nausea, 13% and 11%, respectively). There were fewer adverse events with GEn alone than with either of the combination regimens.

Implications: No significant pharmacokinetic interaction between the 2 drugs was seen in this study. The VAS data suggest that the potential exists for increased adverse effects when GEn and morphine

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Key words: combination, gabapentin enacarbil, morphine, pharmacodynamics, pharmacokinetics.

INTRODUCTION

Gabapentin and gabapentin enacarbil (GEn), a prodrug of gabapentin formulated as an extended-release tablet, are both approved by the US Food and Drug Administration for pain management in postherpetic neuralgia.[1,2] The recommended dosing frequency for gabapentin is TID, owing both to its short half-life and the narrow window of absorption in the upper small intestine.[2,3] In contrast, GEn is absorbed in the small and large intestines by the high-capacity nutrient transporter monocarboxylate transporter type 1 and the sodium-dependent multivitamin transporter; after absorption, it is rapidly converted to gabapentin by nonspecific esterases. Gabapentin is eliminated in the urine with a half-life of 5 to 6 hours.[4] The prolonged absorption window combined with the extended-release formulation allows for the recommended dose to be administered BID.[1] The molecular weight of GEn is nearly twice that of gabapentin; a 600-mg dose of GEn contains 313 mg of gabapentin.[4]

Gabapentin is structurally related to the neurotransmitter γ-aminobutyric acid. Although its analgesic mechanism is unknown, a high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels.[2,3] The most common adverse effects observed in a dose-ranging trial for GEn were dizziness and somnolence; the incidence rates were dose related and were 17% and 10%, respectively, at the recommended therapeutic dose of 1200 mg/d.[5]

Morphine is indicated for the management of moderate to severe pain. It is an opioid receptor agonist, binding at sites in the periaqueductal and periventricular gray matter, the ventromedial medulla, and the spinal cord to produce analgesia. Both its analgesic effect and adverse effects are attributed to opioid receptor agonism. Its adverse effects include dizziness, somnolence, respiratory depression, nausea and vomiting, constipation, and hypotension.[6,7] Morphine is eliminated primarily by liver metabolism; its estimated terminal $t_{½}$ after administration of an extended-release formulation is 11 to 13 hours.[7]

The distinct mechanisms of these 2 drugs raise the possibility that their combination might improve efficacy and/or reduce adverse effects via dose reduction. Conversely, such combinations may also potentiate the adverse effects that are common to both drugs, such as dizziness and somnolence. Gilron et al[8] conducted a study using dose titration to achieve maximal tolerated doses for morphine and gabapentin, alone and in combination, in a crossover design. The authors observed that as combination therapy, the mean dose achieved for each agent was lower than as its respective monotherapy. Despite the lower doses, the combination produced lower pain ratings than the monotherapies. Nonetheless, the frequency of several types of adverse events (AEs), including sedation and nausea, was higher for the combination. Although the pharmacokinetics of neither drug were measured in the trial of Gilron et al, morphine coadministration was shown to increase gabapentin exposure by 44% in healthy subjects in a separate study.[9] Therefore, the differences in efficacy and the AE profile for the combination could conceivably be attributed at least in part to a pharmacokinetic interaction. It is unknown how the pharmacodynamics of the combination compare with those of the individual drugs.

The increase in gabapentin exposure on coadministration with morphine noted in healthy subjects was attributed to morphine's effect of reducing gut motility, thus prolonging gabapentin's absorption time window.[9] Because GEn is absorbed throughout the gastrointestinal tract with a high oral bioavailability of ∼75%,[1] we hypothesized that morphine coadministration would not markedly alter gabapentin exposure after GEn administration. The present study was conducted in response to a request from the US Food and Drug Administration to evaluate the pharmacokinetics and the pharmacodynamic interaction between GEn and morphine.

SUBJECTS AND METHODS

Design

This was a double-blind, 3-part, single-dose crossover study in nonelderly, healthy adult male subjects. The study was conducted at the PPD Phase I Clinic (Austin, Texas) between August 25, 2011, and October 20, 2011. The study protocol (GSK study RXP115720) was reviewed and approved by a national institutional review board (IntegReview IRB, Austin, Texas). It was conducted in accordance with the guidelines for Good Clinical Practice, all