Morphine and Hydromorphone Pharmacokinetics in Human Volunteers: Population-based Modeling of Inter-individual and Opioid-related Variability

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ABSTRACT

Background: Morphine and hydromorphone have differing effect and side effect onset, magnitude, and duration. Differences between opioids in their interindividual variabilities in pharmacokinetics and pharmacodynamics may influence rational drug selection. Crossover drug studies can provide more informative interindividual variability data than parallel group studies. Using data from a crossover study of intravenous morphine and hydromorphone in healthy volunteers, we tested the hypothesis that morphine and hydromorphone differ in their inter-individual pharmacokinetic variability.

Methods: Arterial opioid and metabolite concentrations from a randomized crossover study in 51 volunteers receiving a 2-h IV infusion of hydromorphone (0.05or 0.1 mg kg^{-1}) or morphine (total 0.1 or 0.2 mg kg^{-1}) 1-2 weeks apart were evaluated with a three-compartmental model for parent opioid and incorporating glucuronides using population modeling (NONMEM). The primary outcome was interindividual variability in pharmacokinetics, based on the coefficient of

variation (%CV) of individual model parameters, calculated as $\sqrt{[\exp(\omega^2) - 1]} \times 100$ where ω^2 is the interindividual variability.

Results: Data were analyzed per drug and in a combined morphine-hydromorphone model. Both analyses indicate that interindividual variabilities for hydromorphone and morphine were comparable with %CV ranging from 9 to 31% for structural model parameters (combined analysis). Similarly, additive and relative residual errors had comparable variabilities, 20 to 40% and 72 to 87%, respectively for morphine and hydromorphone (combined analysis).

Conclusions: Morphine and hydromorphone did not differ significantly or clinically meaningfully in their interindividual pharmacokinetic variability. Interindividual pharmacokinetic variability does not appear a meaningful consideration in the choice between these two opioids.