#12_Morphine and hydromorphone pharmacodynamics in human volunteers: Population-based modeling with focus on response variability and utility

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BACKGROUND: Morphine and hydromorphone have been standard opioids for pain treatment for many years. We previously showed that the onset, magnitude, and duration of effects and side effects for both opioids are considerably different for various clinical endpoints, and exhibit considerable interindividual variability.[1] The present investigation is a secondary analysis of our study in healthy volunteers.[1] The purpose is to model morphine and hydromorphone pharmacodynamics (concentration-effect relationships), with a focus on interindividual pharmacodynamic variability.

METHODS: In a balanced crossover, 51 subjects received a single 2 h intravenous infusion of 0.05 mg/kg morphine or 0.2 mg/kg hydromorphone. Measurements lasted for 12 h and included analgesic response to thermal stimulus (maximally tolerated or limit temperature, and verbal analog pain scores at specific temperatures), pupil diameter, respiratory rate, and end-expired CO_2 concentration. Predicate pharmacokinetic analyses used three-compartment models for both opioids.[2] For each clinical endpoint, morphine and hydromorphone pharmacodynamic data were analyzed together in a single model, with drug as a covariate, to allow assessment of interindividual and drug differences. In addition, a physiological model was implemented to characterize respiratory rate and CO_2 concentration in combination. Pharmacodynamic parameters were centered at their average, which improves estimation stability, while a factor (φ) determined the difference from the average. Models were fitted to the data in NONMEM using a sequence of estimation steps. Utility functions were then constructed as a function of the opioid effect-site concentrations.

RESULTS: Analysis focused on potency parameters, blood-effect-site equilibration half-lives ($t½k_{e0}$) and their inter-individual variabilities. For limit temperature, the combined potency ($C_{1D,Limit}$ = 14.9 ng/mL) had a φ = 0.32, which is significantly different from 1. This yields two separate potency values for morphine (46.9 ng/mL) *versus* hydromorphone (4.4 ng/mL). The combined estimate for $t½k_{e0}$ (0.73 min) has a value of φ (1.02) not significantly different from 1, yielding 0.71 h for morphine and 0.75 h for hydromorphone which are not different. Similarly, the φ value of the other parameters, for other outcomes, baseline value, γ and σ, were not significantly different from 1, indicative that morphine and hydromorphone do not differ significantly in these parameter estimates. The $t½k_{e0}$ for morphine was generally slower than for hydromorphone. Pupil diameter was a more sensitive

measure of opioid effect compared with respiratory effects and analgesia. Interindividual variabilities (% coefficient of variation) in parameter estimates for potency (generally referred to as C_{50}) and $t½k_{e0}$ for the effect outcomes were large, and varied between different effect measures, but none of the interindividual variabilities were significantly different between the opioids (Table).

CONCLUSIONS: There was considerable interindividual variability in pharmacodynamic effect parameters for both morphine and hydromorphone, but no major variability differences between the opioids. Pharmacodynamic potencies for the various endpoints were different between hydromorphone and morphine, but of the same order of magnitude within each opioid. The utility function was more favorable for hydromorphone than for morphine. These results may influence opioid selection.

REFERENCES

1. Meissner K, Dahan A, Olofsen E, Göpfert C, Blood J, Wieditz J, Kharasch ED: Morphine and hydromorphone effects, side effects, and variability: A crossover study in human volunteers. Anesthesiology 2023;139:16-34
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Table. Estimated parameter variabilities (% coefficient of variation) of the potency parameters and blood-effect-site equilibration half-lives ($t½k_{e0}$) for various clinical effects

	Coefficient of variation	
Parameter	**Potency**	**$t½k_{e0}$**
limit temperature	57%	64%
T_{50} of VAS scores	180%	190%
end-expired CO_2	35%	75%
respiratory rate	85%	90%
physiological model	47%	72%
pupil size	25%	52%

Data are from the combined analyses of morphine and hydromorphone. %CV = $\sqrt{\exp(\omega^2 + \nu^2) - 1} \cdot 100$, with ω^2 = variance for interindividual variability and ν^2 = variance for inter-occasion variability.

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