Use of Bayesian forecasting to estimate the pharmacokinetic parameters of ropivacaine in the rat

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INTRODUCTION

Bayesian forecasting can be used to estimate pharmacokinetic parameters (PKP) using sparse blood sampling. It is especially useful in therapeutic drug monitoring in clinical settings where few samples can be obtained. Once the PKP are estimated, it allows for tailoring of dose regimens to keep blood fluid concentrations within a safe and effective range of concentrations.

The approach requires knowledge of population average and variances of PKP, known variability in drug assay techniques, and at least one blood sample.

Often in animal PK studies, there may be cases where few samples are available. Adoption of the Bayesian approach might be useful to estimate PKP in such studies. It might also allow for a reduced number of animals to be required in study protocols.

OBJECTIVES

Here we sought to explore its utility in rats given ropivacaine for which there were only a small number of plasma concentrations available.

METHODS

- Estimates of ropivacaine clearance (CL/F), volume of distribution (Vd/F) and time of maximum concentration after subcutaneous doses (tmax) to Sprague-Dawley rats were found in Drug Delivery, 2011; 18(5):361.
- Webplotdigitizer was used to determine the PK profiles after subcutaneous doses of 10 mg to 200 g Sprague Dawley rats.
- The nonlinear curve fitting program PKSolver was used to determine the optimal PK compartmental model for ropivacaine
- Three rats were given 7.5 to 15 mg/kg doses of ropivacaine and two samples per rat were drawn. This was repeated 5 days later.

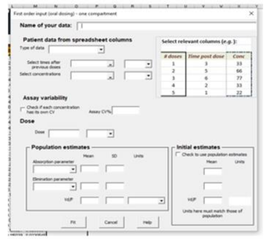
METHODS; Rat study.

jugular veins were cannulated. → Ropivacaine was dosed subcutaneously (7.5mg/kg to 15mg/kg. → two samples per Rat were drawn. → This was repeated 5 days later.

- After each dose, two blood samples were obtained 0.5 to 6 h post dose.
- Plasma was assayed using HPLC-UV.
- Plasma concentrations were input into a Microsoft Excel add in program (PKB-est) along with the literature PKP, an estimate of assay precision drug doses. The program is described in Research in Pharmaceutical Sciences 15 (6), 503.

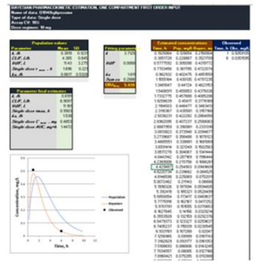
METHODS; Bayesian estimation.

The PKB-est, Add-in for Excel program, was used here to demonstrate the utility of the Bayesian estimation process using a minimum of blood samples



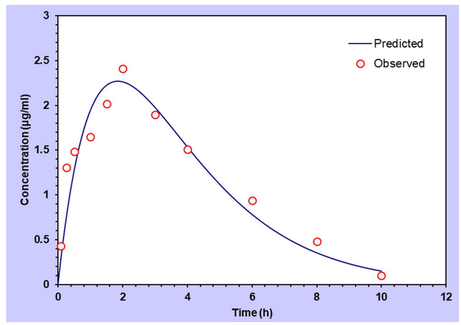
Data entry

Minimize Bayes Objective Function



Report generated with estimated PKP

RESULTS



Comparison between pharmacokinetic parameters from the literature and using Bayesian method

Pharmacokinetic Parameter	CL/F L/h/kg	Vd/F L/kg	Tmax h
From the literature	4.37±0.65	11.4±3.27	1.70±0.22
Using Bayesian method	7.85±2.66	11.4±3.35	0.91±0.16

- The digitized data and the fit from the one compartment model (best model based on Aikake Information Criterion) is shown above
- The PKP were reasonably close in our rats using sparse sampling and Bayesian forecasting to the literature values.
- The Bayesian method yielded higher CL/F ($p<0.05$, Student's t-test for unpaired samples) but similar Vd/F as the literature report.
- However, the weights (428 g) of our rats were higher than in the published study (200 g).
- It is of note that our rats were significantly higher in weight than those in the literature study. The apparent difference in CL/F could reflect an age-related difference in metabolism of ropivacaine. Indeed, it was reported that CYP3A in rat is higher in 400 g than 200 g Sprague-Dawley rats (Biochemical Pharmacology, Vol. 60, pp. 1601–1610, 2000).

CONCLUSIONS

Using sparse sampling the Bayesian method appeared to provide reasonable estimates of the PKP of ropivacaine in the Sprague-Dawley rat.

FUTURE DIRECTIONS

To use the approach to determine PKP in rats with conditions where it is difficult or risky to obtain numerous blood samples (e/g/ obese rats, to study the effects of obesity on drug disposition).