K61 On the Statistical Distribution of V_{max} for Ethanol Pharmacokinetics

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After attending this presentation, attendees will better understand how to model a sample population distribution that is applied to the pharmacokinetics of ethanol and the calculation of appropriate prediction intervals.

This presentation will impact the forensic science community by explaining the difference between confidence, prediction, and tolerance intervals and how they can be calculated and applied to ethanol pharmacokinetics.

Pharmacokinetic parameters such as volume of distribution, maximum blood concentration, and rate constants have been found to be lognormally distributed.[1-3] Although this has been taken by pharmacokineticists to apply to all parameters in pharmacokinetic models, data for V_{max} in ethanol has been lacking. Jones, in his review, gives a frequency histogram for V_{max} values (~ elimination rates) with a normal distribution curve superimposed and stated that the distribution fit well to a normal curve but did not give the results of any goodness of fit tests.[4] Jones also stated that the tails of the distribution are unreliable. This would be the case if they follow a lognormal distribution.

This study extracted a sample of V_{max} values from the literature and used additional data to fit 121 values to both a normal and lognormal distribution.[5-9] Studies were selected if at least a regression was conducted on the terminal values. Studies with only two levels were excluded since ethanol follows a two-compartment open pharmacokinetics model with Michaelis-Menten elimination. The best estimates of V_{max} will be obtained by regression or non-linear regression of the appropriate pharmacokinetic model as outlined by Wagner.[10] A fit of the values to a normal distribution was tested by the Anderson-Darling test, the Cramer-von Mises test, the Kolmogorov-Smirnov (Lilliefors) test, the Pearson chi-square test, and the Shapiro-Wilk test. Only the Kolmogorov-Smirnov test did not reject at the 0.05 level. All tests were conducted in the statistical program R using the package "nortest."

The data was log transformed to obtain the mean ($\bar{x}$=-4.152) and standard deviation (s=0.322) and repeated the tests. None of the tests rejected the null hypothesis. That is, the lognormal distribution seems to be an excellent model for the sample of ethanol elimination rates, V_{max}.

This then brings us to the use of values for the simulation, either forward or backward, of ethanol blood levels. The use of a single value is scientifically invalid and the appropriate way to make a prediction that is used repeatedly is to calculate a tolerance interval. That is, one would like values to predict a range of ethanol blood levels that would cover some specified percentage of the population with 100(1 - α)% tolerance or a lower (or upper) confidence bound to be exceeded by (or to exceed) at least 100*p*% of the population.[11] The concept of prediction and tolerance intervals allows one to calculate the required interval.

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