On Some Approaches for Estimating Tolerance Limits in Dose Finding Studies

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In a dose finding study the aim is to come up with a safe and efficient drug administration (Rowland and Tozer 1995). The question of how much drug should be used and how it should be administered for a given therapeutic purpose can not readily be answered. Basically two different methods have been used to answer the question in a population: empirical and population kinetic. The kinetic method, which is to be considered in this paper, is based on the hypothesis that therapeutic and toxic responses are related to the amount of drug in the body or to the plasma drug concentration. The desired range of concentrations $[v_1, v_2]$ in which the chances of successful therapy is high defines the therapeutic window. Precise limits of the therapeutic window are not definable but approximate limits will be determined by the location of the maximal therapeutic efficacy. Knowing the therapeutic window, it is possible to find the appropriate dosage for a population. In a dose finding study, the estimated statistical tolerance limits of the concentrations from sample data may be compared with the therapeutic window. While the (statistical) tolerance limits provide information about where the population sampled is likely to be concentrated, the dosage of the drug can be calibrated in a repeated study to attain a large proportion of the population within the desired concentration interval $[v_1, v_2]$. If the upper tolerance limit w is less than v_2 the dosage can be increased, and if w is larger than v_2 the dosage must be reduced. The lower limit v_1 is considered only if also low concentrations are toxic.

In this paper a principal question of how to estimate the upper tolerance limit w for a particular drug in a dose finding study is discussed. Two different estimation approaches are considered where $\mathbf{X} = (X_1, \mathrm{K}\ , X_n)$ represents a sample of n measurements: 1.) The conservative approach where $P_{\mathbf{X}}\left[P_{X_i}(-\infty \le X_i \le \hat{w}_{con}) \ge \beta\right] \ge \gamma$ defines a one-sided statistical β-content tolerance interval at the confidence level γ (Wilks 1941). This approach is intended for drugs where the risk of adverse side effects rapidly increases with an overdose, e.g. even a minor overdose may result in death. 2.) The expectation approach where $E_{\mathbf{X}}\left[P_{X_i}(-\infty \le X_i \le \hat{w}_{\exp})\right] = \beta$ defines a one-sided statistical β-expectation tolerance interval (Kotz and Johnson 1988). This approach is intended for drugs where the expected outcome of an overdose is harmless, e.g. discomfort.

Defining efficiency as the proportion of the population within the therapeutic window, the

difference in efficiency of the two approaches can be calculated for some arbitrary estimators (Petzold 2001). A study of the difference was performed for some *n* where the 95:th percentile of the true distribution was used as the fixed upper limit v_2^{95} of the therapeutic window, and the lower limit v_1^p was used as the independent variable over the interval $0 < p < 95$. As can be seen in Figure 1, the difference in efficiency *D* is positive for all values of *n* and *p*. This implies that the expectation approach is expected to attain a larger proportion of the population within the therapeutic window than the conservative approach. Considering this analytical result, it is now obvious that a proper usage of the two approaches is important. To avoid overdoses of drugs with severe side effects, one has to use the conservative approach, but this approach would often be too inefficient to be motivated for drugs with harmless side effects.

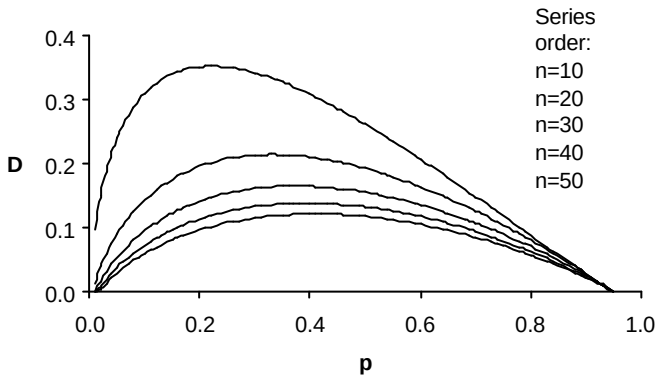

Figure 1. The difference in efficiency *D* calculated as the efficiency of the expectation approach subtracted with the efficiency of the conservative approach for $\beta = \gamma = 0.95$

REFERENCES

Kotz S, Johnson NL, eds. (1988). *Tolerance regions, statistical*, Vols. 9. New York: Wiley.

Petzold M (2001). A comparative study of some approaches for estimating tolerance limits. *Drug Information Journal* 35(3), to appear.

Rowland M, Tozer TN. (1995). *Clinical pharmacokinetics: concepts and applications*. Baltimore: Williams & Wilkins.

Wilks SS (1941). Determination of sample sizes for setting tolerance limits. *The Annals of Mathematical Statistics* 12, 91-6.

RESUME

Une étude comparative de quelques approches d'estimation des limites de tolerance - Dans une étude de recherche de dosage, l'objectif est de trouver une administration du médicament efficace et sûre. En comparant les limites de tolérance estimées des concentrations, avec un intervalle desiré préétabli, c'est-à-dire, la fenêtre thérapeutique, on pourra ajuster le dosage du médicament de façon à atteindre une large proportion de la population comprise dans cette fenêtre. Ici, on compare l'efficacité thérapeutique de deux approches d'estimation communes, en la trouvant considérablement élevée.