DEMONSTRATIONS

Confidence intervals for pharmacokinetic parameters

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When a non-linear curve-fitting procedure has been used to estimate the parameters of a pharmacokinetic model using data from a single subject, users often feel impelled to seek confidence limits for the estimates.

Two methods of obtaining such limits have been described by Boxenbaum, Riegelman & Elashoff (1974) as the 'univariate' and 'support plane' methods. Both of these methods rely on an approximation, which in practice may be very poor, to produce upper and lower limits for each parameter separately.

A confidence region in the form of a hyper-ellipsoid can be constructed (Scheffé, 1959) which is an improvement on these methods in the statistical sense, but which has the disadvantage that it is difficult to visualise and summarise.

Another approach to the determination of a confidence region (Box & Coutie, 1956) depends upon a more realistic approximation than the above methods and defines an unsymmetrical region, not a figure of rotation, from which limits on individual parameters can be derived.

Such regions can be further improved, or their deficiencies indicated, by a modification introduced by Beale (1960).

All methods which purport to place limits on individual parameters yield simple and readily comprehensible information, but may be grossly misleading since the situation is in fact complex and the parameters inter-related.

It is suggested that unless special reasons exist, it may be better not to waste effort calculating confidence limits which are merely deceptive and do not advance the solution of most practical pharmacokinetic problems.

References

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An *in vitro* bioassay for aldosterone (and corticosterone) output stimulating substances

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Capsule strippings of rat adrenals are incubated with collegenase to form dispersed cells consisting mainly of zona glomerulosa cells (about 95% zona glomerulosa and 5% zona fasciculata). The output (supernatant plus cell extract) of aldosterone and corticosterone are measured by immunoassay.

There are four types of responses:

(a) ACTH (or cAMP), at relatively high doses, gives the greatest steroidogenic response. This must be due to some function of the contaminating zona fasciculata as pure zona glomerulosa cells give ACTH (or cAMP) responses of the same order of magnitude as for other stimuli. (Tait, Tait, Gould & Mee, 1974).

(b) The response of aldosterone to K^+ shows a maximum at 8.4 mM K^+. The response then declines at 13 mM. There is a significant effect with a minimum increment of about 0.3 mM at 3.6 mM K^+.

(c) The steroidogenic response to 5-hydroxytryptamine (5-HT) shows a maximum at about 10^{-5} M which remains constant. This maximum response is of the same order as for K^+. There is a significant threshold response with about 10^{-9} M 5-HT.

(d) Angiotensin II significantly increases steroidogenesis at 10^{-10} M but has a constant maximum below that of K^+ and 5-HT. The characteristics of the response to AIII are similar to those of AII with an equivalent maximum response.

A six point assay for angiotensins (output aldosterone v dose peptide) can be operated routinely. Assays of AII v AIII show straight line parallel slopes and an index precision of about 0.25. The potency of AIII is about 10% of AII. Potency ratios of other peptides (using AII as standard) will be given.

As shown by plotting aldosterone/corticosterone[2] against supernatant corticosterone concentration, only K^+ specifically affects the aldosterone/corticosterone