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Dose-Finding and Optimisation Designs

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Introduction

Knowledge of the issues related to clinical research is a requirement to the fuller understanding of the practice of evidence-based medicine (Columb et al. 2003). The prospective double-blind randomised controlled trial is essentially the gold standard for research methodology. Usually, these designs compare fixed levels of one or more variables and different outcomes. However, in dosefinding studies, there are often numerous doses, drugs and combinations to be investigated. Decisions on which combinations are most useful from the plethora of diagnostic tests and biomarkers are related problems (Fischer et al. 2003). Clinical research is driven to identify advantageous mixtures of drugs, to reduce side effects and to possibly identify synergistic combinations. In this article, we briefly consider two methods that have been appearing in recent literature in the setting of dose-finding: Up-Down and Direct-Search designs.

Up-Down Designs

These, sometimes called threshold or sensitivity tests, were promoted by Dixon in the 1960s and are used to concentrate testing about a particular response probability, usually the median effective dose (ED50) in efficacy or lethal dose (LD50) in toxicity trials (Dixon, 1965). The dose used varies up or down based on the outcome of the previous test. Testing gets concentrated around the eventual ED50. If, for example, we try to ascertain the LD50 of a drug (this is an easy example as the outcome of death is clearly a finite one) then the up-down method provides a point estimate of the LD50 and does this rather efficiently for many chemicals by only using six or seven animals (NICEATM, 2000). These methods have been used to estimate minimum alveolar concentration (MAC) for inhalational anaesthesia, minimum infusion rate (MIR) for intravenous anaesthetics, minimum local analgesic concentration (MLAC) for local anaesthetic agents and ED50 for vasopressors. The ED50 is analogous to measures of the central tendency of distributions, such as mean and median. As such, these are estimated with better precision compared to extreme values like the ED95. Therefore, tests of hypotheses using ED50 will have more power to detect differences if these exist.

As testing is concentrated around the eventual ED50, a number of issues follow with regard to the slope of the dose-response curve, ED95 and random versus sequential allocation. It has been suggested (D'Angelo and James, 1999; Columb and D'Angelo, 2006), that, because dosing is centred at ED50, there is little information regarding the slope of the dose-response relationship. In fact, testing at one standard deviation above and below the ED50 corresponds to the ED16 and ED84 point estimates, which essentially are the limits of the most linear part of the cumulative dose-response plot. So in effect, up-down designs actually concentrate testing where the slope is most defined. Errors in testing at extreme values (such as at or above ED95) receive more weight in usual regression analyses, which then are more likely to lead to incorrect estimates of slope. In addition, a pharmacological maxim that drugs, which act via the same receptor or mechanism have parallel doseresponsecurves, suggests that knowledge of the entire distribution is not absolutely required to make inferences. Therefore, drugs with differing slopes generally act by different mechanisms and are usually chemically distinct and from different classes! Since pharmacological potency is defined as the measure of the dilution in which the drug is effective, characterised by the inverse of EC50 (molar), then we can state that drugs with different EC50 values have different potencies. This being the case, they do not occupy the same doseresponse distribution and, by definition, are not bioequivalent. By design, doses are sequentially allocated in up-down studies, not randomised. A possible bias may occur in study of a single sequence when there have been a series of effective or ineffective doses. The longer the series, the greater is the likelihood and expectation of a reversal! In this instance, the researcher may consider running two or more simultaneous sequences such that any subject can be randomised to a particular sequence and the data then can later be pooled for analysis. This improvement allows the design to achieve randomisation, which is more robust and closer to the gold standard design.

Direct-Search or Optimisation Designs

This is again essentially a progressive design, but comparing multiple drugs and doses simultaneously. The fundamental problem with finding optimal combinations is dimensionality, as there are usually different dosing levels, drugs and combinations of both, that can be studied resulting

in a factorial solution. For example, to find the optimum combination from four dose levels of four different drugs there are 256 (44) possible combinations or groups to be studied. Additionally, differing modes of administration make the situation even more complicated. In effect, the dimensionality problem has generally limited studies to only considering two or three drugs in combination due to the number of patients required. An example is the study by Minto et al. (2000) where combinations of midazolam, propofol, and alfentanil were studied and the authors needed 400 subjects to identify an optimum combination of three drugs for loss of consciousness. The process of the direct-search methodology is not unlike and can be described as similar to a multidimensional amoeba crawling along a response surface, sending out sensing pseudopods or combinations, with the elimination of poorly performing combinations advancing the complex to then converge on a peak or optimum combination on the surface (Berenbaum, 1990; Sveticic et al. 2003). Typically, six different combinations are studied as part of a complex. The outcomes are rated and the centroid of the complex is advanced away from poorly performing combinations to suggest more optimal combinations for further evaluation. This process continues until no further improvements occur, or indeed a peak is passed with evidence of worsening outcomes. Further mathematical refinements, which decide on the identification and partitioning of complexes based on performances and outcomes, potentially accelerate an already efficient search algorithm. Therefore, the number of subjects needed to have an effective trial is much lower than expected for such dimensionality problems.

Direct search designs have the distinct advantage where subjects are scarce and the treatments are not without risk, such as with cancer chemotherapy. This clearly does not apply to the setting of anaesthesia. The disadvantage, however, is that as the sample sizes are small, there is little certainty or precision with any estimates. Rather, certain combinations are suggested as attractive for future study. Therefore, although it has been of interest to see these methods have been applied to assess anaesthetic drug combinations, the impact of the results has not been as impressive.

Conclusion

Clinical pharmacology of dose-finding designs is progressing further with trials that combine methodologies such as isobolography and updown designs, which can address issues such as addition, synergism and antagonism (Columb, 2006). Clearly, the trend to using dose-finding rather than fixed dose designs will improve further our understanding of clinical pharmacodynamics.

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