The value of therapeutic drug monitoring to the practising physician – an hypothesis needing sensible application!

Dr McInnes (1989) begins his article on the value of Therapeutic Drug Monitoring (TDM) by describing the non-users' naive concept of the subject – that all clinical measurements and observations are ignored in pursuit of an 'ideal concentration' which is right in the centre of the 'target range' for all patients. This has never been the strategy for TDM. He then goes on to dismiss two of the most relevant contributions which TDM makes to clinical care – the differentiation of drug induced toxicity from other symptomatology and poor drug response from non-compliance. Having dismembered the rationale he then goes on to attack the 'hypothesis'. It could be said of his article: 'Se no e vero ma e ben travato' (Giordo Bruno 1548–1600).

Therapeutic drug monitoring is only applied to a limited group of drugs which have (as Dr McInnes concedes) 'a pharmacological action that is difficult to measure clinically'. We are therefore fortunate in having an additional objective method for assessing these compounds in clinical use. It is probably true to say that when 'target ranges' were established, less rigid criteria were applied to the study design than now. It is, however, also true that target ranges thus developed have stood the test of time around the world – the ultimate test for all drugs and presumably their concentration 'ranges'.

Regarding the first of Dr McInnes 'inherent assumptions', it is naive to interpret rigidly *any* result in relation to a range and this applies to endogenous compounds in Biochemistry just as much as to xenobiotics in Clinical Pharmacology. The 'target range' implies a ranging shot, a first best guess based on the knowledge that the majority of patients will achieve some response without risk of toxicity. However, drug levels are an adjunct to the clinical picture and doses should be modified according to the individual's pharmacodynamic response (based on 'sound clinical judgement') using pharmacokinetic principles to aid titration of the dose to achieve the appropriate end point.

In our opinion TDM is a demanding subject. It demands a knowledge of pharmacokinetics and the influencing factors and a knowledge of pharmacodynamics to assess the side effects and drug interactions which can result in apparent toxicity or lack of effect. To quote his example: knowledge of the effects of electrolyte or thyrometabolic status on digoxin sensitivity are well known to practitioners of TDM: we have to say however that this is often not the case for our requesting physicians. We found 6% of one of our patient sets had hypokalaemia while on digoxin (Watson, unpublished observations). This was detected in half of these only because we always measure serum potassium and digoxin. It is also necessary occasionally to point out that the appropriate therapy is potassium supplementation, not alteration of the digoxin dose.

It has to be said that some applications of 'TDM' are unnecessary and irrelevant and others require more detailed formal study to assess their value. For example, valproic acid monitoring is rarely justified as is the 'routine' monitoring of drugs with no clinical rationale for performing the analysis. However, criticising the concept of TDM on the basis of the requesters inability to sample correctly or interpret the result sensibly argues for an informed service and education of medical staff to utilise the service appropriately, not discontinuation of the service. Clinical pharmacology is not a specialty seen much outside teaching hospitals. However, we have found that adoption of the skills of trained pharmacists and/or biochemists can result in a knowledgeable service and one which we recommend to all. Whether the results are reported in molar SI or mass units is irrelevant provided one knows how to interpret the result and can make an appropriate dosage recommendation (according to clinical targets).

Dr McInnes states that the evidence that target concentrations can be achieved using clinical pharmacokinetic principles is based on a biased population of patients presenting with a clinical problem – if this is true, why was 'sound clinical judgement' not able to hit the correct dose? As the clinician is ultimately responsible for the dose prescribed (NOT the clinical pharmacokineticist) the advice was obviously considered to be clinically relevant or else the dose would not have been changed. Despite Dr McInnes's beliefs, TDM does not demand changes in dose merely to achieve a target concentration particularly when the patient is well controlled with no adverse effects.

With regard to the evidence supporting the improvement of clinical outcome, there is a wealth of data on this subject and Dr McInnes

has chosen to ignore the majority of it. Studies have shown the benefit of TDM for theophylline (Lehman & Leonard, 1982; Mungall *et al.*, 1983), aminoglycosides (Deziel-Evans *et al.*, 1982; Bookman *et al.*, 1979; Noone *et al.*, 1974), anticonvulsants (Ionnides-Demos *et al.*, 1988) and digoxin (Koch-Weser *et al.*, 1974). In a recent review on the cost-effectiveness of TDM, Vozeh (1987) observes 'There are sufficient data to conclude that the cost-benefit ratio can be improved by performing therapeutic drug monitoring with the appropriate expertise'. Destache *et al.* (1989) suggest savings on hospital revenue of over $600,000 pa for an aminoglycoside clinical pharmacokinetics service!

In summary, appropriately interpreted serum drug concentrations provide an objective addition to the medical algorithm termed 'sound clinical judgement'. This algorithm improves with relevant data. The essential point is that there are valid data available for most drugs, but better data are required, clinical trials should be judiciously used. A very similar argument has been put forward by Vozeh (1988) in response to the article by Spector *et al.* (1988).

The final question is – can the practising physician defend the clinical interpretation of drug concentrations incorrectly sampled in a biochemically deranged patient against the weight of evidence that comprises the world knowledge base of therapeutic drug monitoring?

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