The value of therapeutic drug monitoring to the practising physician – an hypothesis in need of testing

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Therapeutic drug monitoring may best be defined as a strategy whereby the dosing regimen for a patient is guided by repeated measurement of plasma (or serum) drug concentrations (Spector *et al.*, 1988). Concentrations above a previously determined 'target' or 'therapeutic' range are considered 'toxic' or 'potentially toxic' and levels below 'subtherapeutic'. Such information allows refinement of the dose to bring the plasma concentration into the target range. Measurement of drug concentrations to confirm toxicity or to assess compliance lies outside this concept.

Individualisation of drug dosage by measurement of plasma concentration to provide an optimal therapeutic response while avoiding the risk of toxicity has an intuitive logic. Unfortunately, not all drugs have properties compatible with therapeutic drug monitoring and relatively few that do are in common clinical use. Lithium has been considered a model drug in this context, and many argue that it is indefensible to prescribe lithium salts unless facilities for frequent assays of plasma concentration are available (Amdisen, 1980; Anonymous, 1979). Other drugs for which regular therapeutic drug monitoring is widely advocated include aminoglycoside antibiotics (Friedman & Greenblatt, 1986; Spector *et al.*, 1988), digoxin (Brodie, 1986; Spector *et al.*, 1988), some anticonvulsants (Brodie, 1986; Davidson, 1983; Scott, 1984) and theophylline (Flenley, 1983). Each of these agents satisfy the following criteria to a greater or lesser extent.

1. There must be an accurate, precise, specific, inexpensive and readily available assay for the drug.
2. The drug should have a pharmacological action that is difficult to measure clinically; there is no advantage in therapeutic drug monitoring if the drug's effect on the patient can be assessed readily.
3. The drug should have a narrow therapeutic index.
4. Plasma drug concentrations should correlate with and reflect the intensity and duration of the drug's effect at its site of action but should not be predicted accurately in individual patients by the administered dose. In these circumstances, pharmacological action would be expected to

relate more closely to plasma concentration than to dose. Implicit in this proposition is the notion, critical to therapeutic drug monitoring, that variability in the concentration-effect relationship is less than variability in the dose-concentration relationship.

These considerations are of great academic interest but are of secondary importance to the practising physician whose main concern is whether the goal of optimal patient care is achieved more efficiently by therapeutic drug monitoring than by conventional practice. Three assumptions inherent to therapeutic drug monitoring are crucial and must be examined to assess its potential clinical value.

1. There is a well-defined target range where the patient experiences maximum clinical benefit with minimum risk of toxicity. This implies a clear and consistent relationship between plasma concentrations and therapeutic or toxic effects.
2. Dosage adjustment based on plasma drug concentration measurements decreases the inter-individual variability in plasma concentrations. Applied to individual patients, outlying values can thus be brought into the target range.
3. Attainment and maintenance of values in the optimal target range by adjustment of dose and dose frequency based on measurement of plasma drug concentrations leads to greater benefit to the patient than can be achieved by the exercise of sound clinical judgment.

Target ranges are widely quoted for the commonly monitored drugs. However, these may not hold for individual patients who frequently show considerable departures from population-determined ranges. For lithium (Amdisen, 1977), aminoglycoside antibiotics (Spector *et al.*, 1988), digoxin (Anonymous, 1985; Aronsen *et al.*, 1978; Beasley *et al.*, 1985; Fogelman *et al.*, 1971; Goldman *et al.*, 1975; Ingelfinger & Goldman, 1976; Smith & Haber, 1970), anticonvulsants (Feldman & Pippenger, 1976; Gannaway & Mawer, 1981; Reynolds *et al.*, 1981) and theophylline (Woodcock *et al.*, 1983), there is often no clear distinction between ineffective, effective and possibly toxic concentrations. As a result, therapeutic effects without toxicity may be observed at concentrations

outside the population target range while toxicity may be encountered within the same range.

Problems in defining clinically useful target ranges arise at least in part from the many factors which can influence the plasma concentration-effect relationship. The risk of renal toxicity at a given plasma gentamicin concentration is influenced by age, sex, and electrolyte and water balance (Kaloyanides, 1984) while myocardial sensitivity to digoxin depends critically on electrolyte and thyroid status, *inter alia* (George, 1983; Sonnenblik *et al.*, 1983). In clinical practice, inter-individual variability in the plasma concentration-effect relationship may be considerable and may even exceed the variability in the dose-plasma concentration relationship (Spector *et al.*, 1988). This is of course the reverse of an essential principle of therapeutic drug monitoring (*vide supra*).

Much therapeutic drug monitoring is rendered useless either by failure to consider the time of sampling in relation to the time of dosing or by polypharmacy. Plasma digoxin concentrations in the first few hours after administration are notoriously misleading since they are confounded by the lag period of distribution and induction of inotropy (Kramer *et al.*, 1979). The relationship between plasma gentamicin concentration and therapeutic efficacy may be altered if another antibiotic is given simultaneously while nephrotoxicity is enhanced without change in plasma concentration by concurrent diuretic administration (Kaloyanides, 1984). The risk of digoxin toxicity with plasma concentrations in the target range is increased not only by diuretic-induced hypokalaemia (Smith, 1971) but also by pharmacodynamic drug interactions particularly with other antiarrhythmics (George, 1982). In these circumstances, sensible interpretation of the results of therapeutic drug monitoring is impossible.

Uncertainty about the relationship between plasma drug concentration and drug action at the presumed 'receptor site' further contributes to the difficulty. Blood concentrations of digoxin and theophylline only approximate to activity at their 'receptors' which appear to exist in an effector compartment remote from the central compartment (Kramer *et al.*, 1979; Whiting *et al.*, 1981). A close association may not hold even for aminoglycoside antibiotics if penetration to the locus of infection is complicated (McCormack & Schentag, 1987). Thus, target ranges may merely act as flawed mirrors which provide distorted reflections of pharmacodynamic actions.

There is abundant evidence in support of the second assumption (Spector *et al.*, 1988). Surveys of routine plasma samples received by drug

monitoring laboratories show a relatively low proportion of patients with values in the target range (Brodie *et al.*, 1985; Whiting *et al.*, 1984; Woodcock *et al.*, 1983) and a dramatic improvement in the number within that range after information on drug levels is made available (Sheiner *et al.*, 1975; Whiting *et al.*, 1984). These findings have been cited to endorse the clinical value of therapeutic drug monitoring (Brodie, 1986; Whiting *et al.*, 1984). However, while they certainly demonstrate that pharmacokinetic advice 'improves' pharmacokinetics in individual patients, such experience provides no evidence that therapeutic drug monitoring improves pharmacodynamic responses in the general clinic population. It is likely that initial samples came from a biased population of patients identified on clinical grounds as presenting a particular therapeutic problem and therefore containing a disproportionate number of values outside the target range.

Away from specialised pharmacokinetic centres there is strong indication that drug assay requests are often inappropriate and that the resultant dosage adjustments are frequently unsound (Gibb *et al.*, 1986). One contributing factor may be that therapeutic drug monitoring has been largely delegated to clinical chemists who have little knowledge of clinical pharmacology. They provide results in inappropriate SI molar units and fail to give an adequate service with relevant advice to the practising physician.

The third assumption is the most important for the practising physician. What evidence do we have that the optimism expressed in this assumption is well founded?

Digoxin toxicity in a hospital with access to a rapid drug assay was significantly less frequent than in a similar institution without such a facility (Duhme *et al.*, 1974). This much quoted study was not randomised, however, and factors other than the availability of a digoxin assay may have influenced the outcome. Interestingly, measurement of digoxin concentrations was not associated with evidence of increased efficacy. Experience in support of therapeutic drug monitoring for other drugs is even less convincing. In a retrospective study of patients treated with aminoglycoside antibiotics (Arroyo *et al.*, 1986), knowledge of the results of drug assays did not appear to improve the outcome of infection or the incidence of nephrotoxicity. A randomised trial (Lehmann & Leonard, 1982), failed to demonstrate an advantage for the individualisation of theophylline dosage on the basis of drug levels when compared to standard prescribing. The evidence in favour of therapeutic drug monitoring of lithium is substantial but entirely

anecdotal (Amdisen, 1977, 1980; Baastrup & Schou, 1967) while the frequently voiced claim that therapeutic drug monitoring facilitates the use of anticonvulsant drugs (Brodie, 1986; Scott, 1984; Shorvon *et al.*, 1985) is not supported by adequate studies. Indeed, recent findings of a gradual spontaneous remission in many epileptics (Callaghan *et al.*, 1988; Shinnar *et al.*, 1985) emphasise the importance of concurrent control patients when assessing the value of therapeutic drug monitoring.

Thus, the evidence that therapeutic drug monitoring improves overall patient outcome is far from compelling. Furthermore, an educational programme has shown that the incidence of digoxin toxicity in a susceptible hospital population can be reduced without the aid of drug assays (Ogilvie & Ruedy, 1973) while therapeutic audit of phenytoin prescribing in one hospital (Cawthorne & Silas, 1981) resulted in a rapid improvement in seizure control, attributable to better dose-titration against fit frequency and not to increased measurements of drug concentrations. Therefore, an equally cogent argument can be made for careful dosage adjustment based on clinical response and biochemical finding with the aim of achieving the lowest dose to control the disease process.

In the final analysis, theoretical considerations, pharmacokinetic studies and the anecdotal experience of enthusiasts cannot provide the evidence necessary to decide whether or not, in the hands of the practising physician, knowledge of plasma drug concentrations results in better therapy. This can be achieved only through rigorous clinical trials. An appropriate approach based on sound methodology has been described recently (Spector *et al.*, 1988). Therapeutic drug monitoring and dosage regimens based on clinical and biochemical information, each administered by knowledgeable and experienced physicians, must be compared in prospective, controlled, randomised trials of adequate size. Since blinding would be difficult or impossible, carefully predetermined quantitative end-points are essential

and assessment of outcome should ideally be carried out by an independent observer ignorant of the assignment of patients to each therapeutic approach. The presumed ethical problem of how to withhold information on drug levels in the management of seriously ill patients should not deter investigators from undertaking these studies since it presupposes that this information is important. Furthermore, unless these trials are conducted, we may be faced with a real ethical dilemma in that the weight of poor quality anecdotal information in the literature may make the necessary clinical trials unethical in the eyes of many.

In the light of all the uncertainties, why is therapeutic drug monitoring so widely advocated? The evolution of therapeutic drug monitoring has paralleled the development of simple drug assays, and great advances in our knowledge of pharmacokinetics and of kinetic-dynamic relationships. It has also coincided with the emergence of clinical pharmacology as a distinct discipline. To some, it appears inevitable that application of the theory of plasma drug level monitoring and clinical pharmacokinetics must improve patient care while, at the same time, offer an arena in which clinical pharmacology will make a major contribution. Unfortunately, this attractive concept remains but an hypothesis. Too much unrealistic enthusiasm for therapeutic drug monitoring as an essential component of rational prescribing confronts the practising physician. Too little effort has gone into testing the hypothesis. The time has surely come to question the 'intuitive logic' of therapeutic drug monitoring.

'The time has come', the Walrus said,
'To talk of many things:
Of shoes – and ships – and sealing wax
Of cabbages and kings
Of why the sea is boiling hot
And whether pigs have wings'

(Lewis Carroll, *Through the Looking Glass*).

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