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Therapeutic drug monitoring beyond 2000

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Clinical Pharmacologists are a paranoid group. I know of no other subspecialty whose practitioners spend their time so openly 'seeking a role' [1], taking 'a view for the 1990s' [2] or reviewing its 'efficacy and prospects' [3]. Cynical outsiders might even suggest that all this introspection indicates lack of sufficient occupation. Indeed a famous and much quoted book review went so far as to ask 'who needs Clinical Pharmacology?' [4]. Mitchell's article [4] makes interesting reading since he seemed to believe that Clinical Pharmacology has nothing to do with therapeutics. His analogy was that prescribing drugs is like driving a car and that it is not necessary to know how the brakes or accelerator work in order to use them. He claimed that in the 'real world' a prescribing doctor simply says 'if it's safe then let's give it to patients with X and see if it works' [4].

I believe that Clinical Pharmacology actually encompasses the entirety of this statement. How can we know that a drug is safe in patients without performing well designed studies? How do we know if it works in X unless we understand all aspects of the pharmacokinetics and pharmacodynamics of the drug? These questions are at the heart of Clinical Pharmacology and interface with therapeutics in a number of ways including therapeutic drug monitoring (TDM).

TDM involves many health professionals; laboratory scientists, clinical pharmacists and junior doctors are all essential to the process. However clinical pharmacologists are often the individuals that provide the overview. Many articles of the 'Whither Clinical Pharmacology' type include sections on drug concentration monitoring as a key element of a Clinical Pharmacology service [5]. Pioneers of drug monitoring in the 1970s focussed on adverse drug reactions and demonstrated quite clearly, that by constructing therapeutic ranges, the incidence of toxicity to drugs such as digoxin [6], phenytoin, lithium and theophylline [7] could be reduced. It was also recognised that a number from a laboratory could not be interpreted in isolation but needed to be reviewed together with clinical details of the patient from whom the sample had been taken. Thus the indications for drug monitoring widened to include efficacy, compliance, interactions etc. [8, 9]. This gave Clinical Pharmacologists a clearly identified role and,certainly in Australia, a number of Clinical Pharmacology departments were established in the late 1970s and early 1980s, with a primary role of performing drug monitoring. Whether part of an academic unit or directly answerable to a teaching hospital, these units not only performed routine services but conducted research in many areas where drug concentrations could easily be incorporated. This engendered a somewhat complacent attitude which was severely punctured by a member of this Journal's present Editorial Board when he claimed that the value of TDM to a practising physician was 'an hypothesis in need of testing' [10]. He threw down the challenge that although TDM is an attractive concept there was very little evidence that it improved overall patient outcome. He argued that there was evidence that careful dosage adjustments based on clinical response and biochemical findings could be just as effective without closing the circuit by including the plasma drug concentration.

There was certainly published literature to support this point of view. A prospective evaluation of drug monitoring in Kansas suggested extensive inappropriate sample collection and misapplication of results causing unjustifiable expenditure [11]. A similar Australian audit also demonstrated inefficient use of services and unnecessary costs [12]. In contrast more recent work has provided some evidence for the usefulness of drug assays in certain specific situations and Cridland has provided a number of ways in which drug monitoring services can be assessed as to their usefulness and cost effectiveness [13]. A meta -analysis of studies on TDM, albeit of a limited number of drugs, showed that TDM does appear to be beneficial for patients taking theophylline or digoxin [14]. The same group also concluded that a clinical pharmacokinetic service run by clinical pharmacists could have a significant influence on the proportion of patients with desirable serum drug concentrations. Furthermore the service reduced the proportion of inappropriately collected samples [15]. Serious efforts to evaluate cost effectiveness with anticonvulsant monitoring concluded that it is unlikely to have a major impact on overall cost but could enhance the efficacy of therapy [16]. This author has emphasised that measuring a concentration in isolation is unlikely to be a useful procedure [17] thus reinforcing the need for Clinical Pharmacologists to assume an interpretive role. Overall I have to confess that I do not think Clinical Pharmacologists have taken up the challenge laid down by McInnes [10] and demonstrated unequivocal benefits of drug monitoring in all instances. This is of course difficult to do as we are not just concerned with costs of materials and personnel but of data related to relapse rates, hospital admissions and increased bed stays due to drug toxicity. There is a danger of being too influenced by pharmaco-economic considerations and forgetting that patient welfare is our ultimate aim. This is often very difficult to assess and quantify.

At the end of the century TDM faces even more challenges. The rapid advent of new, bigger and faster automated analysers is changing both the methods and the sites in which assays are being performed [18]. Many of the Australian departments of Clinical Pharmacology that were founded around drug assay laboratories, my own included, have been forced to combine their resources with Clinical Biochemistry departments in the cause of economic rationalisation. This makes it even more important that Clinical Pharmacologists have clear concepts about just what can and cannot be achieved with TDM. Appropriate use of a limited number of assays is of much more value than undisciplined access to a large number of assays, many of which are

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useless. It is therefore timely for this journal to publish a series of articles on TDM.

The first of the series describes the features necessary for the 'ideal' service and makes the critical distinction between therapeutic drug *measuring* and therapeutic drug *monitoring*. This will be followed by articles grouped by therapeutic class. The long established areas of anticonvulsants, antiarrhythmics and antibiotics will of course be reviewed but there have been some interesting and exciting developments in the areas of immunosuppressants, cytotoxic drugs and psychotropic drugs and the issue of what to monitor, or even whether to monitor, in overdose will also be given an airing. Finally the series will address the issue that pharmacokinetics is only part of the story. We use drugs to produce certain anticipated effects. All too often the pharmacodynamic aspects of interpretation are omitted from discussions on TDM. The final article will focus on these considerations.

All the authors have been given the same briefing and the same format. Obviously different therapeutic areas require slightly different approaches but it is my hope that the articles will all give an up to date overview of key aspects of analysis, when to sample, the usefulness of therapeutic ranges, pitfalls in interpretation of results and available methods of dose prediction where possible. The authors, all experts in their field, have been asked to provide what evidence is available on the cost effectiveness and/or clinical benefits of monitoring and to give some predictions for the future. These latter sections may serve to prove or refute the challenging opinions expressed nine years ago [10]. Perhaps they will stimulate others to audit their own drug monitoring services and to provide critical assessments of outcomes and benefits.

If the first few articles have an Antipodean bias there are good reasons for this. In addition to my own biases, Australasia is particularly strong in the area of TDM and for some reason the southern hemisphere group of authors was better at meeting deadlines.

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