Editors' view

Monitoring therapy

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The word monitor comes from the Latin word *monere*, meaning to advise, warn, or remind. Although the noun form, meaning 'something that advises or gives warning', goes back to the seventeenth century (and earlier than that in other senses), the verb form is surprisingly recent. The earliest examples cited in the *Oxford English Dictionary* are from the 1920s and imply the meaning 'to check or regulate the technical quality of (a sound recording, radio transmission, television signal, etc.) without causing any interruption or disturbance'. In the sense 'to measure or test at intervals, especially for the purpose of regulation or control' the earliest citation is from 1944.

But doctors have been monitoring therapy for centuries. An excellent example of careful monitoring in the eighteenth century is to be found in William Withering's monograph on the use of the foxglove in treating dropsies [1]:

'[The patient, a 33-year-old man] was directed to take [an infusion of *Digitalis purpurea* and juniper berries] every two hours until it should make him sick . . . On Friday and Saturday he made more water than he had done for a week before, and the swellings of his face and body were considerably abated. He was directed to omit all medicine so long as the urine continued to flow freely, and also to keep an account of the quantity he made in 24 hours.'

Over the next two weeks, without any further medication, the patient's urinary volumes totalled nearly 50 pints (28 l), at an average of about 3.5 pints (2 l) a day, the daily amounts being individually detailed. His 'universal anasarca' resolved and 'no swelling [remained] but about his ancles [*sic*], extending at night half-way up his legs'. In other cases Withering recorded the dura-

tions of periods of diuresis and other matters relating to the progress of the disease, its response to therapy, and the adverse effects of the treatment.

However, despite a long tradition of monitoring therapy, our knowledge of how best to do it is surprisingly rudimentary. Consider, for instance, a patient taking digoxin and diuretics, in whom you are keen to avoid potassium depletion. How often should you measure the serum potassium concentration during the early stages of treatment? How do you judge when therapy has stabilized, and when that happens how often should you measure the serum potassium concentration? If the serum potassium concentration falls and the treatment is changed, how often should you measure it? If the patient is also taking spironolactone, an ACE inhibitor, or a glucocorticoid, should the frequency of measurement be different? You will search in vain for hard evidence to inform the answers to these questions.

Since the aims of treatment are to maximize benefits and minimize harms, monitoring the individual patient should provide information that serves those aims. This can be done in different ways.

- *Clinical monitoring* Ideally, one should measure the desired outcomes directly and watch for undesired ones.
- *Pharmacodynamic monitoring* If it is not possible to measure the therapeutic or adverse effects directly, the next best thing is to measure a biomarker, the several types of which I have previously listed [2].
- *Pharmacokinetic monitoring* When all else fails, it may be helpful to measure the concentration of the drug itself in the blood, serum, or plasma [3].

The last of these is commonly known as 'therapeutic drug monitoring', a term that does not serve well to describe the process, for two reasons:

- its restricted use implies that drug concentration measurement is the only method of monitoring drug therapy, which is not so;
- the word 'therapeutic' implies that drug concentration measurement is used only to detect therapeutic efficacy, whereas it can also be used to detect poor adherence to therapy, under-treatment, and toxicity.

A more precise term is 'drug concentration monitoring', but the less precise term is widely used and entrenched in our vocabulary.

Although serum lithium concentrations were already being measured in patients with mania in the 1950s [4], the term 'therapeutic drug monitoring' seems to have been introduced only in the early 1970s, when it was first realized how informative drug concentrations could be in day-to-day clinical practice [5]. This was not unconnected to the invention of sensitive methods for concentration measurement, such as radioimmunoassay, for which Rosalyn Yalow won the Nobel prize in 1977. The earliest publication that I have found in which the term 'therapeutic drug monitoring' occurs in the title was published in 1975 [6] and the journal of the same name first appeared in 1979.

The drugs whose concentrations are most commonly measured are digoxin [7], phenytoin [8], lithium [9], aminoglycoside antibiotics [10], theophylline [11], and ciclosporin [12], although claims have been made for others, such as tricyclic antidepressants [9], some cytotoxic drugs [13], and some drugs that are used to treat HIV infection [14].

In this issue of the *Journal* Ray *et al.* report the results of an observational study on the effects of monitoring plasma concentrations of atazanavir in 110 subjects with HIV infection [15]. The enormous variability in trough concentrations and the high frequency of patients who were exposed to very low concentrations of the drug suggest that concentration monitoring should contribute to the management of these patients. However, a randomized study would be necessary to demonstrate the usefulness of doing this.

Unfortunately, although the authors of papers in this field often call for randomized studies, such studies are uncommon. In one randomized study, monitoring plasma concentrations of nelfinavir and indinavir improved the number of patients with a low viral load [16]. In another randomized study in 180 patients with epilepsy there was no improvement in overall therapeutic outcome [17], although five different antiepileptic drugs were lumped together and it is likely that the value of plasma concentration measurement will differ from drug to drug.

Randomized studies in other areas of monitoring have been reviewed [18], and more are certainly needed. We also need to develop clear criteria for monitoring drug therapy with whatever monitoring tools are available, monitoring both beneficial and adverse effects [18, 19].

References

- 1 Aronson JK. An Account of the Foxglove and its Medical Uses 1785–1985. Oxford: Oxford University Press, 1985: 40–3.
- 2 Aronson JK. Biomarkers and surrogate endpoints. *Br J Clin Pharmacol* 2005; 59: 491–4.
- 3 Shenfield GM, ed. Therapeutic drug monitoring. *Br J Clin Pharmacol* 2001; 52(Suppl 1).
- 4 Noack CH, Trautner EM. The lithium treatment of manic psychosis. *Med J Aust* 1951; 2: 219–22.
- 5 Brodie BB, Reid WD. The value of determining the plasma concentration of drugs in animals and man. In: La Du BN, Mandel HG, Way EL, eds. *Fundamentals of Drug Metabolism and Drug Disposition*. Baltimore: Williams and Wilkins Company, 1971: 328–39.
- 6 Evenson MA. Developments in therapeutic drug monitoring and alkaloid analysis. *Fed Proc* 1975; 34: 2131–3.
- 7 Campbell TJ, Williams KM. Therapeutic drug monitoring: antiarrhythmic drugs. *Br J Clin Pharmacol* 2001; 52(Suppl 1): 21S–34S.
- 8 Eadie MJ. Therapeutic drug monitoring – antiepileptic drugs. *Br J Clin Pharmacol* 2001; 52(Suppl 1): 11S–20S.
- 9 Mitchell PB. Therapeutic drug monitoring of psychotropic medications. *Br J Clin Pharmacol* 2001; 52(Suppl 1): 45S–54S.
- 10 Begg EJ, Barclay ML, Kirkpatrick CM. The therapeutic monitoring of antimicrobial agents. *Br J Clin Pharmacol* 2001; 52(Suppl 1): 35S–43S.
- 11 Aronson JK, Hardman M, Reynolds DJM. *ABC of Monitoring Drug Therapy*. London: BMJ Publishing Group, 1993: 21–4.
- 12 Johnston A, Holt DW. Immunosuppressant drugs – the role of therapeutic drug monitoring. *Br J Clin Pharmacol* 2001; 52(Suppl 1): 61S–73S.
- 13 Lennard L. Therapeutic drug monitoring of cytotoxic drugs. *Br J Clin Pharmacol* 2001; 52(Suppl 1): 75S–87S.
- 14 Back DJ, Khoo SH, Gibbons SE, Merry C. The role of therapeutic drug monitoring in treatment of HIV infection. *Br J Clin Pharmacol* 2001; 52(Suppl 1): 89S–96S.
- 15 Ray JE, Marriott D, Bloch MT, Mclachlan AJ. Therapeutic drug monitoring of atazanavir: surveillance of pharmacotherapy in the clinic. *Br J Clin Pharmacol* 2005; 60: 291–9.
- 16 Burger D, Hugen P, Reiss P, Gyssens I, Schneider M, Kroon F, Schreij G, Brinkman K, Richter C, Prins J, Aarnoutse R, Lange J, Athena Cohort Study Group. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naïve HIV-1-infected individuals. *AIDS* 2003; 17: 1157–65.
- 17 Jannuzzi G, Cian P, Fattore C, Gatti G, Bartoli A, Monaco F, Perucca E. A multicenter randomized controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy. The Italian TDM Study Group Epilepsy. *Epilepsia* 2000; 41: 222–30.
- 18 Glasziou P, Irwig L, Mant D. Monitoring in chronic disease: a rational approach. *Br Med J* 2005; 330: 644–8.
- 19 Pirmohamed M, Ferner RE. Monitoring drug treatment. *Br Med J* 2003; 327: 1179–81.