EDITOR'S VIEW

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Teaching drug therapy

'See one, do one, teach one' runs the old adage, to which some have cynically added 'kill one'. Teaching drug therapy to medical students has become more and more difficult as drug therapy has become more complex and University posts in clinical pharmacology have been eroded. Those who have merely seen one and done one are not competent to teach one, and those who learn in this way cannot themselves be entirely competent either. The latest version of the General Medical Council's document *Tomorrow's Doctors* highlights as important learning objectives the management of disease in general and drug therapy in particular, but does not give specific guidance. The clinical section of the British Pharmacological Society has therefore proposed a detailed curriculum, published in this issue of the *Journal*. Michael Rawlins sets the scene in his editorial (p. 495) and Simon Maxwell and Tom Walley lucidly outline the proposals (pp. 496–503). If deans and others responsible for teaching medical students take note, we may see an end of headlines such as 'Hospital makes 135 drug errors a week' [1].

Adverse effects of selective serotonin reuptake inhibitors

The selective serotonin reuptake inhibitors (SSRIs) are often in the news. There have been monographs about individual patients' experiences with them [2, 3], and recently a BBC documentary, 'Emails from the Edge', broadcast in the Panorama slot on 11 May 2003, highlighted the claims, not new, that they are drugs of dependence and are associated with an increased risk of suicide. The SSRIs undoubtedly can in some patients cause withdrawal symptoms, such as dizziness, headache, nausea, paraesthesia, and occasionally more severe effects, such as vertigo and manic reactions. It is therefore wise, when withdrawing an SSRI, to taper the dose gradually rather than to stop treatment suddenly. However, it is a common error to assume that the occurrence of withdrawal symptoms is evidence of dependence, which is not so; indeed, there is evidence that the SSRIs are not drugs of dependence [4]. And as far as suicide is concerned,

there is evidence in adults that increased use of SSRIs is associated with a reduction in the rate of suicide, not an increase [5].

It is generally thought that the SSRIs are as effective as other antidepressants but safer [6]; for example, the tricyclic antidepressants can cause withdrawal symptoms and also cause unwanted anticholinergic effects, which the SSRIs do not. However, in this month's issue of the *Journal*, De Jong *et al.* (pp. 591–5) report that the SSRIs may increase the risk of gastrointestinal symptoms in patients taking non-steroidal anti-inflammatory drugs (NSAIDs). They found a 12-fold increased frequency of co-prescription of drugs used to treat peptic ulceration (histamine H₂ receptor antagonists, proton pump inhibitors, and prostaglandin analogues) in patients taking SSRIs plus NSAIDs compared with either type of drug alone, and a much smaller and non-significant increase in the frequency of prescription in patients taking tricyclic antidepressants plus NSAIDs.

These results are consistent with a previous report that there is a 15-fold increased risk of gastrointestinal bleeding in patients concomitantly taking SSRIs plus NSAIDs [7], although that result was not confirmed in a study using prescription event monitoring [8].

The explanation for these results is not clear. The authors claim that co-prescription of antiulcer drugs is a good surrogate of upper gastrointestinal symptoms, but in support of this contention they cite the results of a thesis, not widely available for scrutiny. SSRIs inhibit serotonin uptake in platelets, and the authors suggest that they might therefore impair haemostasis; however, such an effect would not necessarily explain upper gastrointestinal symptoms that required treatment with an antiulcer drug, which are often due to reflux oesophagitis and do not necessarily reflect bleeding. Furthermore, the conventional antidepressant drugs, which are non-selective reuptake blockers also block platelet uptake of serotonin. On the other hand, co-prescribing of antiulcer drugs with antidepressants might reflect an increased risk of peptic ulceration in patients with depression or an increased risk of depression in patients with peptic ulceration.

However, until further information becomes available, it would perhaps be wise to consider adding SSRI therapy to the list of factors that prompt the co-prescription of an antiulcer drug in patients who are taking an NSAID.

Drug-induced QT interval prolongation

The long QT syndrome was first described in 1957 [9] and the polymorphous ventricular tachycardia that goes with it in 1964 [10], although it wasn't given its French name of torsade de pointes until Dessertenne described it in 1966 [11]. Several years later the antihistamines terfenadine and astemizole were withdrawn from over-the-counter sales [12, 13] when they were shown to prolong the QT interval and increase the risk of torsade de pointes; and when it was discovered that their arrhythmogenic effect was enhanced by grapefruit juice, which inhibits their metabolism [14], the issue of the effects of drugs on the QT interval became a major one. Now it is *de rigueur* to test all new drugs for their effects on the QT interval. The problem in doing this is that the QT interval varies with heart rate, and there is no entirely satisfactory way of finding the corrected value (the QT_c interval) using population-based data, such as with the method that is most commonly used, Bazett's correction. The only satisfactory way to determine the effect of a drug on the QT_c interval is to measure the QT interval at a wide range of heart rates in each individual with and without the drug. This is reflected in the results of the study by Desai *et al.* (pp. 511–17) in subjects given haloperidol. Subject-specific correction of the QT interval should be the standard for all studies of the effects of new chemical entities.

Chronopharmacology

The effects of some drugs vary depending on the time of day at which they are taken [15]. For example, corticosteroids used for anti-inflammatory purposes are best given as a single dose in the morning, to minimize suppression of the adrenal glands; and it is widely believed that statins have a greater cholesterol-lowering effect after night-time rather than daytime administration, perhaps because the rate of hepatic cholesterol synthesis is greater at night, although the evidence of differential efficacy is limited [16]. Nevertheless, chronopharmacology is a relatively neglected subject. It is interesting therefore to read the study by Tsuruoka *et al.* (pp. 531–7), who gave vitamin D₃ (colecalciferol) to 13 patients with renal osteodystrophy. In 10 patients the effect of vitamin D₃ was greater in the evening than in the morning, although in three cases evening hypercalcaemia warranted withdrawal of therapy. Since renal osteodystrophy

is due to impairment of hydroxylation of vitamin D in the kidneys, most renal physicians in the UK would use alfacalcidol or calcitriol rather than colecalciferol, and it remains to be seen whether this diurnal variation in response to the latter is relevant to treatment with the former. Meanwhile, however, sensible advice to patients who are taking a stable dose of a vitamin D analogue would be to take the dose at the same time every day.

Now who's going to teach all that to the medical students?

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