
should be used only to assure patient compliance or to confirm toxicity due to overdose or adverse interaction". The following case is paradigmatic of the reasons why I find the previous statement too restrictive.

Case report. A 51-year-old Caucasian man, suffering from a moderate depressive illness, was referred to the psychiatric day hospital. On admission he had already been on clomipramine orally 150 mg daily for eight weeks with no clinical response, but at the same time no troublesome side-effects. He was otherwise healthy, with no concurrent medical problems and on no other medications.

It was agreed to increase gradually the dose of the antidepressant and after four weeks on clomipramine 250 mg daily, which is the *British National Formulary's* (BNF) higher limit, the mental state was still unchanged and the only side-effect, easily tolerated, was dry mouth.

It was decided to measure the antidepressant plasma level and the result was that the combined plasma levels of clomipramine and its metabolites had reached dangerous toxic levels, 980 ng/ml, against a higher recommended level of 450 ng/ml. As a consequence the medication was discontinued; on examination there were no signs of toxicity and the electrocardiogram (ECG) resulted within normal limits.

In the review by Preskorn *et al* (1989) it is shown how the central nervous system (CNS) and cardiotoxicity are related to plasma levels. On the other hand the plasma levels reached on a certain dose in an individual are completely unpredictable: the rate at which the drug is metabolised varies greatly from person to person, with a single dose giving rise to a greater than tenfold range of plasma levels (Asberg, 1976). In the case just presented a daily dose within BNF limits resulted in plasma levels that in the review of Preskorn are considered of major cardiotoxic risk, this without any warning side-effects. If the authors' recommendations had been followed, the plasma level would not have been sought, this with potential serious consequences. For these reasons it is my opinion that the choice to request antidepressant plasma levels should be considered by the clinician any time BNF limits are approached and in every case with individual or epidemiological risk factors for cardiovascular system (CVS) or CNS toxicity.

ASBERG, M. (1976) Treatment of depression with tricyclic drugs - pharmacokinetic and pharmacodynamic aspects. *Pharmacopsychiatry and Neuropsychopharmacology*, **9**, 18-26.

BRITISH MEDICAL ASSOCIATION AND ROYAL PHARMACEUTICAL SOCIETY OF GREAT BRITAIN (1993) *British National Formulary* (No. 26). London: BMA & The Pharmaceutical Press.

PRESKORN, S. H. & FAST, G. A. (1991) Therapeutic drug monitoring for antidepressants: efficacy, safety and cost effectiveness. *Journal of Clinical Psychiatry*, **52** (suppl. 6), 23-33.

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Sir: In our article we stated that "some adverse effects (e.g. CNS and CVS toxicity) do seem... to be related to plasma levels". While this is true in general, it is also true that individuals differ greatly in their tolerance to the adverse effects of tricyclic and related antidepressants. The case described here, we feel, illustrates this point.

The patient cited was taking a high dose of clomipramine which afforded a high plasma level of clomipramine and its metabolite. The drug was stopped despite there being no signs of toxicity or ECG changes. We feel a more rational approach in patients on high dose tricyclics is simply to perform an ECG (and monitor carefully for other adverse effects). If the ECG is found to be normal then the drug may be continued.

The two approaches described here would have led to two different methods of treatment: discontinuation or continuation of clomipramine. We feel this case illustrates how plasma levels of tricyclics can be misused, provoking clinicians to assume toxicity where there is none. Our experience is that plasma levels much higher than those quoted here are often used safely and therapeutically. We have observed that high plasma levels are not always associated with CNS or CVS toxicity, making plasma level monitoring of limited value.

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Sir: Taylor and Duncan (*Psychiatric Bulletin*, September 1995, **19**, 548-550) are correct in stating that well defined therapeutic levels have only been accepted for a few tricyclics. We feel that their conclusion, that therapeutic drug monitoring is only useful for assessing compliance or confirming toxicity, neglects another major advantage: detection of asymptomatic toxicity.

While tricyclics have many side-effects, some of which can be serious and life-threatening, toxicity may also be present in the absence of clinical symptoms (Preskorn, 1993). There is a marked increase in central nervous system toxicity when levels exceed 300 µg/l (Preskorn & Jerkovich,

1990) and 6% of patients have been reported to develop tricyclic-induced delirium on conventional doses of 100–300 mg/day. At plasma levels greater than 1000 µg/l, nearly all will show ECG changes (Spiker *et al.*, 1975). The first sign of cardiac toxicity may be a fatal arrhythmia.

Optimisation of clinical response is only one goal of therapeutic drug monitoring and even when well-defined plasma levels are not established for certain tricyclics, it still remains a useful tool in the management of depression. By detecting asymptomatic toxicity, therapeutic drug monitoring can prevent adverse consequences and may have medicolegal implications. Other advantages include assessment of non-responders, provision of a measure of compliance and confirmation of toxicity. In contrast to Taylor and Duncan, we believe that routine estimation of plasma tricyclic levels is an integral component in the rational approach to the management of depression and should be more widely practised.

PRESKORN, S. H. (1993) Sudden death and tricyclic antidepressants (TCAs): a rare adverse event linked to high TCA plasma levels. *Nordic Journal of Psychiatry*, **47**, (Suppl. 30), 49–55.

—, JERKOVICH, G. S. (1990) Central nervous system toxicity of tricyclic antidepressants: phenomenology, course, risk factors and role of therapeutic drug monitoring. *Journal of Clinical Psychopharmacology*, **10**, 88–95.

SPIKER, D. G., WEISS, A. N., CHANG, S. S. (1975) Tricyclic antidepressant overdose: clinical presentation and plasma levels. *Clinical Pharmacology and Therapeutics*, **18**, 539–546.

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Sir: Toxicity may indeed occur in the absence of clinical symptoms. However, 'CNS toxicity' and delirium are clinical symptoms and so plasma level determinations are of little use apart from to confirm that the antidepressant is the cause of the problem. Electrocardiogram (ECG) abnormalities may be asymptomatic and so a plasma level may help identify those at risk. However, an ECG will still need to be performed to identify any arrhythmia and one might argue that this should be done for anyone taking moderate or high doses of tricyclics. We are also unsure of the value of a 'cut-off' level of 1000 mcg/l. Presumably anyone with a level above this would have an ECG performed. One wonders what course of action would be taken with a patient with a level of 999 mcg/l, or 950 mcg/l, or 800 mcg/l. We feel the quickest way to detect occult rhythm abnormalities in patients taking tricyclic and related antidepressants is immediately to perform an ECG.

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Improper terminology

Sir: We warmly welcome the issues raised in the paper by Haghghat & Littlewood (*Psychiatric Bulletin*, July 1995, **19**, 407–410) which raises the issue of potential labelling and stigmatisation of people suffering from mental disorders. It is our duty to treat people with respect; as individuals, yet holistically. This should be made clear in the way that we, as professionals, refer to patients, their problems, and their illnesses.

Since Haghghat & Littlewood's paper, we have been surprised and disappointed to note the continued use of terms such as 'schizophrenics' (e.g. Fagin *et al.*, *Psychiatric Bulletin*, August 1995, **19**, 533) and even 'dements' (*Psychiatric Bulletin*, November 1995, **19**, 704) to refer to patients.

We strongly believe that as "The Journal of trends in psychiatric practice" the *Bulletin* should take the moral lead on this issue, and avoid publication of such pejorative and stigmatising labels.

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Point taken. – Ed.

Correcting drug-induced hyperprolactinaemia

Sir: Duncan and Taylor (*Psychiatric Bulletin*, December 1995, **19**, 755–757) describe possible clinical usage of two drugs relatively unfamiliar to psychiatrists, amantadine and bromocriptine. They suggest this would correct a common side-effect of antipsychotic drugs, hyperprolactinaemia. We believe that a simpler strategy should be followed initially.

Patients treated with antipsychotic medication can experience a variety of unpleasant endocrine side-effects; most commonly gynaecomastia, galactorrhoea and amenorrhoea. This is considered to be due to hyperprolactinaemia caused by antagonism of the action of dopamine on tubero-infundibular neurones (Meltzer & Fang, 1976).

The atypical neuroleptic clozapine is known to cause either a minimal or no rise in serum prolactin (Jann *et al.*, 1993). Clozapine is indicated for the treatment of schizophrenia in patients unresponsive to, or intolerant of, conventional antipsychotic drugs (*British National Formulary*, 1995).

Our practice, in this not uncommon clinical situation, would be to change to clozapine. Duncan and Taylor point out that amantadine may precipitate mania and is unlicensed for hyperprolactinaemia. They also point out that bromocriptine is contraindicated in any psychotic