Anticonvulsant monitoring in psychiatric practice

AIMS AND METHOD
A Medline literature search revealed a large number of articles on anti-convulsant monitoring. More relevant articles were selected with the aim of summarising current best practice in this area.

RESULTS
Most articles were written to address monitoring in epilepsy and not psychiatric illness. Serum ranges should only be regarded as guidelines. Some patients may show toxic signs at therapeutic serum levels while others may show tolerance and require higher levels.

CLINICAL IMPLICATIONS
Appropriate monitoring of serum levels improves efficacy and enhances safety. Clinician ignorance may lead to inappropriate or inaccurate sampling with resultant adverse consequences for the patient.

In psychiatric practice we are regularly involved in the monitoring of anticonvulsant medication that is prescribed in the treatment of a wide range of disorders including mania, aggression, schizophrenia and the augmentation of antidepressant treatment. Many of these indications are not approved by the Committee for the Safety of Medicines (Taylor et al, 2000). The majority of the literature on anticonvulsant monitoring refers to the use of these drugs in epilepsy and not affective or psychotic disorders, for which there appear to be few guidelines regarding serum levels (Bazire, 1999; Edie, 1998).

The most commonly used anticonvulsants in psychiatric practice are carbamazepine and sodium valproate, which are indicated in the treatment of epilepsy and the treatment and prophylaxis of certain psychiatric disorders. Phenytoin is used as an anticonvulsant, but on a much less frequent basis. In recent years there have been the addition of a number of new anticonvulsants, some of which may be used as sole and adjunctive treatment in epilepsy (e.g. lamotrigine) or as combination therapy where all other combinations have proved inadequate (e.g. vigabatrin). There appears to be some evidence that lamotrigine may be efficacious in the

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References


treatment of bipolar depression (Calabrese et al., 1999). Gabapentin and topiramate may have some mood stabilising properties, however there is a need for good quality research and comparison trials with older anticonvulsants (Maidment, 1999). When used in psychiatric disorder these medications should be reserved for those resistant to standard therapies.

Therapeutic drug monitoring began about 30 years ago (Edie, 1995) and is the use of serum drug measurements as an aid to the management of patients receiving drugs that generally have a low therapeutic index, meaning there is only a small window between toxic and therapeutic serum levels.

This review aims to outline the indications for and difficulties with anticonvulsant drug monitoring with a summary of the monitoring guidelines from the literature.

Why monitor drug levels?
The low therapeutic index of these drugs means they may easily become toxic to patients. Wide variations in serum levels may be observed at the same dosage in different individuals and may be influenced by the timing of doses, individual differences, individual differences in hepatic, renal and gastrointestinal function, age, body weight and volume of distribution. Poor compliance may at times prove problematic and management may be aided by serum level measurements.

Problems with drug monitoring
Schoenberger et al (1995) found that only 27% of requests for serum anticonvulsant levels had an appropriate indication and only 50% had been sampled correctly, leading to wasted resources. A study by Taylor et al (2000) discovered true trough specimens had been taken in less than 20% of cases. This results in inaccurate measurements and inappropriate dose changes.

The official serum level ranges are only guidelines and the optimal concentration for a patient may lie outside this range (Johannessen, 1997). Even within the range, some patients may show signs of toxicity. Others may be controlled with levels below the therapeutic range, or tolerate levels above it.

There is a tendency for doctors to change doses on the basis of drug levels alone, without accounting for the clinical picture (Sharpe et al., 1995), thereby treating the blood result rather than the patient (Commission on Antiepileptic Drugs & International League Against Epilepsy, 1993). One study showed that increasing the dose in a well-stabilised patient simply to be within the therapeutic range did not decrease the frequency of seizures but increased the risks of side effects and the need for expensive therapeutic monitoring (Woo et al., 1988).

In the case of drugs with wide diurnal level variations such as sodium valproate and carbamazepine, measurement can be misleading if judged on a single sample (Chadwick, 1987). Trough levels vary and do not predict peak levels that may be accompanied by transient toxicity. In these cases a kinetic profile may be helpful.

Blood parameter monitoring
Carbamazepine can have a number of possible side-effects including dizziness, ataxia, rash, heart block, drowsiness, aplastic anaemia, leucopenia, agranulocytosis and thrombocytopenia. The Association of the British Pharmaceutical Industry (ABPI) compendium of data sheets (ABPI, 1999) suggest full blood count and biochemistry should be checked prior to starting treatment and periodically during treatment. It is important that patients and carers are informed about toxic symptoms – some of the haematological effects can have a very rapid onset and therefore almost daily blood monitoring would be required to detect these (Sobotka et al., 1990). Leucopenia develops more slowly and affects 12% of children and 7% of adults usually in the first 3 months of treatment. The risk is elevated in those with a low or low normal pre-treatment white cell count. Some liver enzymes may be raised – especially gamma glutamyl transferase and alkaline phosphatase. This in itself is not an indication to stop the treatment, however, any signs of active liver disease should lead to cessation and re-evaluation.

The side-effects of sodium valproate include weight gain, tremor, nausea, drowsiness, hepatotoxicity, pancreatitis, thrombocytopenia, leucopenia and pancytopenia. The period of maximum risk of liver failure is between weeks 2 and 12 of treatment. This risk is increased with polytherapy. Full blood count and liver function should be checked prior to treatment and liver function checked regularly over the first 6 months (perhaps 6 weekly) and then annually (Bazire, 1999). A moderate increase in alkaline phosphatase and transaminase is common in these patients and is no cause for alarm. The British National Formulary suggests reassessing clinically, including prothrombin time measurement, until levels return to normal (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2000). If the prothrombin time remains prolonged the drug should be discontinued.

In the early stages of liver failure serum changes are not always present. It is therefore important to warn patients about signs and symptoms associated with liver failure, such as jaundice and oedema (Schmidt & Siemes, 1998). Pathology data suggest that some cases of sodium valproate induced hepatic failure are the result of chronic liver damage and cirrhosis. By the time clinical symptoms develop hepatic failure may be irreversible (Wyllie & Wyllie, 1991). Routine liver monitoring may therefore be helpful for the early detection of chronic adverse reactions such as subclinical hepatotoxicity and thrombocytopenia.

Phenytion side-effects include drowsiness, a decline in memory, ataxia, blurred vision, diplopia, gum hyperplasia, rash and liver damage. The drug should be discontinued in the case of a rash because of the risk of lupus erythematosus, Stevens–Johnson syndrome or toxic
epidermal necrosis. Full blood count, calcium, folate, liver function tests and thyroid function tests should be measured pre-treatment and at 6 monthly intervals.

Of the newer anticonvulsants lamotrigine is perhaps the most commonly used. The side-effects include rash, fever, drowsiness and worsening of seizures. In each case the drug should be withdrawn. Rarely the drug may be associated with aplastic anaemia and pancytopenia and therefore it is important to be alert for symptoms suggestive of bone marrow failure, e.g. bruising and anaemia. Serious skin rashes are most likely in the first 8 weeks of treatment.

The main side-effects of vigabatrin are visual and include visual disturbance, photophobia and retinal disorders. Urgent ophthalmological opinion should be sought if visual field loss is suspected. With gabapentin the main side-effect reported is drowsiness and with topiramate the main side-effects are abdominal pain, nausea and anorexia. Pre-treatment baseline blood parameters are recommended with all these drugs and at least annual liver function and full blood count with lamotrigine. Urea and electrolytes should be monitored with gabapentin and vigabatrin, which are renally excreted.

Summary of anticonvulsant level monitoring guidelines

There is a limited role for the serum level monitoring of sodium valproate (ABPI, 1999). There is a wide circadian variation in levels, with toxic effects often showing no relationship with level (Sharpe, 1995). In the treatment of epilepsy, the therapeutic range is 50–100 mg/l; however, guidelines suggest the optimum dosage be determined by seizure control (ABPI, 1999).

Carbamazepine levels should initially be monitored twice weekly until stable and then every 3–6 months. The target range for a psychiatric disorder is considered to be 8–12 mg/l and 4–12 mg/l in epilepsy (Taylor et al, 1999). Monitoring is described as only 'fairly useful' (Bazire, 1999).

Owing to dose dependent pharmacokinetics, drug monitoring of phenytoin is essential (Bazire, 1999; Taylor et al, 1999). When stabilised, levels should be monitored approximately every 6 months. The therapeutic range is 10–20 mg/l.

Of the newer anticonvulsants, lamotrigine has the recommended target concentration of 1–4 mg/l, although a clear relationship is not yet demonstrated between concentration and effect or toxicity. It is therefore suggested that the dose is adjusted according to efficacy and tolerability (Taylor et al, 1999). Gabapentin, topiramate and vigabatrin have no recommended target concentrations and no clear correlation between trough plasma concentration and therapeutic response. This is partly owing to the fact they are used as 'add on' therapies in epilepsy, which confounds this interpretation (Taylor et al, 1999; Johannessen, 1997).

Anticonvulsant drugs are used frequently in psychiatry and it is therefore important that the clinician is aware of monitoring requirements. This will aid the safe prescribing of these drugs and optimise the clinical management of the patient.

References


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