Plasma Level Monitoring of Anticonvulsants

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Summary

The plasma concentrations of anticonvulsant drugs, and of certain of their biologically active metabolites, tend to be proportionate to the antiepileptic effects of these drugs. Consequently, anticonvulsant drug levels in plasma are monitored to help guide the clinician in managing his patients' epilepsies. In making use of the measurements, the clinician needs to know the relation between plasma level and biological effect for the various drugs. He also needs to have some awareness of simple pharmacokinetic principles. These are important in deciding when plasma levels should be monitored in relation to the patients' clinical state, to the dosage interval, and to change in the dosage of anticonvulsant or other drug.

The clinician also requires pharmacokinetic knowledge in altering anticonvulsant drug dosage in his patients, and in interpreting plasma anticonvulsant level data, particularly when the patient is concurrently suffering from non-neurological disease. The ability to monitor plasma anticonvulsant levels has appreciably improved the treatment of epilepsy, but to obtain maximum benefits from the method, both pharmacokinetic insight and clinical wisdom are required.

A few years ago the measurement of plasma anticonvulsant concentrations in epileptic patients was largely a research activity. Now in many countries the monitoring of plasma levels of these drugs is rapidly becoming part of the routine management of patients with epilepsy. The rapid expansion of the practice of managing epilepsy in relation to plasma anticonvulsant level data has occurred before there has been time for thorough exploration of all the clinical correlations of the measurements and before the pharmacokinetics of the relevant drugs in man have been fully worked out. Nevertheless, it may be useful to assess the current practice of plasma anticonvulsant level monitoring in the light of pharmacokinetic principles and clinical considerations.

1. Theoretical Basis for Monitoring Plasma Anticonvulsant Levels

The great majority of drugs appear to exert their actions after forming reversible bonds with tissue molecules ('receptors'). For such drugs the intensity of biological action tends to be proportionate to drug concentration in the biophase in
the vicinity of the receptors. Leaving aside the question of exact sites of cellular or intracellular action, antiepileptic drugs clearly exert their anticonvulsant effects within the brain. Anticonvulsant drug molecules in cerebral extracellular water are in a dynamic equilibrium with drug molecules in plasma water (fig. 1). Therefore, anticonvulsant concentration in plasma water is a measure of anticonvulsant concentration in brain, and thus provides a measure of antiepileptic effect. If an anticonvulsant drug in plasma is in part bound to plasma proteins there will be a further dynamic equilibrium between drug bound to protein, and drug free in plasma water. Hence the more simply measured anticonvulsant drug concentration in whole plasma also provides a measure of drug concentration in brain, and an indication of potential anticonvulsant effect. The clinician needs to know the latter in order to manage his epileptic patients. Experience has shown that there are relatively poor correlations between doses of the commonly used anticonvulsants and the drug plasma levels produced in treated populations (Eadie and Tyrer, 1974). The clinician finds the anticonvulsant plasma level a better guide to antiepileptic effect than is the drug dose itself.

Epilepsy is a disorder requiring drug treatment over long periods of time. In practice, almost all monitoring of plasma anticonvulsant levels is done with the patient presumably in a steady state as regards intake and output of his drug. Rarely, as in treating acute epileptic crises, the monitoring of plasma drug levels may be done when the patient is not in the steady state as regards drug intake and output. Here, because of time factors involved in achieving the various distributional equilibria, the usual steady state quantitative correlations between plasma and brain anticonvulsant levels may not necessarily apply, though detailed information on this aspect is lacking.

In the remainder of this review, it is assumed that steady state considerations apply when plasma anticonvulsant levels are being considered.

2. Why are Plasma Anticonvulsant Levels Monitored in Practice?

It may sometimes be easy for the clinician to know if he has prescribed an adequate anticonvulsant dose for his patient. This is so particularly when seizures occur frequently, as they do in petit mal absence epilepsy and myoclonic epilepsy, and less often in other forms of generalised epilepsy or in partial epilepsy. If such frequent seizures cease soon after a particular anticonvulsant dosage is prescribed, it is highly probable that an effective dose of the anticonvulsant has been given, whatever the plasma concentration of the drug may happen to be. In this circumstance, measurement of plasma anticonvulsant level is largely an academic exercise, though it may be useful for future reference to know the plasma drug concentration at which a patient's attacks ceased. His seizures might relapse later, and one might find that the plasma drug level had fallen though the nominal drug dose had not changed.

However, many epileptic patients have only occasional seizures, perhaps 2 or 3 a year, or less, yet these individual seizures can have devastating effects psychologically and socially. In such patients, if anticonvulsant therapy is managed purely on clinical grounds, much time can elapse, and much disappointment can occur, before the