Dose-Related Adverse Effects of Anticonvulsants

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Summary

The serum concentration at which a given drug has full efficacy in delivering seizure control bears no predictable relationship to the concentration at which
adverse effects will appear. In theory, the threshold for adverse effects should be considerably higher than that for efficacy. For each agent this obviously happens most of the time, or the anticonvulsant would not be on the market, but there are also patients in whom this relationship is reversed. The adverse effects of this class of drugs are discussed from three points of view: the adverse effect type, the kinetic factors that so frequently determine the presence of adverse effects, and the specific characteristics of each drug. Some less well recognised adverse effects syndromes that are not strictly dose related are considered. The importance of adverse effects in therapeutic monitoring is then addressed, and some strategies for maximising efficacy without the burden of long term functional impairment or distress are discussed. The usefulness of monotherapy is stressed with due attention to rational choice of second drugs, when necessary, based on mechanisms of antiepileptic action and adverse effects profiles. While most of these symptoms evolve gradually, there are times when acute, drastic, and even life threatening clinical overdose situations present themselves. Special attention is given to these scenarios, drawing on the drug profiles and clinical pharmacokinetics that define these events to propose methods of coping with the problems efficiently and effectively.

1. Types of Adverse Effects

Three principal adverse effect symptom groups predominate for the commonly used drugs: alterations in cognition and mentation, the deterioration of motor performance (primarily coordination), and gastrointestinal symptoms. Since this combination resembles the neurological consequences of the overconsumption of alcoholic beverages, these effects are commonly called 'anticonvulsant intoxication'. Under usual clinical circumstances, however, only one of these symptoms presents itself. Each individual has a personal threshold for each type of adverse effect for each drug, and no one such effect is necessarily related to any of the others nor to the serum concentration at which efficacy in seizure control is achieved in that person. Some of the newer drugs tend to have fewer of the 'classical' effects, but create gastrointestinal or anxiety-insomnia symptoms.

1.1 Motor Effects

The most readily appreciated symptom is impairment of coordination, since it is documentable by anecdote from observers and easily tested in a graded fashion by the examining physician. A minimal complaint might be trembling of the hands while holding a cup, or slight staggering in rounding corners, particularly in the dark. Confirmation will be found in mild limb ataxia on examination. Progressively more serious difficulty can be seen to the point of so gross an ataxia that seated posture is impossible. This graded spectrum is most commonly encountered with the hydantoins, mesuximide, carbamazepine and primidone; it occurs less