Adverse Neuropsychiatric Effects of Anticonvulsant Drugs

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Clinical and electrical evidence of peripheral neuropathy may result from long term treatment with phenytoin or barbiturates, especially in combination, or after repeated exposure to toxic blood concentrations of either drug. Prolonged acute toxicity with phenytoin may rarely lead to permanent residual ataxia. Reversible dystonia may occasionally be precipitated by phenytoin or carbamazepine; asterixis by phenytoin, barbiturates or carbamazepine; and, more commonly, tremor by valproate.

All the major anticonvulsant drugs, especially in combination, can produce occasional subacute cognitive or behavioural syndromes. In varying degrees, the drugs also impair attention, concentration, memory, mental speed or processing, or motor speed. Possible mechanisms of impaired mental function include neuronal damage, or disturbance of folic acid, monoamine or hormonal metabolism.

The relative influence on neurological or psychological function is an important factor in the choice of anticonvulsant drug for the treatment of epilepsy.

There are many unsatisfactory aspects of the drug treatment of epilepsy, in particular the widespread use of multiple drugs on a long term basis, which in turn leads to many undesirable long term toxic consequences (Reynolds, 1976a). Over the last 20 years there has been a growing awareness of many previously unsuspected insidious toxic effects of anticonvulsant therapy (Oxley et al., 1983; Reynolds, 1970, 1975a; Schmidt, 1982; Trimble and Reynolds, 1976). During the same period, the development of techniques for blood level monitoring of anticonvulsants has facilitated a trend towards a more simplified and effective use of the drugs. It has become apparent that most newly diagnosed epileptic patients can be controlled with single-drug therapy (Reynolds and Shorvon, 1981; Reynolds et al., 1983). In chronic epileptic patients there is no particular advantage in using more than 1 or 2 drugs per seizure type. Reduction in unnecessary polytherapy in the latter patients has increased our awareness of the subtle effects of anticonvulsant drugs on cognitive function, and behaviour in particular (Fischbacher, 1982; Shorvon and Reynolds, 1979; Thompson and Trimble, 1982).

Recent reviews have been concerned with general aspects of long term toxicity (Oxley et al., 1983; Schmidt, 1982). In this review, we are concerned specifically with the neuropsychiatric complications of prolonged anticonvulsant therapy. Partic-
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ular emphasis will be placed on recent studies of cognitive function and behaviour (Reynolds, 1983; Trimble and Reynolds, 1976; Trimble, 1981). More general aspects of toxicity will be considered only insofar as they are relevant to neuropsychiatric sequelae. In view of the increasing trend towards single-drug treatment for epilepsy, attention will be given to the relative differences between the major anticonvulsant drugs, where this information is available.

1. Adverse Neurological Effects

1.1 Peripheral Neuropathy

There have been widely varying reports on the incidence of clinical or electrical evidence of peripheral neuropathy in selected groups of treated epileptic patients (Shorvon and Reynolds, 1982). Clinical features which have been described in up to one-third of patients have consisted usually of absent lower limb reflexes and impaired vibration sense at the ankles. Distal sensory symptoms or motor weakness are very rare. Electrophysiological abnormalities have been found more often than clinical manifestations, and have consisted of a slight reduction in motor or sensory conduction and reduced or absent sensory action potentials. All authors have attributed the neuropathy to phenytoin, but Shorvon and Reynolds (1982) found evidence that long term barbiturate therapy may also lead to clinical or electrical abnormalities of peripheral nerve function.

Problems in interpreting the published studies have arisen for several reasons: firstly, the selected nature of the chronic patients, most of whom were on polytherapy; secondly, the failure to distinguish acute reversible anticonvulsant-induced electrophysiological changes from chronic irreversible abnormalities; thirdly, the failure to relate the findings to the duration of the treatment and to clinical and metabolic variables, such as drug toxicity, serum anticonvulsant concentrations and folate levels. In newly diagnosed epileptic patients followed prospectively on carefully monitored single-drug treatment with either phenytoin or carbamazepine for up to 5 years, Shorvon and Reynolds (1982) found no evidence of clinical neuropathy. Slight electrophysiological abnormalities were found in 18% of those on phenytoin but none of those on carbamazepine. The presence of electrophysiological abnormalities in the phenytoin group was significantly related to previous exposure to high serum phenytoin and low serum folate concentrations, or both. In non-epileptic subjects with megaloblastic anaemia due to folate deficiency, clinical evidence of neuropathy was found in 18% (Shorvon et al., 1980).

It therefore seems that phenytoin and barbiturates can contribute to anticonvulsant neuropathy, but there is no evidence incriminating carbamazepine or sodium valproate. Much of the previously reported clinical and electrical neuropathy has been associated with polytherapy, and perhaps especially with prolonged or repeated exposure to toxic concentrations of phenytoin or phenobarbital and/or prolonged folate deficiency. The incidence of clinical and electrical abnormalities could be greatly reduced by careful monitoring of single-drug therapy.

1.2 Cerebellar Ataxia

Although it is well known that acute toxicity with barbiturate and hydantoin drugs may commonly lead to a reversible cerebellar syndrome, there has been some controversy as to whether permanent pathological or clinical changes may result. Certainly, there are several case reports of a permanent cerebellar syndrome following phenytoin intoxication (Bittencourt, 1983; livanainen et al., 1977; Munoz-Garcia et al., 1982; Reynolds, 1975a). There are also a number of reports of phenytoin-induced loss of or damage to Purkinje cells in different species, although Dam (1972, 1983) has criticised these experimental studies on methodological grounds. He emphasises that it is well known, as he has confirmed, that frequent seizures may themselves be responsible for such changes. However, it is difficult to exonerate anticonvulsant drugs in some patients in several of the clinical reports, in view of the close temporal relationship to acute toxicity and the presence of other features of tox-