Benign familial tremor treated with primidone

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Abstract

Primidone given to a patient for epilepsy produced an unexpected reduction in benign familial tremor. Over the next eight years the drug was therefore tried in a prospective study of 20 other patients with benign familial tremor alone. Of these, six could not tolerate the drug because of vertigo and nausea but 12 obtained a good response, which in some cases was dramatic. Investigations in two patients suggested that the effect was mediated predominantly by derived phenylethylmalonamide, though primidone had some effect, since tremor recurred slightly on withdrawing the drug despite a constant or rising blood phenylethylmalonamide concentration.

Primidone is highly effective in benign familial tremor. More patients with the condition are intolerant of the drug than are usually found with epilepsy.

A Propos de Richard, dit Coeur de Lion, Roi d'Angleterre

Richard's outward aspect was imposing; he was wondered at for his height, his immense strength, held in check though it was by a constantly recurring ague, 'which kept him, dauntless though he was, in a tremor as continual as the tremor of fear in which he kept the rest of the world; this made him a paladin of charity.'—Giraldus Cambr. *De Instruc Princ.* 3, 27, (1).¹

Introduction

A patient with epilepsy and benign familial tremor was treated with primidone, and a remarkable effect was observed on the tremor. This chance finding led to the present study.

BENIGN FAMILIAL TREMOR

Benign familial tremor, or essential tremor, is common. It may cause only mild inconvenience, but in many patients it has a disabling effect on handwriting, drinking from a cup, doing up buttons, and other fine manipulations. Critchley² reviewed early descriptions of the condition and quoted several brief accounts in continental reports from 1836; the first description in English was by Dann in 1887.

In a genetic and epidemiological study of 210 subjects, Lason and Sjögren³ found evidence that the condition was inherited as an autosomal dominant, though sporadic cases often occur. The average age at onset was 50 years (range 10-70), and there appeared to be full penetrance of the gene by the age of 70. The phenomenon of anticipation from one generation to the next was not found, though this has been reported,² and there was no increased incidence of other neurological diseases or thyroid disease.

Familial tremor usually starts in the hands and may remain barely noticeable for many years. Often fairly rapid deterioration occurs in the fifth or sixth decade, with increased tremor progressing to arm,

head, tongue, and, finally, the legs. The tremor is never present when the affected part is completely relaxed; it is an action or postural tremor, and it is best observed when the patient is asked to hold the arms outstretched. There may be a "cerebellar component" with exaggeration of the tremor towards the end of the excursion in the finger-nose test, and sometimes this is quite pronounced. Marshall⁴ suggested that the tremor is an exaggeration of the normal physiological tremor and follows the usual change in frequency with aging—that is, about 6 Hz in childhood, increasing to 10 Hz in adult life, and slowly returning to about 6 Hz in old age. No pathological abnormalities have ever been described.

PRIMIDONE

Primidone is a well-established anticonvulsant. 60-80% of an oral dose is absorbed, principally from the stomach and upper small bowel. Blood concentrations reach a peak at three to five hours. The half life is around 12 ± 6 hours in patients established on the drug but only about five hours after a single dose. About 20% of an oral dose remains as primidone and is excreted unconjugated by the kidneys. About half is converted to phenylethylmalonamide, which is also unconjugated and has a half life of about 30 hours. Less than 5% is converted to phenobarbitone, which has a half life of around 100 hours and is 60% protein bound. Derived phenobarbitone is measurable in blood about a week after starting treatment, reaches the same concentration as primidone in about two weeks, and stabilises after a further week in a ratio to primidone of about 2:1. The precise ratio varies with the time of blood sampling after the last dose of primidone because of the disparate half lives. Blood concentrations of primidone up to about 14 mg/l are not usually associated with side effects, though unsteadiness with nausea and vomiting occasionally occurs after a single dose of 125 mg.

Present study

Over eight years 20 patients aged 15-78 with benign familial tremor were treated with primidone and closely followed. Of these, six could not tolerate the drug because of vertigo, unsteadiness, and nausea, and four showed this reaction after only 125 mg taken at night. The remaining 12 obtained a good response, and in several the improvement was dramatic.

FIG 1—Case 1. Handwriting (a) before treatment; (b) when established on primidone.

CASE 1

A 64-year-old right-handed electrician had had fine tremor of both hands for many years, which had become particularly troublesome over the past five years. He had worked in the electricity industry for 30 years, the last decade in a clerical job, and he had been a trade union official for 25 years. A few months before he was first seen (1973) he had lost his clerical job because of deterioration in his handwriting and he had been downgraded to a labouring job. Shortly afterwards he lost his union post for the same reason. He sought medical advice because of a request from his bank to give his wife power of attorney as they were unable to read his signature (fig 1(a)).

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Examination showed slight titubation and a coarse action tremor of both hands, worse on the right. There were no other abnormal signs. Blood pressure was 145/95 mm Hg. He had not been treated for the tremor and there was no family history of tremor. Thyroid function tests were normal. Treatment was started with primidone 125 mg at night and increased to 750 mg daily over two weeks. The tremor and his handwriting improved almost at once and continued to do so. Nine months later he was reinstated in his clerical job and as a union official (fig 1(b)).

In the past six years the tremor has shown a slight tendency to deteriorate, although it has remained under reasonable control, except when he had an exacerbation of his chronic bronchitis, a cold, or other intercurrent infection. Primidone was increased to 1 g daily in December 1975, giving a blood phenobarbitone concentration of 15 mg/l and a primidone concentration of 10 mg/l. In October 1977 propranolol 120 mg daily was added with additional benefit.

CASE 2

A 61-year-old right-handed lecturer had had tremor of both hands for nearly 20 years with recent deterioration. He was unable to drink from a cup without spilling and his writing had deteriorated considerably. He was seen several times over five years (1969-74), during which the tremor had gradually deteriorated and had not responded to amylobarbitone sodium 120 mg daily, diazepam 15 mg daily, and propranolol 40 mg daily. Examination at the age of 66 (1974) showed a coarse action tremor of both hands with definite terminal exaggeration in the finger-nose test. There was slight titubation. Blood pressure was 130/90 mm Hg. Thyroid function tests were normal. Treatment was started with primidone, increasing to 750 mg daily, and the tremor improved considerably. Over the next six years the tremor worsened slightly, and in November 1975 propranolol 40 mg daily was added with some benefit.

Methods, results, and comment

Clinical observation showed a marked improvement in essential tremor during treatment with primidone, but it was not known whether this was due to the drug itself or to one of its principal metabolites, phenobarbitone and phenylethylmalonamide. Phenobarbitone was unlikely to be the cause because it and other barbiturates had been used for years with little or no benefit. The patients in cases 1 and 2 agreed to take part in a study to determine this point.

(a) But when I had left these grave and kindly men, the echo of their voices remained with me; the deep valley of the Enza seemed lonely, and as I went lower and lower down towards the noise of the river I lost the sun. Time taken to write - 10 mins.

(b) But when I had left these grave and kindly men, the echo of their voices remained with me; the deep valley of the Enza seemed lonely, and as I went lower and lower down towards the noise of the river I lost the sun. Time taken to write - 8 mins.

(c) But when I left these grave and kindly men, the echo of their voices remained with me; the deep valley of the Enza seemed lonely, and as I went lower and lower down towards the noise of the river I lost the sun. Time taken to write - 8 mins.

FIG 2—Case 2. Handwriting (a) while established on primidone; (b) when taking phenobarbitone; (c) when re-established on primidone after four days.

Phenobarbitone 90 mg daily was substituted for primidone to maintain the blood phenobarbitone concentration, and within 24 hours both patients showed a deterioration in tremor; by four days they had great difficulty writing and could not drink from a full cup. Phenobarbitone was stopped and primidone restarted and within a few days tremor improved (fig 2). The gradual deterioration of tremor over four days after stopping primidone suggested that the effect was due to phenylethylmalonamide (reported half life 30 hours) rather than primidone (half life 12 hours). One patient (case 2) was taking

propranolol at the time of the study, and a similar procedure was adopted to compare the effect of primidone and propranolol. This showed a slight deterioration when propranolol was stopped and primidone continued and a marked deterioration when primidone was stopped but propranolol continued (fig 3).

Primidone and propranolol

(a) So I pulled out my two francs, and going into a little shop, I bought bread, sausage, and a very little wine for fourpence, and with one franc eighty left I stood in the street eating and wondering what my next step should be. Time to write 10 mins.

Propranolol only

(b) So I pulled out my two francs, and going into a little shop, I bought bread, sausage, and a very little wine for fourpence, and with one franc eighty left I stood in the street eating and wondering what my next step should be. Time to write 7 mins.

Primidone and propranolol

(c) So I pulled out my two francs, and going into a little shop, I bought bread, sausage, and a very little wine for fourpence, and with one franc eighty left I stood in the street eating and wondering what my next step should be. Time to write 10 mins.

Primidone only

(d) So I pulled out my two francs, and going into a little shop, I bought bread, sausage, and a very little wine for fourpence, and with one franc eighty left I stood in the street eating and wondering what my next step should be. Time to write 11 mins.

Primidone and propranolol

(e) So I pulled out my two francs, and going into a little shop, I bought bread, sausage, and a very little wine for fourpence, and with one franc eighty left I stood in the street eating and wondering what my next step should be. Time to write 12 mins.

FIG 3—Case 2. Handwriting (a) while established on primidone and propranolol; (b) after seven days of propranolol alone; (c) while established on primidone and propranolol; (d) after seven days of primidone alone; (e) when re-established on primidone and propranolol.

FIG 4—Case 1. Blood concentrations of primidone, phenobarbitone, and phenylethylmalonamide over 10 days.

It was then necessary to determine whether the effect was due to primidone or phenylethylmalonamide. Serial measurement of blood concentrations after a single encapsulated dose of phenylethylmalonamide 100 mg in a normal volunteer (MDO'B) showed a half life of 28 hours (1.0 mg/l at two hours; 0.9 mg/l at four, six, and eight hours; 0.8 mg/l at 11 hours; and 0.5 mg/l at 28 hours); 20% of the dose was excreted in urine over the first 10 hours. Phenylethylmalonamide 200 mg daily was substituted for primidone in both patients, and neither noticed any change in tremor in the first 24

hours (figs 4 and 5). At 48 hours one patient (case 2) showed no change but in the other the tremor was slightly worse. We assumed that this patient was not receiving enough phenylethylmalonamide and increased the dose to 400 mg daily. After 72 hours the tremor had improved in case 1 and was only slightly worse in case 2. Phenylethylmalonamide was then stopped and tremor deteriorated. Four days later both patients were incapacitated. Phenylethylmalonamide was restarted at 300 mg daily in case 2 and 400 mg daily in case 1, with rapid improvement. Phenobarbitone showed a plasma half life of 103 and 130 hours, primidone 16 hours, and phenylethylmalonamide 53 hours (nitrogen-selective gas chromatography⁵).

FIG 5—Case 2. Blood concentrations of primidone, phenobarbitone, and phenylethylmalonamide over 10 days.

Conclusion

Primidone is highly effective in benign familial tremor, and this effect appears to be mostly due to derived phenylethylmalonamide. Primidone itself appears to have some effect, however, since in both patients tremor deteriorated a little after stopping primidone despite a constant phenylethylmalonamide concentration in one and a rising phenylethylmalonamide concentration in the other. Primidone was more effective than propranolol and in some patients nearly as effective as alcohol. Adding propranolol resulted in some further improvement. More patients (about 30%) with benign familial tremor were intolerant of primidone in small doses than is our clinical experience in patients with epilepsy.

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Effect of discothèque environment on epileptic children

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Abstract

A free-field study of 22 epileptic children, selected on the basis of past electroencephalographic abnormality, identified a group who exhibited a significant increase in epileptiform discharge rate on electroencephalography in a discothèque environment ($p < 0.05$). Laboratory investigations showed that these children were activated by a wide range of stimuli, including intermittent photic stimulation and exercise. The response to exercise was a good predictor of a child's electroencephalographic response in a discothèque.

The findings suggest that most epileptic children are not particularly vulnerable in a discothèque environment.

Introduction

The current popularity of discothèques has heightened the anxiety that loud music and flashing lights might be harmful, particularly to children with epilepsy. Consequently, some avoid discothèques, either on medical advice or because of their own or their parents' fears. This could be a social handicap.

The aims of this study were, firstly, to examine the neurophysiological effects of a simulated discothèque environment on a group of epileptic children by monitoring their electroencephalograms; and, secondly, to see whether those at risk could be identified by the use of electroencephalographic activation techniques in conventional laboratory surroundings.

Patients and methods

Twenty-two children aged 10-16 years met the criteria for admission to this study: normal intelligence and a history of epilepsy with sufficient epileptiform discharges in the electroencephalogram for changes to be measurable over short periods of time. Nearly all had suffered from generalised tonic-clonic seizures; 10 had a clinical history of photosensitivity. Fourteen avoided discothèques, nine because they had experienced discomfort when attending them.

Each recording session was in two parts: an initial electroencephalographic examination of about one hour's duration, including hyperventilation, exercise, and photic stimulation; followed by a period of about three-quarters of an hour in a simulated discothèque with other children. The electroencephalogram was recorded by radiotelemetry

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