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ACUTE EFFECTS OF INTRAVENOUS PHENYTOIN ON THE FREQUENCY OF INTER-ICTAL SPIKES IN MAN

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1 Phenytoin was administered intravenously to six adult epileptic patients in doses ranging from 500–1000 mg (equivalent to 5.6 mg/kg–20 mg/kg body weight).

2 A significant decrease in the frequency of inter-ictal spikes in the EEG was seen and this effect was most marked 10–20 min after the infusion, when the mean spike count was reduced to 27% (s.d. 17%) of the control ($P < 0.05$).

3 In one subject the decrease in inter-ictal spikes coincided with a decrease in fit frequency.

4 Adverse reactions affecting the vestibular system occurred in three patients at doses of 15–20 mg/kg. No cardiovascular complications were observed in any subject.

5 The overall results suggest that doses of 7.5–10 mg/kg would be sufficient to significantly reduce the frequency of inter-ictal spikes in the EEG.

Keywords phenytoin inter-ictal spikes epilepsy fit frequency

Introduction

Although attempts to correlate EEG findings with efficacy of chronic antiepileptic drug therapy have proved difficult (particularly with carbamazepine) the evaluation of the EEG response to single test doses given parenterally may provide an alternative approach.

Several investigators have demonstrated a reduction of inter-ictal spikes following single doses of intravenous diazepam (Neidermeyer, 1970; Booker & Celesia, 1973) but Ahmad *et al.* (1977) were the first to suggest that spike counting could be used for the short term assessment of new compounds given intravenously. By modifying the method of Ahmad *et al.* (1977) we have previously demonstrated the efficacy of single dose rectal administration of diazepam in reducing epileptiform abnormalities in the EEG (Milligan *et al.*, 1982). Before this technique can be extended to new compounds a series of placebo-controlled studies are needed demonstrating the effectiveness of the established antiepileptic drugs in reducing the frequency of inter-ictal spikes, thus validating the technique. Although there is evidence to suggest that chronic therapy with phenytoin leads to a reduction of inter-ictal epileptic discharges (Wilkus *et al.*, 1978), the acute effects of this drug on the EEG following intravenous administration in man have never previously been reported. The present investigation addressed the effect on inter-ictal spikes of single dose intravenous administration of phenytoin.

In one case reported here the investigation coincided with a period of poor seizure control. Phenytoin was prescribed chronically following the administration of a loading dose and this permitted comparison of the acute EEG and clinical effects of this drug.

Methods

Six subjects, mean age 31.8 years (range 20–39) and resident at the Chalfont Centre for Epilepsy, gave their signed informed consent to take part in this study. All subjects suffered from severe epilepsy, resistant to conventional antiepileptic drugs.

They were selected primarily on the basis of frequent spontaneous (3–23/min) inter-ictal spike, polyspike and spike and wave discharges in their routine EEGs. Subjects taking phenytoin were not included. Chronic antiepileptic drug therapy consisted of the following either singly or in combination: primidone, carbamazepine, phenobarbitone and sodium valproate. This was continued unchanged throughout.

In this study we used Epanutin (Parke Davis) ready mixed parenteral solution containing phenytoin sodium 50 mg/ml. Subject 1 received phenytoin 20 mg/kg. Subjects 2–4 received phenytoin 15 mg/kg, and subjects 5 and 6 were given a fixed dose (500 mg) of phenytoin equivalent to 9.3 mg/kg and

5.6 mg/kg, respectively. An equivalent volume of normal saline was used as a placebo control and the order of treatment was randomised. Each agent was administered single blind on two occasions, separated by at least 7 days, and given intravenously over 20 min (phenytoin infusion rates ≤ 50 mg/min) by injecting the drug into the side arm of a fast flowing intravenous drip infusion of normal saline. Periodic checks of blood pressure, heart rate and respiration were made during the injections. A 10 min baseline EEG recording was made immediately before drug administration and this was used as a control. Seven subsequent 10 min recordings were made at intervals over a 3 h period following drug administration. EEG recordings were achieved using an eight channel SLE (Galileo model E8 B) electroencephalograph recorder and bipolar electrodes positioned according to the 10–20 system. Recordings were made from the montage which provided best definition of spikes and this was usually from a lateral ring of electrodes. Time 0 was taken as midway through the infusion, i.e. 10 min from the beginning of the injection. The EEGs were then code numbered and subsequently analysed blind and in random order using the method described by Ahmad *et al.* (1977). The number of spikes in each 10 min EEG after treatment was counted and expressed as a percentage of that in 10 min of control EEG before treatment. Spike counting was confined to the one EEG channel in which the spikes were most clearly defined. An example of this is shown in Figure 1. Sharp waves were included in the counting where these were clearly of epileptic origin, i.e. where they were accompanied by spikes in adjacent channels or where they were phase reversing. In general the duration of sharp waves included did not exceed 150 ms (accepted range 70–200 ms). The percentage reduction of spike counts after active treatment and placebo was compared on a within-subject basis and the Wilcoxon sign-rank matched-pairs test was used for statistical analysis.

In Subject 1 the EEG study coincided with an increase of clinical seizures which occurred for no apparent reason. There had been no alteration in medication in the previous 12 months and compliance had not been a problem. Seizures were of a focal adversive type affecting the left side of the body and in the week immediately preceding the investigation these were almost invariably followed by secondarily generalised tonic-clonic fits. This, and possibly the continuing subclinical electroencephalographic epileptic activity, resulted in a profound Todd's paresis such that, at the height of her illness, the patient was almost hemiplegic with only minimal movement of the fingers of the left hand. Chronic therapy with phenytoin (300 mg/day) was begun 24 h after the intravenous infusion and this was administered orally in divided dosage. Blood samples for measurement of serum phenytoin concentrations were taken at 12 h and 24 h after intravenous infusion of the drug and at 6 days after the introduction of chronic therapy. In addition, a detailed record of fit frequency was made by the nursing staff before and after the introduction of phenytoin.

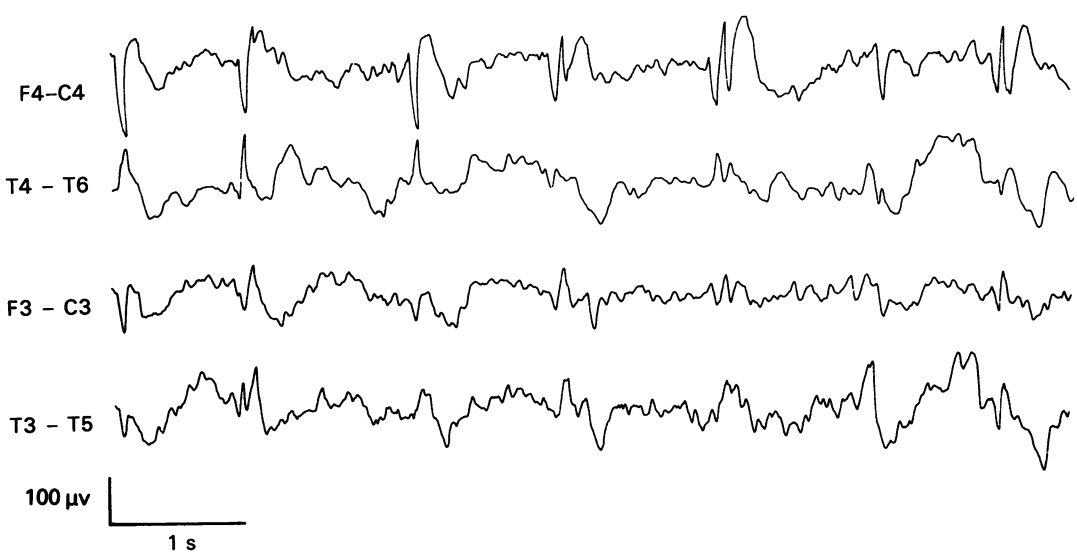

Figure 1 EEG sample from Subject 1 showing frequent inter-ictal spikes over the right cerebral hemisphere (top two channels). In this example spikes would be counted by eye in channel F4–C4 and in doubtful instances reference would be made to channel T4–T6.

Results

Adverse effects

No seizures were observed following the injections in Subjects 2–6 and there were no cardiovascular complications in any patient. Subjects 1–3 exhibited central vestibular adverse effects (nystagmus, dysarthria, vertigo, nausea and/or vomiting) either at the end of the infusion or soon afterwards. A further patient (Subject 4) became extremely agitated and restless immediately after receiving 1000 mg (15 mg/kg) of phenytoin and this persisted for 40 min before resolving. There were no serious adverse effects in the two patients who received a fixed dose (500 mg) of phenytoin.

Inter-ictal spikes

Phenytoin, given intravenously in doses of 500–1000 mg, produced a significant decrease in the frequency of inter-ictal spikes in the EEG in all subjects. The effect was most marked 10–20 min after the infusion, when the mean spike count was reduced to 27% (s.d. ± 17%) of the control ($P < 0.05$) (Figure 2, 15 min). Significant depression of the spike count occurred during all periods of observation except at 90 min and 120 min, where differences from placebo were not statistically significant. Analysis of raw data revealed similar findings (Table 1).

Fit frequency

As shown in Figure 3, there was a marked reduction in seizure frequency in Subject 1 following the introduction of phenytoin but this was not clearly evident until 48 h after the infusion. The EEG response to an acute intravenous administration of phenytoin in this patient is illustrated in Figure 4.

The decrease in seizure frequency was accompanied by a decrease in seizure severity. Although brief focal adversive seizures continued, the incidence of secondarily generalised tonic-clonic fits was dramatically reduced immediately following the infusion. One week after the introduction of phenytoin the patient was able to use the left arm and walk with the aid of a zimmer frame, whereas before this she had been hemiplegic. The serum phenytoin concentration 24 h after the infusion (51 μmol/l) was within the therapeutic range (up to 80 μmol/l). Although still within the therapeutic range 6 days later (72 μmol/l), the presence of clinical evidence of phenytoin intoxication required a reduction of the maintenance dose. Fit control was not affected adversely by this measure and all signs of anticonvulsant intoxication subsequently disappeared.

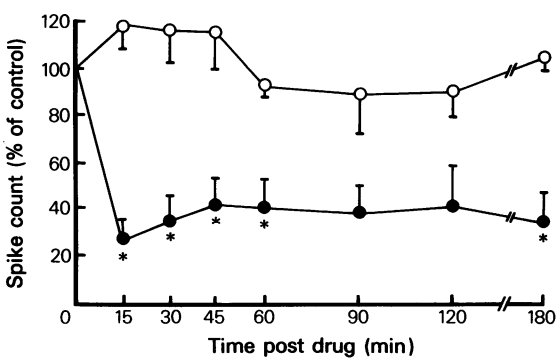

Figure 2 Mean spike counts (expressed as a percentage of the control) in Subjects 1–6 following intravenous administration of saline (○) and phenytoin (●). Assessment was by spike counting in 10 min of control EEG and in seven 10 min recordings after treatment (5 min either side of times shown). Observations after phenytoin significantly different from saline $*P < 0.05$ Wilcoxon sign-rank matched pairs test. Bars represent 1 s.e. mean.

Discussion

Previous reports have suggested that EEG epileptiform abnormalities are reduced during chronic therapy with phenytoin (Rodin *et al.*, 1974) but these studies have often been made in comparison with other antiepileptic drugs rather than a placebo. In a double-blind comparison of chronically administered phenytoin and carbamazepine, Wilkus *et al.* (1978) reported significantly fewer generalised epileptic discharges during treatment with phenytoin but focal EEG abnormalities were not significantly altered. However, the acute effects of this drug on the EEG following intravenous administration in man have never previously been reported. These results show that phenytoin given in doses ranging from 500–1000 mg produced a significant pharmacodynamic effect within 10–20 min as judged by a reduction of inter-ictal spike counts in the EEG. These findings are in contrast with earlier reports from animal studies showing no effect of intravenous phenytoin on cortical spike foci induced by either alumina cream or penicillin inoculations (Rand *et al.*, 1966; Edmunds *et al.*, 1974).

Since most antiepileptic drugs, including phenytoin, penetrate poorly into areas of abnormal brain (Sherwin *et al.*, 1976), the striking results in this study were somewhat surprising as five of the six subjects had focal abnormalities in their EEG. The results in Subject 1 show that reduction in spike counts coincided with an improvement in seizure freqency although this was delayed for 48 h. The most obvious immediate clinical effect following intravenous phenytoin was a decrease in seizure severity as the incidence of secondarily generalised tonic-clonic fits

Table 1 Mean spike counts (± s.d.) in six adult epileptic patients following intravenous administration of normal saline and phenytoin.

		Time post drug (min)						
Drug	*Control*	*10–20*	*25–35*	*40–50*	*55–65*	*85–95*	*115–125*	*175–185*
Saline	120 ± 70	134 ± 69	125 ± 62	121 ± 46	106 ± 57	91 ± 35	84 ± 30	107 ± 47
Phenytoin	101 ± 50	26 ± 17 (T − 0)*	35 ± 21 (T − 0)*	43 ± 24 (T − 0)*	45 ± 34 (T − 0)*	41 ± 39 (T − 2)	49 ± 54 (T − 4)	29 ± 20 (T − 0)*

*$P < 0.05$ Wilcoxon sign-rank matched pairs test

was dramatically reduced immediately post infusion. Continuing seizures were of a brief focal adversive type and these improved gradually with continuance of maintenance therapy. This was reflected in the return of motor function to the left sided limbs. A tendency towards a preferential improvement of generalised seizures supports the observations of Wilkus *et al.* (1978) (see above), and is in keeping with the hypothesis that phenytoin acts by preventing the spread of abnormal electrochemical activity through a membrane stabilising effect (Woodbury, 1980; Rall & Schleifer, 1980).

Studies show that phenytoin crosses the blood–brain barrier rapidly following intravenous administration and brain concentrations exceed serum levels within 20 min after infusion (Wilder *et al.*, 1977). The rapid entry of phenytoin into the brain was demonstrated in our study by the early appearance of central vestibular adverse effects occurring at the end of the infusion or soon afterwards. Subject 1 received phenytoin 20 mg/kg for therapeutic reasons but doses of up to 27 mg/kg have been used by others in the acute treatment of seizures without serious adverse effects (Cranford *et al.*, 1978). However, adverse reactions may not be evident when this drug is given therapeutically in status epilepticus due to the clinical condition of the patient. This may explain the relatively low reported incidence of toxic effects when intravenous phenytoin is used in the acute treatment of seizures (Wilder *et al.*, 1977). Conversely, a higher incidence of adverse reactions may be anticipated in patients with severe epilepsy, as these subjects often have chronic neurological disability in addition to their epilepsy which may predispose them to the adverse effects of this drug (Ahmad *et al.*, 1975). A dose of 15 mg/kg was used in Subjects 2–4 because of the occurrence of vestibular side effects at a dose of 20 mg/kg in Subject 1. The persistence of toxic effects at this reduced dosage required a further modification and the remaining two patients received a fixed dose (500 mg) of phenytoin. Slight discomfort at the injection site was the only complication observed in these two subjects, and this can be minimised by injecting into a large vein in the antecubital fossa and by using a fast flowing drip infusion. The two patients who received a fixed dose of phenytoin (9.3 mg/kg and 5.6 mg/kg) responded with a fall in spike counts to 6% and 41% of the control values respectively at 15 min but this effect waned more readily towards the end of

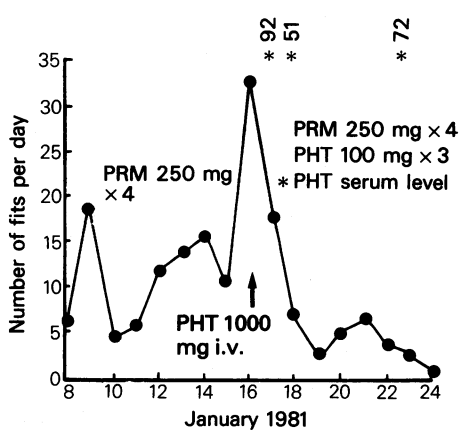

Figure 3 Fit frequency (adversive ± secondarily generalised tonic-clonic) in Subject 1 before and after the introduction of phenytoin. At the time of phenytoin infusion the patient had a profound left sided Todd's paresis. Seven days later she could walk with assistance. PRM = primidone; PHT = phenytoin. Serum levels are given in μmol/l.

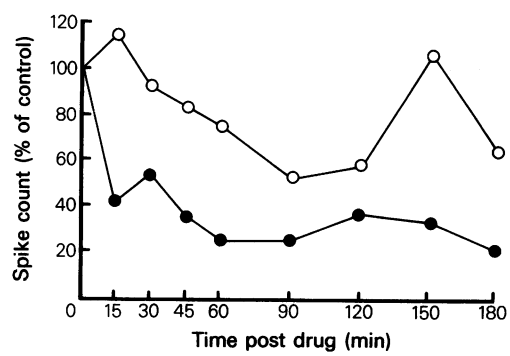

Figure 4 Spike counts (expressed as a percentage of the control) in Subject 1 following intravenous saline (○) and phenytoin (●) before the introduction of chronic therapy with phenytoin. Note the placebo effect following saline. Assessments as indicated in Figure 2.

the study in that patient receiving the smaller weight-related dose.

In summary this study has shown that intravenous administration of phenytoin in doses of 500–1000 mg produced a significant improvement in the EEG as judged by a reduction in the frequency of inter-ictal spikes. In one patient this coincided with an improvement in fit frequency. Although no causal relationship has been established between depression of inter-ictal spikes following single test doses of antiepileptic drugs and control of clinical seizures, such changes do indicate a cerebral pharmacodynamic effect and it is reasonable to assume that agents capable of reducing these abnormalities might possess antiepileptic properties. Spike counting is an easy and quick technique that can be used for the preliminary evaluation of new compounds and the effects of the established antiepileptic drugs provide a yardstick against which new compounds can be measured. If phenytoin is to be used as a reference drug, the total amount given should be tailored to patient body weight and the results from this study suggest that a dose of 7.5–10 mg/kg would be sufficient to reduce the frequency of inter-ictal spikes.

In addition, the occurrence of adverse reactions at this dosage would be minimised. The main limitations of this technique as a method of assessment of anti-epileptic drugs are that it can only be used in patients who have frequent inter-ictal spikes in their EEG and for drugs that penetrate rapidly into the brain. It may not be suitable, therefore, for drugs that penetrate slowly into the brain or for those that are active by metabolite formation.

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