CONTROL OF EPILEPSY WITH A SINGLE DAILY DOSE OF PHENYTOIN SODIUM

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1 Fifty-three patients in an epileptic centre have been studied. All were receiving phenytoin and many were also receiving other antoconvulsant drugs.

2 Thirty-six patients took part in a three month cross over study. There was no significant change in the frequency of epileptic seizures or in the late morning serum concentration of phenytoin when the treatment was changed from two to three spaced doses of phenytoin sodium/day to a single dose at 12.00 hours.

3 Seventeen patients acted as a control group. They received phenytoin sodium as two or three spaced doses/day throughout the study. There was no significant change in the frequency of epileptic seizures or in the late morning serum concentration of phenytoin between the first and second three month periods of observation.

4 It is concluded that the total daily dose of phenytoin sodium may be given once daily without reduction of the anticonvulsant effect.

Introduction

The decay of serum phenytoin concentration in man is slow. Mawer, Mullen, Rodgers, Robins & Lucas (1974) observed a mean fall from 12.5 to 7.5 $\mu\text{g/ml}$ over a 24 h period in fifteen patients. Many other authors have made similar observations.

Wilder, Streiff & Hammer (1972) and Buchanan, Kinkel, Goulet & Smith (1972) measured serum concentrations of phenytoin in healthy subjects or in epileptic patients given several spaced doses of phenytoin/day. They showed that the same total dose could be given once daily without producing significantly greater fluctuations in serum phenytoin concentration. The present study was therefore planned to determine if the single daily dose also had an equivalent anticonvulsant effect. This has proved to be the case.

Since this study was completed an independent report of similar results has appeared (Strandjord & Johanessen, 1974).

Methods

Patients

Fifty-three patients in the Langho Epileptic Centre, Blackburn, were studied; their ages ranged from 16-20 years. Most were receiving several anticonvulsant drugs (Table 1) and all were receiv-

Table 1 Number of patients receiving other anti-convulsant drugs in addition to phenytoin. Several patients were receiving more than two drugs.

<i>Drugs</i>	<i>Patients</i>
phenobarbitone	34
primidone	14
carbamazepine	8
ethosuximide	8
benzodiazepines	7
sulthiame	5
acetazolamide	1
methoin	1

ing phenytoin (Epanutin, Parke-Davis). The patients were living in separate houses in groups of about twenty. The nursing attendant for each house was responsible for recording a brief description of each epileptic seizure observed and the time at which it occurred. These events were recorded during active and sleeping hours on specially designed record sheets which were collected weekly. Each event was allocated to one of two categories according to its disruptive effect on the patient's usual daily activities.

Seizures were classified as minor when the patient did not fall, did not injure himself and was not incontinent of urine, when consciousness was retained or regained rapidly and there was immediate return to normal activity. Seizures were classified as major when the patient fell or injured himself, was incontinent or remained unconscious for more than half a minute or was not able to return immediately to his normal activity.

The patients at the Centre are encouraged to be active and it was inevitable that many daytime epileptic seizures would be observed by workshop, garden, kitchen and cleaning staff who had no medical training. These were reported to the nursing attendant responsible for the patient and included in the record. A more complex classification of the seizures would have been unjustified in this context.

The study was explained carefully to each patient and six refused to take part because they were unwilling to give blood samples or to take their phenytoin as a single daily dose.

Phenytoin dose adjustment

Preliminary measurements of serum phenytoin concentration in the fifty-three patients showed that only seven had values within the range of 10-20 µg/ml. Individual doses were therefore increased and as a result twenty-eight patients attained concentrations within this range. This adjustment was made during the three months which preceded the cross over study but during the study itself the daily doses of the anti-convulsant drugs were not changed. The purpose of the adjustment was to increase the likelihood that the phenytoin therapy was actually producing a significant anticonvulsant effect. Seven patients showed a dramatic reduction in fit frequency as a result of the dose increase.

Alternative dose schedules

Fifteen men in house A were observed for a three month period during which they each received their daily phenytoin as a single dose at 12.00 hours. Twenty-one men in house B were observed

for the same period during which they each received their daily phenytoin as usual in two (08.00 h and 16.00 h) or three (08.00 h, 12.00 h and 16.00 h) spaced doses. Staffing problems did not permit more even spacing. At the end of three months each group of patients changed to the alternative dose schedule for a further three months. Seventeen women in house C were maintained on the spaced dose schedule throughout both three month periods.

Analysis of samples

Samples of venous blood were obtained from each patient shortly before noon at intervals of about three weeks on a minimum of six occasions during the cross over study. Serum was stored at -20°C until required for analysis.

The drugs were extracted from acidified serum into toluene containing the internal standard (5-(4-methylphenyl) 5-phenylhydantoin) and then into the methylating agent (tetramethylammonium hydroxide in methanol) in preparation for methylation at 290°C in the injection port of the gas chromatograph (Macee, 1970).

Chromatography was carried out using 3% (w/v) OV17 on 80-100 mesh H.P. Chromosorb W in 2 m x 1.7 mm (i.d.) glass columns. These were mounted in the Perkin-Elmer F11 fitted with dual flame ionisation detectors. The flow rate of the nitrogen carrier was 27 ml/minute. Good resolution of well formed symmetrical peaks was obtained using an oven temperature of 170°C for 4 min rising by 5°C/min to 235°C.

Standard solutions of phenytoin, phenobarbitone and primidone in pooled blank serum were prepared for calibration purposes. The coefficients of variation of peak height ratios determined by repeated extractions of standards on the same day were 2.3, 4.4 and 6.3% respectively. The corresponding values for variation between days were approximately double. For this reason a fresh calibration curve was determined on each assay day.

Mr A. Cocks participated in the national quality control scheme organized by Dr A. Richens of St Bartholomew's Hospital, London.

Results

There was no change in the frequency of epileptic seizures, by day or by night (Table 2a) and no change in the measured serum concentrations of the anticonvulsant drugs (Table 3a) when the patients of houses A and B were changed from spaced doses of phenytoin to a single daily dose.

As expected the control patients in house C

Table 2 Number of epileptic seizures observed during treatment with single and spaced doses of phenytoin:
(a) Patients in cross over study (houses A and B), $n = 36$

Dose schedule	Major seizures by day		Minor seizures by day		Major seizures by night		Minor seizures by night		Total	
	Single	Spaced	Single	Spaced	Single	Spaced	Single	Spaced	Single	Spaced
Total seizures	113	105	102	89	69	83	126	104	410	381
Seizures per patient	3.14	2.92	2.83	2.47	1.92	2.31	3.50	2.89	11.3	10.6
P (paired t -test) ¹	0.37		0.31		0.32		0.15		0.30	

(b) Patients in control group (house C), $n = 17$

Period	Major seizures by day		Minor seizures by day		Major seizures by night		Minor seizures by night		Total	
	1	2	1	2	1	2	1	2	1	2
Total seizures	21	19	100	80	18	12	22	36	161	147
Seizures per patient	1.24	1.12	5.88	4.71	1.06	0.71	1.30	2.12	9.47	8.65
P (paired t -test) ²	0.39		0.07		0.05		0.16		0.12	

¹ Single versus spaced dose

² Period 1 versus period 2.

Table 3 Concentrations of anticonvulsant drugs ($\mu\text{g/ml} \pm \text{s.e. mean}$) in serum taken shortly before 12.00 h during treatment with single and spaced daily doses of phenytoin:
(a) Patients in cross over study (houses A and B)

Drug	n	Single	Spaced	P (paired t-test)
Phenytoin	34*	8.6 ± 1.7	8.6 ± 1.2	0.49
Phenobarbitone ¹	25	24.6 ± 2.2	23.3 ± 2.1	0.10
Primidone	10	6.4 ± 0.8	6.6 ± 0.5	0.26

*Insufficient samples were obtained from two patients who were, therefore, excluded

(b) Patients in control group (house C)

Drug	n	Period 1	Period 2	P (paired t-test)
Phenytoin	16 ²	7.8 ± 0.9	7.7 ± 0.8	0.34

¹ This was derived from primidone in some cases

² Insufficient samples were obtained from one patient who was therefore excluded.

showed no change in the frequency of epileptic seizures (Table 2b) or in the serum concentrations of phenytoin (Table 3b) between the two three month periods of observation.

Discussion

Many authors have suggested or implied that phenytoin could be given as a single daily dose without loss of anticonvulsant effect. (Buchanan *et al.*, 1972; Remmer, Hirschmann & Greiner, 1969; Wilder *et al.*, 1972.) This suggestion is based on the observation that serum phenytoin concentrations fluctuate over only a narrow range in subjects receiving regular doses even when these are given at 24 h intervals.

The advantage of a once daily dose schedule is obvious; it is likely to be more acceptable to patients leading a full and active life and to result in fewer forgotten doses. However, physicians and neurologists are not convinced by arguments based solely on drug kinetics and convenience. It has been necessary to demonstrate in patients that once daily phenytoin therapy does not lead to an increase in seizure frequency and does not alter the serum concentrations of other anticonvulsant drugs.

Our results are consistent with those of Strandjord & Johanessen (1974) who treated a group of nineteen epileptic inpatients with a formulation of phenytoin acid which was given initially as a morning dose and an evening dose; this was then changed to a regime in which the

same total daily dose was given once daily in the evening. The change in regime produced no significant change in the frequency of epileptic seizures or in the serum concentration of phenytoin before the evening dose.

Several other anticonvulsants show an even slower rate of decay of serum concentration. Serum concentration half-times between 53 and 140 h have been observed for phenobarbitone (Maynert, 1972). Primidone half-times are shorter (3.3-12.5 h; Gallagher & Baumel, 1972) but since this drug is substantially converted to phenobarbitone it is likely that the half-time for the anticonvulsant effect is much longer. Ethosuximide has a prolonged serum concentration half-time (24-49 h; Sherwin & Robb, 1972) as do the benzodiazepines (de Silva, Koechlin & Bader, 1966). There is therefore a case for assessing once daily dosage of other anticonvulsant drugs. It is possible that patients with epilepsy can take their entire daily dose of anticonvulsants at one convenient time each day.

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