Effect of a delayed-action phenytoin preparation on blood phenytoin concentration

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SUMMARY In a cross-over study in a group of epileptic patients it was shown that replacement of the evening dose of an ordinary phenytoin preparation with the same phenytoin dose in a delayed-action preparation produced no significant change in the next morning's mean blood phenytoin concentration. However, replacement of the entire daily dose of an ordinary phenytoin preparation with the delayed-action preparation did increase mean blood phenytoin levels after some days, possibly because the latter preparation contained an additional 6% active drug, as compared with the former. In most circumstances, it seems doubtful if the delayed-action preparation offers any advantage over ordinary phenytoin in treating epilepsy.

Delayed-action preparations of phenytoin (diphenylhydantoin) have been used at times in the treatment of epilepsy. These preparations contain acid phenytoin, whereas ordinary phenytoin preparations usually consist of the sodium salt. The rationale for the use of delayed-action preparations presumably lies in the belief that they may have a more prolonged therapeutic effect than ordinary preparations. For example, if the delayed-action phenytoin is taken in the evening in place of ordinary phenytoin, it might be hoped that it would produce by the next morning higher blood and tissue concentrations of phenytoin than would the ordinary preparation, thus reducing the risk of an early morning epileptic seizure. Certainly there is evidence (Dill, Kazenko, Wolf, and Glazko, 1956) that, after single doses, blood phenytoin levels are maintained for longer periods by acid phenytoin than by sodium phenytoin.

Data have accumulated showing how slowly phenytoin disappears from the blood after its administration is ceased, its half-life being a matter of some 22 ± 9 hours (Arnold and Gerber, 1970). Therefore it seems unlikely that omission of phenytoin doses for some 12 hours during the night would produce any profound fall in blood and tissue phenytoin concentrations by the next morning. Since it is known that blood phenytoin concentration correlates with its

biological effect (Kutt and McDowell, 1968), the rationale for using a delayed-action preparation of phenytoin at night, or at other times, appears uncertain. We have attempted to see if delayed-action phenytoin offers advantages over the ordinary preparation by investigating the response of blood phenytoin concentrations to replacement of oral doses of ordinary phenytoin by similar doses in a delayed-action preparation which is currently available on the Australian market.

METHODS

Two studies were carried out. In the first, blood phenytoin concentration was measured by the Wallace (1966) spectrophotometric assay. In the second, plasma phenytoin concentration was measured by a minor modification of the MacGee (1970) gas chromatographic assay.

The first study was designed to approximate to the conditions under which the delayed-action phenytoin often is used in practice. Eleven epileptic patients taking phenytoin, and with chronic neurological illness necessitating long-term hospitalization, were divided into groups of five and six. All entered the trial simultaneously. They continued to receive all their pre-trial therapy in unchanged dosage throughout the study but group A took their evening phenytoin dose (100 mg) as the delayed-action preparation for the first 10 days of the study and then crossed-over to receive their evening dose

as ordinary phenytoin for the second 10 days. Group B took the above phenytoin preparations in the reverse order during the same time periods. Blood was taken for phenytoin estimation between 8 a.m. and 9 a.m. on the mornings after the eighth, ninth, and tenth days of each trial period.

In the second study six patients from the population described above were divided into groups of three. All patients were taking 100 mg phenytoin three times a day and all entered the 14 day trial simultaneously. One group took their entire daily phenytoin dose as the delayed-action preparation (in three doses) for the first week and then reverted to taking the ordinary phenytoin preparation, while all of the second group took the two preparations in reverse order. Blood phenytoin concentrations were measured on the second, fourth, and seventh days of each trial period.

RESULTS

The results of the first part of the study are set out in Table 1. The delayed-action phenytoin given in a single dose in the evening did not produce higher mean blood phenytoin levels the next morning than the mean levels produced by ordinary phenytoin, an analysis of variance showing that the difference between the means was not significant statistically ($P>0.05$).

The inference could be drawn from the above finding that ordinary phenytoin and the delayed-action phenytoin were equivalent on a dose for dose basis. However the findings for the second

part of the study did not confirm this (Table 2). There was no statistically significant difference between mean plasma phenytoin levels before the patients entered the trial (21.9 $\mu\text{g/ml.}$) and after seven days of taking the ordinary phenytoin preparation (22.8 $\mu\text{g/ml.}$) ($t=0.9$, $P>0.40$), but mean plasma phenytoin level rose significantly

TABLE 2
BLOOD PHENYTOIN LEVELS IN $\mu\text{G/ML.}$ PRODUCED BY THE ORDINARY AND THE DELAYED-ACTION PREPARATIONS

Subject	Pre-trial	Blood phenytoin concentration					
		Ordinary preparation			Delayed-action preparation		
		Day 2	Day 4	Day 7	Day 2	Day 4	Day 7
A	8.4	9.5	12.7	10.7	12.8	11.3	17.6
B	22.2	26.4	25.2	20.8	23.8	30.3	27.5
C	22.9	31.9	28.4	23.3	26.5	30.3	30.7
D*	12.6	14.3	14.0	16.7	—	12.6	15.1
E*	30.2	35.3	23.0	27.8	31.6	34.6	35.0
F*	35.0	40.5	35.7	37.2	42.0	47.5	48.1
Mean	21.9	26.3	23.2	22.8	24.7	27.8	29.0

* Took the delayed-action preparation first.

to 29.0 $\mu\text{g/ml.}$ ($t=3.64$, $P<0.02$) after one week of replacement of the ordinary phenytoin preparation with the delayed-action phenytoin.

DISCUSSION

At first sight the two studies appear to have produced conflicting findings, but to some extent they can be reconciled. It is clear that no evidence has been obtained that, in a group of patients, the delayed-action phenytoin given, as it often is, in a dose of 100 mg at night, produces higher mean blood phenytoin levels the next morning than does the same dose of ordinary phenytoin. This finding, which might be anticipated from knowledge of phenytoin metabolism in man, suggests that the traditional use of delayed-action phenytoin at night offers no advantage over the use of ordinary phenytoin preparations. Yet, despite this, the delayed-action phenytoin preparation has been shown in the second part of the study to produce higher mean blood phenytoin levels than the ordinary preparation. There are two possible reasons why

TABLE 1
BLOOD PHENYTOIN CONCENTRATION ON MORNINGS AFTER THE 8TH, 9TH, AND 10TH DAYS OF EACH TRIAL PERIOD*

Subject	Ordinary phenytoin ($\mu\text{g/ml.}$)			Delayed-action phenytoin ($\mu\text{g/ml.}$)		
	Day 8	Day 9	Day 10	Day 8	Day 9	Day 10
A	8.4	6.2	10.6	5.5	7.4	10.6
B	3.3	3.3	4.7	0.6	2.2	1.5
C	23.4	36.2	20.7	20.0	22.0	24.2
D	6.0	9.6	(7.7)†	6.3	5.5	6.8
E	2.0	0.9	3.7	1.5	2.8	3.8
F	36.9	33.6	36.6	45.4	32.4	33.8
G	2.8	4.5	5.3	2.1	3.0	6.3
H	18.8	19.3	20.8	18.9	17.8	19.7
I	1.0	1.9	2.3	0.9	0.6	1.7
J	9.7	9.0	11.1	14.2	13.5	14.8
K	17.5	61.4	20.9	18.0	17.1	20.9
Means	12.73			12.16		

* The first five patients took the delayed-action preparation first.
† Missing value calculated after Goulden (1952).

the second part of the study may have shown this effect, whereas the first part did not. The doses of delayed-action phenytoin used in the second part were three times as high as those used in the first part, and the second part of the study happened to be carried out in a group of patients who had a substantially higher mean blood phenytoin level (around 21.9 $\mu\text{g/ml.}$) than that in the first part (12.7 $\mu\text{g/ml.}$). It has been shown (Bochner, Hooper, Tyrer, and Eadie, 1972) that, at higher blood phenytoin levels, small dosage changes have proportionately greater effects on blood phenytoin concentration than they do at lower blood levels. Therefore the second study was, as it were, set to be a more sensitive detector of differences than was the first study. Its findings suggest that the delayed-action phenytoin, dose for dose, may have contained slightly more active ingredient than the ordinary preparation.

In the delayed-action preparation the phenytoin is present as the free acid (molecular weight 252.3), whereas in the ordinary preparation the drug is present as the sodium salt (molecular weight 268.3). If both preparations contain 100 mg of active ingredient—that is, acid phenytoin, or sodium phenytoin—the delayed action preparation should contain some 6.34% more phenytoin itself than the ordinary preparation, and this has been confirmed by assay. This difference in phenytoin contents may be too small to have a significant effect in the majority of patients when only 100 mg of the delayed-action phenytoin preparation is taken each night, but in the occasional patient whose blood phenytoin concentration already is fairly high in the so-called 'therapeutic' range of 10–20 $\mu\text{g/ml.}$, the delayed-action phenytoin may produce an increment in blood phenytoin concentration which would be of therapeutic value. This could explain some clinicians' impressions that the delayed-action preparation sometimes

has been of use. While it could be argued that a slightly higher oral dose of an ordinary phenytoin preparation would have been equally helpful, in practice it may be difficult to provide this slightly higher dose because oral phenytoin preparations usually are available only in 30 mg, 50 mg, and 100 mg units and in the circumstances where delayed-action phenytoin might produce a useful rise in blood phenytoin level—namely, when the level is in the range 15–20 $\mu\text{g/ml.}$ —even a further 30 mg phenytoin daily may lead to a marked rise in blood phenytoin level with drug intoxication (Bochner *et al.*, 1972).

It appears that the slightly greater content of phenytoin in the delayed-action preparation, tested, rather than any difference in its duration of action, may provide a sufficient explanation for the occasional therapeutic advantage this preparation may have.

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