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INHIBITION OF PHENYTOIN METABOLISM BY SULTHIAME IN EPILEPTIC PATIENTS

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1 Measurements have been made of steady state serum phenytoin concentration, serum half-life of ^{14}C-labelled phenytoin, and the urinary ratio of the major metabolite of phenytoin to the unchanged drug (p-HPPH : DPH ratio) in epileptic patients on and off sulthiame therapy.

2 Starting sulthiame treatment produced an increase in serum phenytoin concentration, a prolongation of the half-life and an increase in the p-HPPH : DPH ratio. The total urinary output of phenytoin plus p-HPPH was unaltered by sulthiame.

3 The results indicate that sulthiame or one of its metabolites inhibits the parahydroxylation of phenytoin by hepatic enzymes.

Introduction

Sulthiame (Ospolot) is a sulphonamide derivative with carbonic anhydrase inhibiting properties. In animal experiments (Wirth, Hoffmeister & Sommer, 1961), it has been shown to protect mice against the clonic component of electro-shock seizures. It has been widely used in the last few years as an anti-convulsant drug for focal or generalized epilepsy, but in most clinical trials it has been added to existing therapy rather than used as the sole treatment (Green & Kupferberg, 1972). The incidence of adverse effects has been high in several studies (La Veck, de la Cruz & Thomas, 1962; Ingram & Ratcliffe, 1963; Gordon, 1964) and the clinical features of toxicity have often resembled those of phenytoin intoxication. The reason for this is that sulthiame causes an elevation of the serum concentration of phenytoin when added to existing therapy (Hansen, Kristensen & Skovsted, 1968). These authors suggested that the parahydroxylation of phenytoin by liver microsomal enzymes was inhibited because they found a prolongation of the serum half-life following addition of sulthiame to the patients' treatment. However, Olesen & Jensen (1969) concluded that this was unlikely as they could not demonstrate a decrease in the urinary output of the major metabolite of phenytoin, 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH). They concluded that the elevation of serum phenytoin concentration produced by sulthiame in their patients was probably due to displacement of phenytoin from its binding to proteins in, for example, red cells. This was supported by the immediate onset of the interaction in their patients, although Hansen *et al.* (1968) had previously found a latent period of a week or more before the serum phenytoin concentration began to change following introduction of sulthiame therapy.

We have re-examined this question by measuring serum phenytoin concentrations, phenytoin half-lives and the urinary ratio of p-HPPH to unchanged phenytoin (p-HPPH : DPH ratio) in a group of patients with and without sulthiame therapy. Our preliminary results have been reported previously (Houghton & Richens, 1973a). We have attempted to answer two questions, (a) whether or not there is a latent period between starting or stopping therapy and the resulting change in serum phenytoin concentration, and (b) whether the interaction is caused by an inhibition of metabolism or by some other mechanism.

Methods

Patients

Residents of the National Hospital–Chalfont Centre for Epilepsy were studied. Serum phenytoin concentrations, phenytoin half-lives and urinary p-HPPH : DPH ratios were measured in eight patients who were receiving sulthiame in addition to phenytoin and other anti-convulsant drugs. Sulthiame was then abruptly withdrawn without any other drug change and the patients were re-assessed approximately four weeks later. In two patients the serum phenytoin concentration was measured at frequent intervals to follow the time course of the fall to a new equilibrium

level. Four further patients, whose fits were poorly controlled by conventional anti-convulsant therapy, were started on sulthiame in order to assess its clinical value in those patients. Initially 200 mg daily was given, increasing to 400 mg daily after two weeks. The indices of phenytoin metabolism were measured before and approximately four weeks after starting sulthiame therapy. The serum phenytoin concentrations of two of these patients were estimated at frequent intervals to follow the time course of the increase.

Drug estimations

Serum phenytoin was estimated on serum samples collected at approximately 7 h 00 min and 18 h 00 min over four days, these same specimens being used also for determining the serum half-life of a tracer dose of phenytoin (see below). The values quoted for serum phenytoin are the means (±S.D.) of the concentrations found in 6-8 specimens. Urinary phenytoin and p-HPPH were estimated in a single 24 h urine collection obtained on one of the four days during the half-life.

A GLC method was used for drug estimations, and was performed on a Perkin Elmer F11 gas chromatograph, with dual flame ionization detectors. It was fitted with six foot columns packed with 2½% w/v 0.V.17 on chromosorb G, 100-120 mesh. The oven was operated at 250° C, with a preheater block temperature of 340°-350° C. A flow rate of 20 ml/min of nitrogen was used. The gas pressures at the detectors were 22 psi of oxygen and 20 psi of hydrogen. The amplifiers were operated at an attenuation of 1×10^2 or 2×10^2.

The methods for the estimation of phenytoin in serum and in urine were identical in principle, but the volumes of reagents used were altered to give comparable peak heights between phenytoin and the internal standard, 100 μg/ml of 5-(p-methyl-phenyl)-5-phenylhydantoin (MPPH) (Ralph Emmanuel Ltd.). One ml of serum or 2 ml urine were measured into a large centrifuge tube containing either 0.1 ml (serum method) or 0.05 ml (urine method) of the internal standard. The tubes were then acidified with 0.25 ml 0.66 M hydrochloric acid. The phenytoin was extracted by shaking with either 10 ml (serum method) or 12 ml (urine method) of chloroform for 3 minutes. The two phases were separated by centrifuging at 2,000 r.p.m. for 3-5 min, and the lower chloroform layer was then removed into a 15 ml centrifuge tube using a disposable Pasteur pipette.

The chloroform was blown down to dryness and a small amount of methanol was used to wash down the sides of the tube. This was also blown down to dryness to remove any traces of chloroform, which would interfere with the methylation step. Thirty μl of a 25% w/v solution of tetramethyl-ammonium hydroxide (Sigma) was then added to each centrifuge tube. This was gently blown down to a volume of 2-5 μl, and an aliquot of 1-2 μl was injected into the GLC.

The major metabolite of phenytoin, 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH), is present in the urine mainly in the conjugated form and it is necessary to break this conjugate before extraction. Therefore 0.5 ml of the urine to be estimated was heated at 95°-105° C for 70-90 min with an equal volume of concentrated hydrochloric acid.

After the tubes had cooled, 0.1 ml of the internal standard, MPPH, was added. The tubes were then brought to pH 6.6 using sodium hydroxide and hydrochloric acid. An aliquot (2.5 ml) was taken and the remainder discarded. The 2.5 ml portion was placed in a centrifuge tube, and 15 ml of chloroform added. The tube was stoppered and shaken for 5 minutes. The sample was then centrifuged, the chloroform taken off and blown down, and the methylation procedure carried out exactly as in the phenytoin method.

When calculating phenytoin or metabolite concentrations the ratio of the peak height of the phenytoin or metabolite peak to the peak height of the internal standard was calculated. The ratio of p-HPPH to phenytoin in urine was a micromolar ratio. The daily excretion of p-HPPH plus phenytoin (DPH) was estimated by calculating the amount of phenytoin (as the acid) required to yield the quantity of p-HPPH plus phenytoin in a single 24 h collection of urine. This has been expressed as a percentage of the daily dose of phenytoin.

Sulthiame was shown not to interfere with the estimation of phenytoin or p-HPPH.

Phenytoin half-life

The serum half-life of ^{14}C-labelled phenytoin (Radiochemical Centre, Amersham) was performed by the administration of a capsule containing 10 μCi (0.21 mg) of the labelled drug (specific activity 12 mCi/mmol) dissolved in ethanol and absorbed on lactose. Seven or eight samples were taken at 12 h intervals over four days. The patients continued taking their anti-convulsant drugs during this time. Serum (2 ml) was added to 12.5 ml of Instagel (Packard). When shaken, this mixture was a clear homogeneous solution which counted at an efficiency of 50-65% on a Packard Tri-Carb scintillation counter. The counts were converted to disintegrations/min, and

the half-life calculated by the method of least squares. Whereas the decay of the serum concentration following single doses of unlabelled phenytoin is dose-dependent (Arnold & Gerber, 1970) and is non-linear on logarithmic plot against time because elimination changes from a zero order to a first order process as the serum concentration falls (Atkinson & Shaw, 1973), the decay of the serum concentration of ^{14}C-labelled drug in our patients was always linear on logarithmic plot (i.e. a first-order process). The reason for this was that our patients were in steady-state with regard to phenytoin, and we were measuring the rate of elimination of a tracer dose from a pool of phenytoin which was of constant size.

The half-life obtained by measuring total serum radioactivity is determined almost entirely by the rate of disappearance from the serum of the unchanged drug, for the serum concentration of phenytoin metabolites is very low (Glazko & Chang, 1972). One normal volunteer was given sodium phenytoin 300 mg daily for four weeks. With the last dose of drug a single ^{14}C-labelled tracer dose was given, and the half-life of the drug measured both by gas chromatography and liquid scintillation counting. The values obtained were 19.6 h and 17.9 h respectively.

Results

Serum phenytoin concentration

Each of the eight patients in whom sulthiame treatment was abruptly stopped showed a marked fall in his serum phenytoin, the fall varying from 16-72% of the control value (mean 46%). In each case this fall was highly significant (Table 1). Three of the patients had phenytoin concentrations in the toxic range at the beginning of the study when they were receiving combined therapy. In our experience, patients with a concentration of 100 μM (25 μg/ml) or above usually show clinical signs of intoxication and we therefore regard this as the toxic range. These three patients in fact had marked clinical signs, namely coarse nystagmus, ataxia and (in two cases, MS and PH) slurred speech. Sulthiame treatment was discontinued in these patients in the expectation that their serum phenytoin concentrations would fall to within the therapeutic range without any other drug change. This expectation was realized in two of the cases, although the third (PH) required also a small reduction in phenytoin dose. The case histories of MS and PH have been presented in full elsewhere (Houghton & Richens, 1973b).

The serum phenytoin concentrations of the four patients who were started on sulthiame for

Table 1 Drug dose and serum phenytoin concentrations in eight patients who were taken off sulthiame. There was an interval of approximately one month between the drug change and subsequent phenytoin estimation. The values quoted for serum phenytoin concentration for each patient are the means of 6-8 estimations over four days.

Patient (age and sex)	*Dose of phenytoin (mg/day)*	*Dose of sulthiame (mg/day)*	*Serum phenytoin concentration (μM)**		*%*	*Significance of difference between concentrations†*
			On sulthiame (mean ± S.D.)	*Off sulthiame (mean ± S.D.)*	*change*	
FW(23M)	150	600	23 ± 3.9	11 ± 2.9	−52	<0.01
RC(43M)	300	400	47 ± 6.3	28 ± 6.4	−40	<0.01
CH(28F)	300	600	77 ± 4.2	40 ± 3.0	−48	<0.01
JR(22M)	300	400	78 ± 5.0	65 ± 4.5	−16	<0.01
WP(44M)	300	600	82 ± 3.1	42 ± 3.9	−49	<0.01
RB(35M)	400	400	141 ± 5.8	39 ± 5.7	−72	<0.01
MS(25M)	300	400	144 ± 11.2	57 ± 7.8	−60	<0.01
PH(22M)	300	600	178 ± 6.9	116 ± 4.8	−33	<0.01
Arithmetic mean			95 μM	50 μM	−46	

* 4 μM = 1 μg/ml.
† Student's *t* test.

therapeutic purposes (Table 2) increased significantly in each case, the increase varying from 46-117% of the control value (mean 78%). Three patients (MP, DC and DW) developed signs of drug intoxication and, despite a reduction in fit frequency in two of them (MP and DC), sulthiame treatment had to be stopped (Houghton & Richens, 1973b). Following this change they returned to their previous state.

Phenytoin half-life

In each of the patients who were taken off sulthiame the serum half-life of phenytoin decreased, the change varying from 11-68% (mean 44%) (Table 3). Changes in the opposite direction were seen in the four patients in whom sulthiame treatment was started, although the magnitude of the changes tended to be less (Table 4). Peak serum radio-activity following administration of the tracer dose was not altered by sulthiame therapy.

The lengthening of the serum half-life by sulthiame was shown to be reversible in two of the patients (MP and DW) in whom sulthiame treatment was started and then stopped again five weeks later because of drug intoxication. The values before, during and after treatment for MP were 27.0, 36.3 and 27.0 h respectively, and for DW were 51.1, 57.0 and 50.9 h respectively.

In order to see whether the change in half-life was the result of a change in the steady state serum phenytoin concentration, two patients were studied who were not receiving phenytoin in their maintenance therapy. Patient RC was an 18-year-old male receiving sulthiame 400 mg and phenobarbitone 180 mg daily. A half-life was estimated before and one month after withdrawal of sulthiame. Because of frequent fits he was put back on to the drug two months later, and a third half-life was determined after a further month. The values obtained were 45.3, 27.0 and 72.6 h respectively. Patient GK was a 21-year-old female receiving sulthiame 800 mg and ethosuximide 750 mg daily. Sulthiame was withdrawn gradually over six weeks without change in the frequency of her minor attacks, and with complete disappearance of the marked hyperventilation which sulthiame had caused. Half-lives determined while on sulthiame, and again six weeks after its withdrawal, gave values of 27.6 and 12.1 hours.

Urinary p-HPPH : DPH ratios and total excretion

An increase in the urinary p-HPPH : DPH ratio, i.e. a change in favour of the metabolite, was seen in each of the seven patients in whom this was estimated before and after discontinuing sulthiame

Table 2 Drug dose and serum phenytoin concentrations in four patients who were put on sulthiame. There was an interval of approximately one month between the drug change and subsequent phenytoin estimation. The values quoted for serum phenytoin concentration for each patient are the means of 6-8 estimations over four days.

Patient (age and sex)	*Dose of phenytoin (mg/day)*	*Dose of sulthiame (mg/day)*	*Serum phenytoin concentration (μM)**		*%*	*Significance of difference between concentrations†*
			Off sulthiame (mean ± S.D.)	*On sulthiame (mean ± S.D.)*	*change*	
AE(30M)	300	400	23 ± 5.0	50 ± 5.2	+117	<0.01
MP(30F)	300	400	57 ± 4.0	83 ± 5.9	+46	<0.01
DC(30F)	300	400	63 ± 6.4	112 ± 7.5	+78	<0.01
DW(25M)	300	400	78 ± 4.3	133 ± 7.0	+71	<0.01
Arithmetic mean			55 μM	95 μM	+78	

* 4 μM = 1 μg/ml.
† Student's *t* test.

Table 3 Serum half-life of ^{14}C-labelled phenytoin, urinary p-HPPH : DPH ratio and total excretion of phenytoin plus p-HPPH in eight patients before and after stopping sulthiame therapy.

	Phenytoin half-life (h)		%	*p-HPPH : DPH ratio*		%	*p-HPPH + DPH excretion (%)†*	
Patient	*On sulthiame*	*Off sulthiame*	*change*	*On sulthiame*	*Off sulthiame*	*change*	*On sulthiame*	*Off sulthiame*
FW	34.2	18.2	−47	40.8	74.0	+72	55	59
RC	31.2	16.6	−47	28.6	81.4	+185	60	45
CH	46.3	22.5	−51	14.3	27.7	+94	72	49
JR	45.3	40.5	−11	−‡	19.9		–	–
WP	66.4	40.6	−39	12.0	16.4	+37	–	–
RB	68.1	21.5	−68	11.4	87.6	+669	62	62
MS	77.0	41.2	−46	13.5	40.2	+198	50	75
PH	79.4	45.6	−42	4.6	5.2	+13	28	23
Arithmetic mean	56.0	30.9	−44	17.6	46.6	+181	53	52
	$P < 0.01$*			<0.02*			NS§	

* Wilcoxon's test for pair difference.
† Expressed as % daily dose of phenytoin.
‡ Specimen not obtained. Patient's results excluded from calculation of mean ratio.
§ Paired Student's *t* test.

Table 4 Serum half-life of ^{14}C-labelled phenytoin, urinary p-HPPH : DPH ratio and total excretion of phenytoin plus p-HPPH in four patients before and after starting sulthiame therapy.

	Phenytoin half-life (h)		%	*p-HPPH : DPH ratio*		%	*p-HPPH + DPH excretion (%)**	
Patient	*Off sulthiame*	*On sulthiame*	*change*	*Off sulthiame*	*On sulthiame*	*change*	*Off sulthiame*	*On sulthiame*
AE	36.3	47.7	+29	−†	–		–	–
MP	27.0	36.3	+34	28.8	16.4	−43	61	38
DC	34.1	47.6	+40	20.8	17.9	−14	21	57
DW	51.1	57.0	+12	11.4	9.9	−13	41	21
Arithmetic mean	37.1	46.9	+29	20.3	14.7	−23	41	39

* Expressed as % daily dose of phenytoin.
† Specimens not obtained.

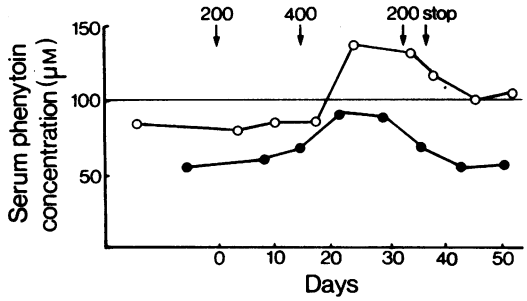

Fig. 1 Time course of the elevation of serum phenytoin concentration by sulthiame. Two patients, DW (○) and MP (●), were started on 200 mg sulthiame in addition to their daily dose of phenytoin (300 mg). The dose of sulthiame was increased to 400 mg after 14 days, and then reduced and finally stopped on day 36 because of clinical signs of intoxication. Note the 10-20 days delay before the phenytoin levels increase appreciably.

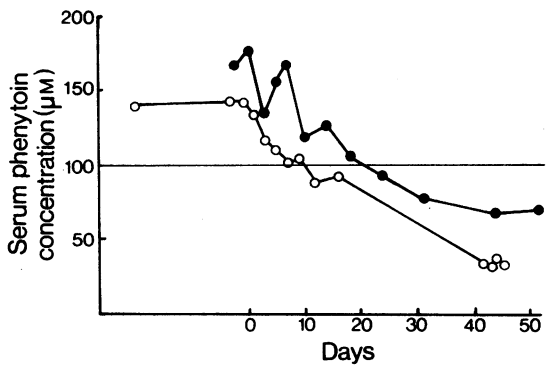

Fig. 2 Time course of the fall in serum phenytoin concentration on stopping sulthiame therapy. Patient RB (○) was receiving 400 mg of phenytoin and 400 mg of sulthiame daily. Patient EC (●) was receiving 60 mg phenobarbitone, 300 mg phenytoin, 750 mg ethosuximide and 600 mg sulthiame daily. On day zero sulthiame was abruptly withdrawn in each patient without any other drug change.

(Table 3). The ratios varied widely from patient to patient confirming the wide range of rates of phenytoin metabolism found by others (Kutt, 1972). In particular, PH had a very low ratio even when sulthiame had been stopped, and was therefore genetically a slow metabolizer. This was reflected also in the failure of his serum phenytoin concentration to fall below the toxic level after removal of sulthiame (Table 1).

Measurements of p-HPPH : DPH ratio were made in three of the four patients started on sulthiame (Table 4). In each case there was a decrease in the ratio.

The 24 h urinary output of p-HPPH plus unchanged phenytoin varied considerably both within and between patients (Tables 3 and 4). No consistent direction of change was found, however.

Time course of the interaction

Figure 1 illustrates the time course of the increase in the serum phenytoin concentrations in two of the patients who were put on to sulthiame. A delay of 10-20 days occurred before an increase was seen. On the other hand, when sulthiame was stopped in RB and EC the serum phenytoin concentration began to fall a day or two later and continued to fall over the next month (Figure 2).

Discussion

Our findings have confirmed those of Hansen *et al.* (1968) and Olesen & Jensen (1969) that sulthiame causes an elevation of serum phenytoin concentration when the two drugs are given concurrently. This has been our experience also in a study of phenytoin concentrations in patients newly admitted to the National Hospital–Chalfont Centre for Epilepsy (Houghton & Richens, 1973b). The incidence of phenytoin intoxication in patients on combined therapy (40%) was significantly higher than in patients not receiving the drug (13%).

Like Hansen *et al.* (1968) we have consistently observed prolongation of the half-life of a tracer dose of ^{14}C-labelled phenytoin when treatment with sulthiame was started and, conversely, a shortening when the drug was withdrawn.

The prolongation of the half-life was always accompanied by a decrease in the urinary p-HPPH : DPH ratio, signifying a relative decrease in parahydroxylation of phenytoin by liver enzymes. The reverse change occurred when the half-life was shortened by withdrawing sulthiame therapy.

These changes can be explained in one of two ways, either (a) the hepatic hydroxylase enzyme is inhibited by sulthiame or one of its metabolites, or (b) sulthiame in some way increases the serum concentration of phenytoin, which in turn causes a saturation of the hydroxylase enzyme. It is now well recognized that an increase in the dose of phenytoin leads to an increase in the serum half-life of the drug and fails to be accompanied by a proportionate increase in the urinary output of p-HPPH (Arnold & Gerber, 1970; Bochner,

Hooper, Tyrer & Eadie, 1972; Atkinson & Shaw, 1973). In low dosage the elimination approaches a first order process whereas in high dosage it more closely satisfies the criteria of a zero order process (Atkinson & Shaw, 1973). Thus our findings could be explained by sulthiame causing an increased serum concentration of phenytoin by, for example, enhanced absorption from the gastro-intestinal tract, causing a shift from first towards zero order elimination. We consider, however, that this is unlikely, for phenytoin sodium is normally well absorbed (Glazko & Chang, 1972). Indeed, Kutt, Haynes & McDowell (1966) found no change in the serum concentration in several patients in whom the route of administration was changed from oral to intravenous, the dose remaining constant. Furthermore, our patients showed no consistent change in the total combined urinary excretion of phenytoin plus p-HPPH, although it must be admitted that the excretion of these compounds varied considerably. In experiments on dogs, the serum half-life of phenytoin given intravenously was found to be more than doubled by pre-treatment with sulthiame (Green & Kupferberg, 1972). Thus a change in absorption cannot explain the results of these animal experiments.

Perhaps more convincing is the change in phenytoin half-life seen in our two patients who were not receiving phenytoin maintenance therapy. The changes were of a similar order to those occurring in patients receiving regular phenytoin treatment, and cannot, therefore, be explained on the basis of altered phenytoin kinetics secondary to a change in the steady-state serum concentration.

A further possibility which must be considered is that sulthiame reduces the volume of distribution of phenytoin by displacing it from tissue binding sites. This could produce the observed rise in steady-state serum phenytoin concentration and the accompanying change in half-life and urinary p-HPPH : DPH ratio seen in our patients. We did not measure unbound serum phenytoin in this study so we could not calculate volume of distribution. However, two observations suggest that this explanation is unlikely: (a) the peak serum radio-activity following the administration of the tracer dose of phenytoin was not altered by sulthiame therapy, whereas an increase would have been predicted if volume of distribution had been reduced; and (b) patients RC and GK (not on phenytoin maintenance therapy) would have been expected to show an increased rate of elimination of the tracer dose if its volume of distribution had been reduced by sulthiame, for more would have been available for metabolism. In fact the reverse was seen.

Thus, in agreement with Hansen *et al.* (1968), we favour the hypothesis that sulthiame inhibits parahydroxylation of phenytoin. Olesen & Jensen (1969) opposed this view because they were unable to demonstrate a reduction of the 24 h urinary output of p-HPPH by sulthiame. However, a number of factors influence the estimation of this substance, not least of which is error in collection of 24 h samples. We have preferred to estimate unchanged phenytoin in addition, and calculate the ratio between the two compounds, as we consider that this value is less subject to error. Furthermore, it is a more sensitive index of change in metabolism, for the concentrations of the two substances vary inversely with each other.

In accord with Hansen *et al.* (1968), but in conflict with Olesen & Jensen (1969), we have found a delay in the onset of the interaction. This delay suggests either that a slowly accumulating metabolite of sulthiame causes direct inhibition of the hydroxylase enzyme, or that sulthiame (or one of its metabolites) inhibits the synthesis of the enzyme (Hansen *et al.*, 1968). It is not possible on current evidence to decide which of these mechanisms is involved.

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