TABLE 1 *Antipyrine elimination in thyroid disease*

Thyroid state	No. of patients	Antipyrine Half-life (hr)	Volume of distribution (l)	Clearance (l/hr)
Hyperthyroid	18	7·9±0·6 p<0·001	28·2±0·8 p<0·001	2·6±0·2 p<0·05
Normal	36	10·8±0·4	33·1±0·8	2·2±0·1
Hypothyroid	20	16·2±2·3 p<0·005	36·5±2·1 N.S.	2·0±0·2 N.S.

Values shown as means ±S.E.M.
The probabilities shown relate to differences between the means for abnormal thyroid subjects and for the corresponding controls.

In thyrotoxic patients treated with the antithyroid drug carbimazole, the plasma antipyrine half-life increased from 8·9±1·0 h (mean±S.E.M.) after one week's treatment to 11·4±1·1 h after nine weeks. During the same period plasma ^{35}S–methimazole half-life values increased from 7·9±0·4 h to 11·2±1·2 h. To study the relative influence of carbimazole therapy and changing thyroid state on drug metabolizing ability, a further group of thyrotoxic patients was studied during treatment with carbimazole and triodothyronine. In this group, antipyrine half-life values increased much less rapidly than in the group treated with carbimazole alone.

These findings suggest that marked changes in drug metabolizing ability occur in abnormal thyroid states and during treatment. Evidence is provided that the level of circulating thyroid hormones is important in controlling the rate of drug metabolism in this condition. These human studies are in general supported by our animal studies on the effects of thyroxine administration to rats.

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Inhibition of phenytoin metabolism by sulthiame

G. W. HOUGHTON* and A. RICHENS

Department of Clinical Pharmacology, St. Bartholomew's Hospital, London E.C.1

Sulthiame causes an elevation of serum phenytoin levels when added to existing phenytoin therapy (Hansen, Kristensen & Skovsted, 1968 ; Olesen & Jensen, 1969), and often produces phenytoin intoxication (Houghton & Richens, unpublished). The mechanism of this interaction has been disputed. Hansen *et al.* (1968) found an increase in the serum half-life of phenytoin when sulthiame treatment was begun, and suggested that hepatic hydroxylation of the drug was inhibited. However, Olesen & Jensen (1969) found no change in the 24 h urinary excretion of the major metabolite of phenytoin, 5–(p-hydroxyphenyl)–5–phenylhydantoin (HPPH), and considered that displacement of bound phenytoin from sites such as red cells might be the cause of increased serum levels. This question has been re-examined in a group of 6 epileptic patients who were receiving a combination of phenytoin and sulthiame and in most cases a variety of other anticonvulsant drugs. Serum and urinary phenytoin, and urinary HPPH, were estimated by gas chromatography (Houghton, Latham & Richens, 1973), and the serum half-life of phenytoin was measured by giving 10 μCi of ^{14}C-labelled phenytoin orally. These estimations were performed before, and one month after, stopping sulthiame treatment. In all 6 patients serum phenytoin levels fell, half-lives shortened and the ratio of urinary HPPH to phenytoin (HPPH : DPH ratio) changed in favour of the metabolite (Table 1). These results suggest that sulthiame interferes with the hepatic hydroxylation of phenytoin.

TABLE 1. *Serum phenytoin levels, phenytoin half-lives and HPPH:DPH ratios in 6 patients on sulthiame, and repeat estimations one month after sulthiame was stopped*

Patient (age and sex)	Dose of phenytoin (mg/day)	Dose of sulthiame (mg/day)	Serum phenytoin (μM)		Phenytoin half life(h)		HPPH:DPH ratio	
			Before	After	Before	After	Before	After
FW (23M)	150	600	20	10	34·2	18·2	40·8	74·0
RC (43M)	300	400	46	23	31·2	16·6	28·6	81·4
CH (28F)	300	600	78	43	46·3	22·5	14·3	27·7
WP (44M)	300	600	82	46	66·4	40·6	12·0	16·4
MS (25M)	300	400	142	56	77·0	41·2	13·5	40·2
PH (22M)	300	600	180	112	79·4	45·6	4·6	5·2
*Mean			72·9	37·7	51·9	28·3	19·0	40·8
**Significance of difference			<0.05		<0.05		<0.05	

*Means for serum phenytoin level and half-life based on logarithmically transformed data,

**Wilcoxon's test for pair differences.

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Anti-nociceptive effects in N-substituted cyclohexylmethylbenzamides

R. T. BRITTAIN*, D. N. KELLETT, M. L. NEAT and R. STABLES

Department of Pharmacology, Allen & Hanburys Limited, Ware and Huntingdon Research Centre, Huntingdon

In the mouse, certain N-substituted cyclohexylmethylbenzamides markedly inhibited writhing induced by phenylquinone and the nociceptive responses to being placed on a hot plate (55° C) (Table 1). The results indicated that these compounds possessed analgesic activity and [3,4–dichloro–N–{1–(dimethylamino)cyclohexyl] methylbenzamide (AH 7921) was selected for detailed study in higher species.

In the conscious dog the minimal oral effective doses of AH 7921, morphine and codeine required to completely suppress the pain response to electrical stimulation of the dental pulp (Neat & Peacock, 1971) were $1{\cdot}25 \pm 0{\cdot}8$, $1{\cdot}25 \pm 0{\cdot}3$ and $3{\cdot}5 \pm 0{\cdot}6$ mg/kg respectively. In a similar test using the conscious rhesus monkey the minimal anti-nociceptive doses of AH 7921, morphine and codeine were $13{\cdot}8 \pm 1{\cdot}2$, $\leqslant 5{\cdot}0$ and $11{\cdot}3 \pm 0{\cdot}8$ mg/kg respectively. Anti-nociceptive doses of AH 7921 caused no overt behavioural effects in the mouse, dog or monkey but higher doses (50 mg/kg orally) caused slight central nervous system depression. The addictive liability of AH 7921 was next investigated.

AH 7921 was administered orally to rats, 5 mg/kg 3 times a day increasing to 20 mg/kg 3 times a day over 5 days. On the fifth day the animals were challenged with naloxone, 0·25 mg/kg s.c., which caused an abstinence syndrome similar to that produced in animals that had received morphine on a similar dosage schedule. In the rhesus monkey single doses of AH 7921, 5–10 mg/kg s.c., completely alleviated the abstinence syndrome in morphine-dependent animals. In addition, AH 7921, 7·5 mg/kg s.c. twice daily, increasing to 30 mg/kg s.c. twice daily over 30 days, produced physical dependence in naïve monkeys which was demonstrated in two ways. Nalorphine, 2 mg/kg s.c., induced an abstinence syndrome typical of that seen following morphine withdrawal in morphine-dependent monkeys. Secondly, on terminating AH 7921 treatment abstinence signs appeared over a period of 24–48 h. AH 7921 would be classed as a narcotic