Neither of the trials showed any statistically significant differences between the effects of bromhexine and placebo treatment on biscuit eating time, the patients' feeling of moistness in the eyes and mouth, or the blood values.

Several patients complained of side effects during both trials, pain in different sites being the commonest symptom. These complaints were equally distributed over the bromhexine and placebo periods. Two patients stated that a feeling of dryness of the skin and vagina was reduced while on bromhexine treatment but not when taking placebo.

Discussion

The statistically significant effects of bromhexine on the Schirmer test values in trial 2 indicate that bromhexine stimulates lacrimal secretion in patients with Sjögren's syndrome. The near significant result for break-up time agreed with this finding. Overall the results for the Schirmer test and break-up time in trials 1 and 2 suggest that the effect of bromhexine on lacrimal secretion is dose-related. Patients with Sjögren's syndrome secondary to SLE seemed to respond to treatment with bromhexine more readily than patients with primary Sjögren's syndrome, but our data are insufficient to permit general conclusions on this aspect.

We found no evidence that bromhexine had any effect on salivary gland function. But the methods used to estimate salivary secretion were crude and of doubtful value.

Our results therefore suggest that bromhexine is effective for treating the dry eyes of Sjögren's syndrome. Although further investigations are needed to assess the benefit of this treatment more precisely, we consider that bromhexine is a relevant first choice for treating Sjögren's syndrome.

We thank all the patients who participated in the study; B Mølgaard, K Garmer, and P Gaede for technical help; the staff of medical department C, Gentofte Hospital, for referring patients; and the staff of eye department E, Rigshospitalet, for making rooms and instruments available to us. All tablets used were kindly supplied by Boehringer Ingelheim A/S (F Mølgaard).

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(*Accepted 10 April 1978*)

Anticonvulsants and thyroid function

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British Medical Journal, 1978, **1**, 1581-1583

Summary and conclusions

Serum total and free thyroid hormone concentrations were estimated in 42 patients with epilepsy taking anticonvulsants (phenytoin, phenobarbitone, and carbamazepine either singly or in combination). There was a significant reduction in total thyroxine (TT4), free thyroxine (FT4), and free triiodothyronine (FT3) in the treated group compared with controls. Free hormone concentrations were lower than total hormone concentrations, suggesting that increased clearance of thyroid hormones occurs in patients receiving anticonvulsants.

Detailed analysis indicated that phenytoin had a significant depressant effect on TT4, FT4, FT3, and reverse T3 (rT3). Phenobarbitone and carbamazepine had no significant main effects, but there were significant interactions between phenytoin and carbamazepine for TT4 and FT4. phenobarbitone and carbamazepine for FT3, and phenytoin and phenobarbitone for rT3.

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Introduction

The depression of serum protein-bound iodine by phenytoin was first described by Oppenheimer *et al*[1] but was not associated with any change in thyroid state. Early in-vitro studies showed that phenytoin reduced the binding of thyroxine (T4) by thyroxine-binding globulin (TBG).[2-4] Other studies, however, have indicated that the reduction in total T4 (TT4) concentration in vivo results from increased catabolism of T4 due to enzyme induction by phenytoin[5-9] Low serum concentrations of free T4 (FT4), estimated by indirect techniques, have also been reported in patients receiving the drug.[6 9] Similar enzyme-inducing activity by barbiturates with alterations in T4 metabolism has been described in patients with Graves's disease[10] and in animals.[11]

Serum concentrations of total 3,5,3'-triiodothyronine (TT3) are normal or low in patients given phenytoin[7 8 12] and are thought to be maintained by increased deiodination of T4, despite increased catabolism. There is also some dispute over possible changes in serum thyrotrophin (TSH) concentrations in patients receiving anticonvulsants.[7 8 13]

Our objective was to define the effect on thyroid function of long-term anticonvulsant treatment with phenytoin, pheno-

barbitone, and carbamazepine, with particular emphasis on direct measurement of serum free thyroid hormone and reverse T3 (rT3) concentrations.

Patients and methods

We studied 45 patients with epilepsy who were receiving long-term anticonvulsant treatment. The survey was restricted to patients who had been taking phenytoin, phenobarbitone, or carbamazepine either singly or in combination for at least one year. A single blood sample was obtained from each patient, and TSH,[14] TT4,[15] TT3,[16] and rT3[17] concentrations were estimated by radioimmunoassay. FT4 and FT3 were measured by direct radioimmunoassay,[18] and a thyroid-hormone binding test (Thyopac-3, Radiochemical Centre, Amersham) was carried out. The sera were stored at −40°C and all samples assayed in one batch at the end of the study. Plasma concentrations of the anticonvulsants were measured by a gas-liquid chromatographic method.[19]

The means and standard deviations of the thyroid hormone concentrations were calculated for the patients receiving anticonvulsants and a group of 52 controls. A *t* test was used to test the differences between means. The data were analysed to determine the effect of each drug. Because of the unequal number of patients in each category the data were treated as an unbalanced factorial design. The analysis was carried out with the GLIM (Generalised Linear Interactive Modelling) package program,[20] which estimates and fits effects for the different factors in sequence. Initially only the data from the epileptic patients taking anticonvulsants were analysed, so that any spurious results which might have been caused by a difference between normal subjects and patients with untreated epilepsy were avoided. The analysis was subsequently repeated using the data from the controls.

Results

Three patients were excluded from the study because of undetectable plasma drug concentrations. The analysis therefore related to the remaining 42 patients, of whom 27 were male (aged 14-72) and 15 female (aged 13-59). Table I shows the mean plasma concentrations of the anticonvulsants, and table II the thyroid hormone and TSH concentrations in all 42 patients and 52 controls. TT4, FT4, and FT3 concentrations were significantly lower in the patients receiving anticonvulsants.

The data were further analysed to investigate any differences in the effects of the three anticonvulsants and possible interactions. Assessment of interactions was based on the simple model in which, when considering patients receiving more than one drug, it is assumed that the effects of the drugs are additive—that is, if drug A has a depressant effect of x units on thyroid hormone concentrations and drug B an effect of y units then a patient receiving both drugs would experience a depressant effect of x + y units. A significant interaction corresponds to a departure from this model, when the effect of the two drugs together does not equal the sum of the effects of the drugs taken separately. Analysis of the data from the patients receiving anticonvulsants showed that phenytoin had a significant depressant effect on TT4 ($P < 0.01$) and rT3 ($P < 0.001$). There was a significant interaction effect between phenobarbitone and carbamazepine in the case of FT3, though the main effects of these drugs were not significant. No other significant effects were detected.

The analysis was repeated using the control data and treating them as if they were from epileptics not receiving anticonvulsants (table II). As we had already found that phenytoin had a significant effect on the patients its effect on the controls was the first to be assessed. TT3 and Thyopac-3 were not significantly affected, which agreed with the original *t* test, but phenytoin significantly depressed TT4, FT4, FT3, and rT3 concentrations ($P < 0.001$ in all cases). Neither of the other drugs had a significant main effect after that of phenytoin had been allowed for. Nevertheless, there were significant interaction effects, which were between phenytoin and carbamazepine in the cases of TT4 and FT4 ($P < 0.05$), between phenobarbitone and carbamazepine in the case of FT3 ($P < 0.05$), and between phenytoin and phenobarbitone in the case of rT3 ($P < 0.01$). The concentrations in the phenytoin-carbamazepine interactions were higher than could be accounted for by the estimated main effects of the drugs; in the other interactions the concentrations were lower.

TABLE I—*Plasma concentrations of anticonvulsant drugs in 42 patients with epilepsy*

	No of patients	Mean (± SE) plasma concentration (mg/l)
Phenytoin	35	9·2 ± 1·05
Phenobarbitone	20	16·9 ± 2·17
Carbamazepine	8	3·6 ± 0·60

Combinations of drugs taken by the 42 patients were: phenytoin (16 patients); phenobarbitone (5); carbamazepine (2); phenytoin and phenobarbitone (13); phenytoin and carbamazepine (4); and phenytoin, phenobarbitone, and carbamazepine (2).

Discussion

These results confirm that depression of TT4 occurs in patients receiving anticonvulsant drugs. A comparable reduction in T3 was not seen. There were, however, significant reductions in FT4 and FT3 concentrations with a fall in the ratio of free to total hormones. The findings strongly support the view that anticonvulsant treatment increases the rate of clearance and catabolism of thyroid hormones. Possibly the enzyme-inducing actions of the anticonvulsant drugs lead to a significant increase in thyroid hormone clearance in the early stages of treatment, followed by the observed changes in total and free hormone concentrations. Clearly a new steady state is established since these patients have no clinical or biochemical evidence of hypothyroidism, and probably the increased rate of thyroid hormone clearance is balanced by a reduction in the free thyroid-hormone pool in patients established on treatment. This observation emphasises that clinical thyroid state is not solely dependent on the concentrations of serum free thyroid hormones.[18] The greater effect of anticonvulsants on TT4 and FT4 may be attributed to enhanced peripheral conversion of T4 to T3. Interestingly, FT4 and FT3 concentrations are also significantly reduced during pregnancy despite an increase in total hormone concentrations, and a similar reduction is not seen in patients receiving oral contraceptives.[21] The finding that free thyroid-hormone concentrations are reduced in patients with increased peripheral utilisation of thyroid hormones—that is, during anticonvulsant treatment and pregnancy—clearly implies that the rate of cellular clearance and degradation of thyroid hormones play a major part in determining the size of the free

TABLE II—*Mean (± SD) thyroid hormone and TSH concentrations in patients receiving various anticonvulsant drugs and in controls*

	Phenytoin (n = 16)	Phenobarbitone (n = 5)	Phenytoin and phenobarbitone (n = 13)	Phenytoin and carbamazepine (n = 4)	All patients (n = 42)	Controls (n = 52)
TT4 (nmol/l)	71·38 ± 10·65***	93·4 ± 22·88	62·77 ± 19·02***	74·75 ± 15·33**	72·4 ± 17·6***	108 ± 23
TT3 (nmol/l)	1·65 ± 0·28	1·89 ± 0·26	1·48 ± 0·36	1·58 ± 0·37	1·63 ± 0·32	1·66 ± 0·31
FT4 (pmol/l)	5·89 ± 2·11***	7·54 ± 2·61	5·67 ± 1·25***	6·45 ± 1·61***	6·0 ± 2·0***	10·35 ± 3·15
FT3 (pmol/l)	7·49 ± 2·62**	9·26 ± 1·99	8·09 ± 2·83*	9·75 ± 2·18	7·9 ± 2·7***	10·1 ± 2·8
Thyopac-3	103 ± 7·13	110·8 ± 9·81	102·92 ± 8·39	108 ± 8·29	105 ± 8·1	106 ± 8·0
rT3 (nmol/l)	0·22 ± 0·06	0·32 ± 0·10	0·17 ± 0·06***	0·23 ± 0·07	0·22 ± 0·08	0·25 ± 0·06
TSH (mU/l)	2·13 ± 1·10	2·78 ± 1·05	2·29 ± 1·30	2·43 ± 1·05	2·2 ± 1·3	2·4 ± 1·7

Compared with controls: *P < 0·05. **P < 0·01. ***P < 0·001.
Conversion: SI to traditional units—Thyroxine (T4): 1 nmol/l ≈ 78 ng/100 ml. Triiodothyronine (T3): 1 nmol/l ≈ 0·65 ng/ml.

thyroid-hormone pool. Much emphasis has been placed on the role of the circulating thyroid-hormone binding proteins in regulating the peripheral turnover of thyroid hormones, and the importance of cellular factors has not been adequately stressed. Probably the effect of anticonvulsants on TBG binding is a relatively minor one in patients receiving these drugs. The normal results of the thyroid-hormone binding test indicate that there is no decrease in residual binding sites on TBG, which may result from the occupancy of some sites by the anticonvulsants, a reduction in TBG concentration, or a combination of these factors.

Our detailed analysis of the effects of individual anticonvulsants indicates that phenytoin significantly depresses TT4, FT4, and FT3 concentrations. The other two drugs had no main effects, but with 35 of the 42 patients receiving phenytoin this finding may merely reflect a lack of sufficient data to detect the effects.

Dr P P B Yeo was supported by the Nuffield Foundation, and this work forms part of a dissertation to be submitted to the University of Singapore for the degree of MD. The support of the Scientific and Research Committee of the Newcastle AHA(T) is gratefully acknowledged.

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(*Accepted 10 April 1978*)

High incidence of a concentration-dependent skin reaction in children treated with phenytoin

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British Medical Journal, 1978, **1**, 1583-1586

Summary and conclusions

A particularly high incidence of rash was seen in children with epilepsy treated with phenytoin. Ten children with untreated epilepsy were therefore included in a prospective study and given either 3 (group 1) or 6 (group 2) mg of phenytoin/kg body weight/day for five days followed by 6 mg/kg body weight/day for both groups. Four of the five children in group 2 compared with only one of the five in group 1 developed a rash seven to 12 days after the start of treatment. Patients with rashes had significantly higher plasma phenytoin concentrations. Whenever the phenytoin concentration was higher than 14 μmol/l on day 5 a rash occurred.

These findings indicate that the generalised skin reaction is caused by a high body burden of phenytoin, which results from either a high load of the drug or a low clearance rate.

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Introduction

About 5% of children treated with phenytoin develop a mild transient maculopapular rash, usually within two weeks of the start of treatment.[1 2] Adverse systemic effects do occur after phenytoin but are less common than the skin reaction.[3-6] A severe exanthem[7] and blood dyscrasia[8] have been seen in patients with therapeutic or exceptionally high plasma phenytoin concentrations. The nature of such reactions (allergic or toxic) is obscure. Unfortunately in most patients presenting with a rash plasma concentrations of phenytoin and its metabolites have not been measured. An assessment of the amount of drug in the body at different times after the start of treatment and at the time of an exanthem is needed to elucidate the mechanisms responsible for the skin reaction.

In a study[9] on the plasma profile of phenytoin and its p-hydroxylated metabolite in children who received loading or conventional doses of the drug we encountered an unexpectedly high incidence of rash (8 out of 13 children developed a rash). We therefore performed a prospective study using two regimens of phenytoin to determine the incidence of rash and its relation to the kinetics of phenytoin.

Patients and methods

All epileptic children who presented in the paediatric clinic of Huddinge Hospital in Stockholm and were treated with phenytoin were recruited into the study. The children and their parents were told about the possibility of a rash after phenytoin treatment, and the study was approved by the Huddinge Hospital ethical committee.

Ten children (five boys and five girls aged 6-15 years), all untreated