one hour. Stenotic lesions in the carotid artery were also found more often after short episodes in the study of Pessin *et al.*⁶ This relation may reflect the small size and friability of embolic material arising on a stenosed carotid lesion.⁷

We found that short attacks were more common in patients over 60. Only 8% of patients with attacks lasting over one hour had carotid stenosis. This suggests that disease of the neck vessels is often not the cause of such episodes. A more likely explanation for these longer attacks is that they are the result of embolism from the heart or aorta.⁸ Their longer duration may reflect the slower restoration of flow to a vessel temporarily obstructed by material arising in the heart and differing in constitution from the platelet fibrin embolus that arises on an atheromatous carotid lesion.

The presence of a bruit is known to increase the likelihood of finding angiographic stenosis.³ The results of our study further suggests that there is a better chance of finding operable carotid stenosis in patients with TIAs lasting no more than an hour.

This may be helpful in selecting patients for angiography. Paradoxically, the patient with the more obtrusive and symptomatically worrying long attack is less likely to have an operable lesion on investigation.

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Sjögren's syndrome treated with bromhexine: a randomised clinical study

K FROST-LARSEN, H ISAGER, R MANTHORPE

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Summary and conclusions

Existing treatment for Sjögren's syndrome is unsatisfactory, and uncontrolled observations have suggested that bromhexine may be effective. Twenty-nine patients with Sjögren's syndrome were therefore assigned to two randomised double-blind crossover trials with bromhexine and placebo, each comprising two two-week periods. In the first trial bromhexine 24 mg/day was given by mouth; in the second the dose was increased to 48 mg/day. After each treatment period the Schirmer test response, break-up time, Bijsterveld score, and the time taken for the patient to eat a dry biscuit were recorded, as well as the patient's estimate of moistness in the eyes and mouth.

In the second (higher-dose) trial values on the Schirmer test were significantly higher after bromhexine than after placebo and the break-up time was also increased after bromhexine, which suggested that the drug has a dose-dependent effect on lacrimal gland secretion in Sjögren's syndrome. It had no effect on salivary gland function.

Bromhexine is therefore valuable in the treatment of Sjögren's syndrome.

Introduction

Treatment of Sjögren's syndrome is unsatisfactory, and some of the drugs used—for example, immunosuppressive agents—

produce side effects out of proportion to the chronic and usually benign course of the disease.^{1 2} The dry eyes of Sjögren's syndrome (keratoconjunctivitis sicca) are usually treated topically with tear substitutes or soft contact lenses, or both, but the ocular complaints are rarely relieved.

We recently observed an apparently complete remission of dryness of the eyes and mouth in a patient with Sjögren's syndrome who had been given bromhexine (Bisolvon) for dry bronchitis. The dryness recurred when the drug was discontinued and disappeared again when it was resumed; the Schirmer test responses showed the same pattern.³ Other uncontrolled observations also support the alleviating value of bromhexine in these cases.^{4 5}

Bromhexine has been used for treating chronic bronchitis for the past decade. Clinical studies have shown that it increases the quantity of bronchial secretion and reduces its viscosity, but its mechanism of action is not fully known. Reported side effects have been harmless and infrequent.⁶

Our aim was to determine whether any differences could be shown in the effect on lacrimal and salivary gland secretion between bromhexine and placebo in patients with Sjögren's syndrome.

Patients and methods

Two trials (of low and high doses), both of double-blind crossover design, were carried out consecutively. Each trial comprised two two-week periods, and balanced numbers of patients were randomly allocated for treatment with bromhexine in one of the periods and with placebo tablets of identical appearance in the other. The dose of bromhexine in trial 1 was 8 mg three times daily by mouth; this dose was doubled in trial 2 (16 mg three times daily). The doses of other drugs being administered were kept constant throughout the trials. The patients were seen every two weeks, when their tablets were counted and a new supply issued. The variables described below were measured at the same time. The ophthalmological variables (in both eyes) were checked by one of us (KF-L).

The criterion for including a patient with Sjögren's syndrome in the trial was a Schirmer test result of less than 10 mm in both eyes on two consecutive occasions. Thirty-one of our patients fulfilled this criterion. After an oral and written explanation of the purpose and

Gentofte Hospital, DK 2900 Hellerup, Denmark

K FROST-LARSEN, MD, clinical assistant, eye department

Rigshospitalet, Tagensvej, DK 2200 Copenhagen N, Denmark

H ISAGER, MD, PHD, department of infectious diseases M

R MANTHORPE, MD, medical department TA

design of the study consent was obtained from all but two of the patients, which reduced the total number to 29. Apart from four patients, all had abnormal findings on salivary gland scintigraphy (with technetium-99m pertechnetate). All but one were women. Eighteen patients had primary Sjögren's syndrome (no other known connective tissue disease), while in eight the main diagnosis was systemic lupus erythematosus (SLE) and in three rheumatoid arthritis. Two patients took part only in the first (low-dose) trial. One dropped out because one of the preparations used in the first trial caused such abundant lacrimation that she considered that any further increase would be unduly unpleasant. When the trial code was broken the preparation was found to be bromhexine. The other patient, who had been suffering from SLE for years, suddenly died of septicaemia.

OPHTHALMOLOGICAL VARIABLES

Standardised Schirmer test—A standardised strip of blotting paper was inserted into the lower conjunctival fornix at the junction of the middle and nasal third of the lower margin of the eyelid, and the patient was told to keep the eyes closed without undue effort or strain. After five minutes the extent of the moistened area on the strip was measured and a value below 10 mm was accepted as a true reduction of tear production.⁷

Break-up time (wetting time)—Normally a stable precorneal tear film (consisting of an outer oily layer, an intermediate aqueous layer, and an inner mucin layer) protects the corneal epithelium from desiccation during the intervals between blinks. In Sjögren's syndrome the precorneal tear film breaks up during the intervals, and randomly distributed dry spots develop on the corneal epithelium. They can be visualised by instilling one drop of 0.125% fluorescein solution into the lower conjunctival fornix. The break-up time, a quantitative evaluation of the stability of the precorneal tear film, was defined as

the time between a complete blink and the appearance of the first dry spot.⁸ A slit-lamp was used to scan the tear film through cobalt blue filtered light at a magnification of $\times 16$ with a 3-mm wide vertical beam. The patient was asked to blink several times and then to stare directly ahead without blinking and, if necessary, to hold the eyelids apart. The mean of two slit-lamp measurements was used. A break-up time of less than 10 seconds was considered abnormal.^{9 10}

Bijsterveld score—To estimate the extent of damage to the corneal and conjunctival epithelium, we used a scoring system introduced by Bijsterveld,¹¹ which measures vital staining of the damaged epithelial cells with Rose Bengal in a 1% solution. After one drop of the solution had been instilled into the lower conjunctival fornix, the patient was asked to blink at normal frequency for 5 minutes to ensure an even distribution and to eliminate surplus dye. Then the numbers of stained dots on the bulbar conjunctiva medially, on the cornea, and on the bulbar conjunctiva laterally were estimated, using slit-lamp magnification; these estimations were repeated after a further 5 minutes. Each area was scored from 0 to 3 and the scores were added to make a total for each eye. A score above 4 indicated pathological epithelial damage.

NON-OPHTHALMOLOGICAL VARIABLES

The time taken by a patient to eat a dry biscuit was recorded. The patients were also asked to estimate the feeling of moistness in the eyes and mouth on two scales,¹² and they were questioned about possible side effects.

The following blood values were measured: packed cell volume; leucocyte and platelet counts; erythrocyte sedimentation rate; fibrinogen, haptoglobin, and immunoglobulin (IgG, IgA, IgM) concentrations; and antinuclear and salivary gland antibodies.

We used Wilcoxon's signed rank test to analyse the data.¹³

TABLE I—Mean and range of Schirmer test values, break-up time, and Bijsterveld score after bromhexine and placebo in patients with Sjögren's syndrome

Trial:	Schirmer test (mm)		Break-up time (s)		Bijsterveld score (points)	
	1	2	1	2	1	2
<i>Bromhexine</i>						
Median	4	7	9	12	7	5
Interquartile range	0-22	2-25	4-29	5-30	1-15	0-14
<i>Placebo</i>						
Median	3	4	7	8	9	9
Interquartile range	1-15	0-12	5-23	4-23	0-13	0-14
P value	NS	<0.02	NS	0.06	NS	NS

NS = Not significant (Wilcoxon's signed rank test).

TABLE II—Schirmer test values and break-up time after bromhexine and placebo (in trial 2*) in patients with Sjögren's syndrome according to main diagnosis. Results are numbers of patients

Main diagnosis	Total	Schirmer test values			Break-up time		
		Higher after bromhexine	Higher after placebo	No difference	Higher after bromhexine	Higher after placebo	No difference
Secondary Sjögren's syndrome:							
SLE	8	7	0	1	7	1	0
RA	3	2	1	0	1	2	0
Primary Sjögren's syndrome ..	18	11	6	1	10	5	3

*Except for two patients who completed only trial 1.
SLE = Systemic lupus erythematosus. RA = Rheumatoid arthritis.

TABLE III—Schirmer test values and break-up time after bromhexine and placebo (in trial 2*) in patients with Sjögren's syndrome according to duration of syndrome. Results are numbers of patients

Duration of Sjögren's syndrome	Total	Schirmer test values			Break-up time		
		Higher after bromhexine	Higher after placebo	No difference	Higher after bromhexine	Higher after placebo	No difference
0-7 years	15	11	3	1	10	4	1
8-20 years	14	9	4	1	8	4	2

*Except for two patients who completed only trial 1.

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.

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Anticonvulsants and thyroid function

P P B YEO, D BATES, J G HOWE, W A RATCLIFFE, C W SCHARDT, A HEATH, D C EVERED

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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.

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 disease¹⁰ and in animals.¹¹

Serum concentrations of total 3,5,3'-triiodothyronine (TT3) are normal or low in patients given phenytoin^{7-9,12} 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.^{7-9,13}

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

University of Newcastle upon Tyne, Newcastle upon Tyne 1

P P B YEO, MB, MRCP, Nuffield research fellow, department of medicine (present appointment: lecturer, University Department of Medicine, Singapore General Hospital, Singapore)

D BATES, MB, MRCP, consultant neurologist

J G HOWE, MB, MRCP, neurological registrar (present address: Northern General Hospital, Edinburgh)

C W SCHARDT, MA, biochemist

A HEATH, BA, MSC, medical statistician

D C EVERED, MD, FRCP, consultant physician, university department of medicine

Radioimmunoassay Unit, Glasgow Royal Infirmary, Glasgow

W A RATCLIFFE, BSC, PHD, biochemist