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A double-blind clinical trial of hydroxyethylrutosides in Menière's disease

by

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Introduction

The many and varied theories of the pathogenesis of Menière's disease are reflected in the considerable number of drugs which have been used for its treatment. Very few of them have any solid basis of evidence of clinical efficacy—as indeed is true of many of the surgical procedures which have been devised (Jongkees, 1980). Among the few which have been subjected to controlled clinical trials are hydrochlorothiazide (Klockhoff and Lindblom, 1967) and betahistine hydrochloride (Wilmot and Menon, 1976; Frew and Menon, 1976).

Based on the hypothesis that one of the contributory factors to Menière's disease may be an oversecretion of endolymph it was decided to investigate the effect of O-(ß-hydroxyethyl)-rutosides (HR§) in a double-blind cross-over clinical trial. HR has been shown experimentally to inhibit microvascular permeability (Arturson, 1972; Hilton, 1980), probably *via* a 'tightening' of interendothelial cell junctions (Hammerson, 1970; Arturson 1972; Hladovec and Rossman, 1973; Prerovsky and Hladovec, 1979). These effects have also been confirmed in man, both in peripheral tissues (Roztocil *et al.*, 1971, 1977) and in retinal capillaries (Tschopp *et al.*, 1970). In addition, HR has been shown to improve capillary perfusion (McEwan and McArdle, 1971) possibly due to an effect on red cell aggregation and deformability (Van Haeringen *et al.*, 1973; Schmid-Schönbein, 1975).

Material and Methods

Patients

A total of 39 patients (29 from Graz and 10 from Omagh) entered the trial and all patients fully completed the investigation. The basic inclusion criteria were a clinical history of at least six months of recurrent episodes of:

—peripheral fluctuating recruiting cochlear (sensori-neural) hearing-loss in one or both ears;
—tinnitus (usually of low tone);
—rotatory vertigo.

These findings were confirmed by the following *audiometric assessment:*

pure tone a/c and b/c audiometry, tuning fork tests, speech audiometry and Békésy audiometry, and the recruitment test,

and by the following *vestibular function tests:*

gaze nystagmus, positional nystagmus and caloric tests, in which the speed of the

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slow component for 10 seconds, starting 10 seconds after cessation of stimulus for 40 seconds (Omagh centre), or the number of beats during this same 10-second period (Graz centre), were recorded.

In addition, it was required to demonstrate intact tympanic membranes, positive Rinne's responses, and a negative treponemal serology. Only patients who demonstrated a clear willingness and ability to co-operate fully in the study, after a full explanation, were recruited.

Exclusion criteria were pregnancy, middle-ear disease, defective conductive hearing-loss and eustachian tube dysfunction, malignancy, organic disease of the central nervous system, essential hypertension, diabetes mellitus, coronary artery disease, hepatic and renal disorders, and abuse of alcohol. Regular use of psychotropic drugs such as antidepressants, major tranquillisers, etc. was also excluded, but patients receiving minor tranquillisers, and in whom it was not practicable to stop this therapy, were allowed to continue on a fixed dosage.

The characteristics of the patients are shown in Table I, which shows that the great majority of patients had unilateral disease, with considerable variation in the length of history, as well as in the frequency and duration of attacks. In general, the 29 patients from Graz had a longer history (median: five years) than in Omagh (median: two years), and also a greater frequency of attacks (median: 10) than in Omagh (median: four).

TABLE I

PATIENT CHARACTERISTICS

Number of patients	39
Sex	M/24 F/15
Age (mean±SD)	48.3 years±11.5 (range 22–68 years)
Site of disease	35 unilateral (R:18/L:17) four bilateral
Length of history (median)	Five years (range one to 30 years)
No. of attacks in preceeding six months (median)	Six (range one to 60)
Average duration of attacks (median)	Two hours (range 20 minutes to 12 hours)
Sequence	HR/placebo = 19; placebo/HR = 20

From Table II, which shows the initial severity of symptoms, it can be seen that all patients did fulfill the basic triad of inclusion criteria: vertigo, deafness, and tinnitus. The majority of patients also complained of nausea and vomiting with the attacks, and of a 'fullness of the ear', but relatively few presented with headaches.

Trial design

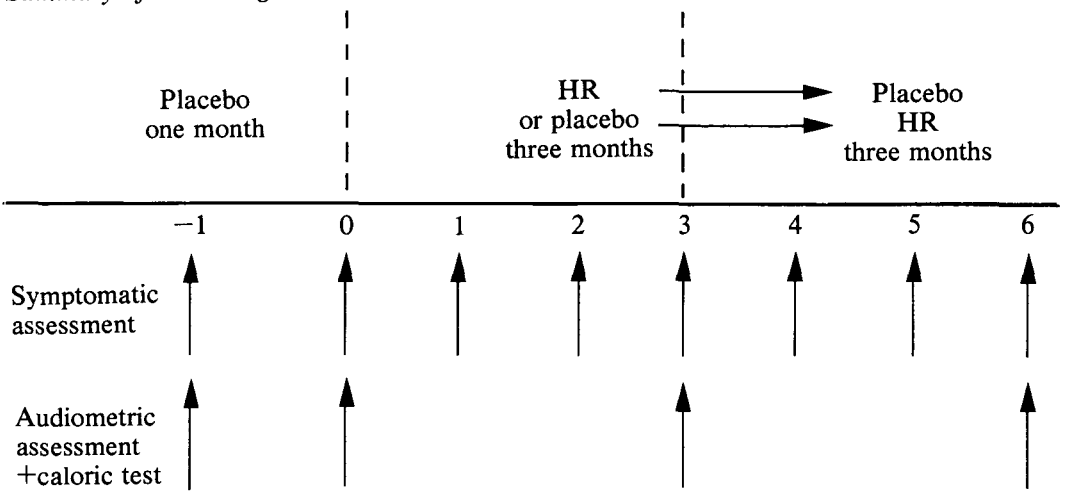
The trial was prospective, double-blind, cross-over, placebo-controlled, with an initial 'run-in' period of one month when all the patients received a placebo, followed by two consecutive periods each of three

TABLE II

INITIAL SEVERITY OF SYMPTOMS

	Absent	Mild	Severe	Very severe
Rotatory vertigo (n = 39)	0	4	17	18
Nausea (during attacks) (n = 39)	2	8	16	13
Vomiting (during attacks) (n = 39)	9	4	16	10
Deafness (n = 43 ears)	0	35	18	0
Tinnitus (n = 43 ears)	2 'bilateral' patients	22	17	2
Fullness in ear (n = 43 ears)	11	27	5	0
Headache (n = 39)	26	10	3	0

Summary of trial design:



months, when they received HR followed by placebo or *vice versa*. The assignment to one or the other sequence was randomized.

HR was dispensed as tablets of 500 mg. in the Graz centre (two tablets twice daily) and as capsules of 250 mg (four capsules twice daily) in the Omagh centre, because of local regulatory restrictions. The dissolution times of these two dosage forms were demonstrated to be equivalent. Total daily dosage in all patients was therefore 2 g./day. The placebos were identical in appearance to the corresponding dose form—tablet or capsule. The capsules or tablets were dispensed in bottles containing treatment for a period of one month.

The main purposes of the run-in period were:

(a) as a wash-out for any previous drug therapy;
(b) to enable the patients to familiarise themselves with the trial procedures;
(c) to obtain some data on the degree of 'stability' and severity of the patients' symptomatology.

Frequency of examinations

The patients were examined each month during the total trial duration of seven months, and the severity of symptoms and occurrence of any side-effects were recorded. At each monthly visit, the previous bottle of tablets was returned, the number of remaining tablets counted, and a new bottle issued. In addition, the audiometric assessments and the caloric tests were undertaken at the beginning and end of the placebo run-in period, at the time of cross-over, and at the end of the second treatment period.

Results

Symptoms

Table III shows the overall results for all symptoms in those patients who showed any particular symptom at the beginning of the trial—i.e. beginning of the run-in period. The most striking finding was that the majority of patients showed a clear improvement in symptoms (particularly vertigo, nausea, and vomiting) during this initial placebo period. Indeed, a considerable number of patients became free from some symptoms and remained so for the remainder of the trial. We therefore excluded these patients from our subsequent statistical analyses for those particular symptoms. Nevertheless, on this basis, no significant differences appeared on comparing the severity of each symptom of each patient during the HR sequence with the severity during the placebo period.

However, on assessing the data, it became clear that the improvements on placebo were

TABLE III

SYMPTOMS; ONLY THOSE PATIENTS SHOWING THE SYMPTOMS ON ENTRY TO THE TRIAL

	No. who improved in placebo 'run-in'	No. who were then symptom free during all subsequent six months	HR sequence superior to placebo sequence	Two sequences equal	Placebo sequence superior to HR sequence
Vertigo (n = 39)	29	14	11	5	9
Nausea (n = 37)	25	23	5	0	9
Vomiting (n = 30)	23	20	3	0	7
Tinnitus (n = 39)	11	3	10	19	7
Deafness (n = 39)	6	0	5	28	6
Fullness in ear (n = 30)	10	9	8	9	4
Headache (n = 13)	2	0	4	7	2

much more frequent in those patients who had their placebo sequence after their HR sequence, suggesting strongly the persistence of a beneficial effect from the HR treatment into the subsequent placebo period. This 'carry-over' effect was probably due to the fact that the original protocol did not foresee a wash-out period between the two sequences, since this would have further prolonged the total trial duration.

We therefore undertook a further analysis of the data, restricted to those patients who only received HR after an initial placebo period and, as in the first analysis, among those patients in whom symptoms persisted after the 'run-in' period. Although this somewhat reduced the number of patients involved, it gave a much clearer picture of a possible drug effect. The results are shown in Table IV, which shows that the 'performance' for each symptom under HR was always superior to that under placebo. Statistical analysis of these data was not possible because of the small numbers for each symptom individually and since the total of all symptoms is based on different numbers of patients for each symptom.

Audiometry

The initial values of air conduction or bone conduction between the two different groups of patients were never significantly different (Tables V and VI). During the first sequence of treatment, with no possible interference from 'carry-over' effects, it was very striking that there was always a significant improvement in hearing for all five frequencies under HR treatment, but never under placebo, resulting in significant differences between the two groups of patients for all five frequencies. This was true for both air and bone conduction (with the exception of bone conduction/500 Hz., where the difference

TABLE IV

SYMPTOMS: ONLY THOSE PATIENTS IN WHOM SYMPTOMS PERSISTED AFTER PLACEBO RUN-IN AND WHO RECEIVED HR IN THE SECOND SEQUENCE

	HR sequence superior to placebo sequence	Two sequences equal	Placebo sequence superior to HR sequence
Vertigo (n = 13)	8	2	3
Nausea (n = 8)	3	5	0
Vomiting (n = 4)	2	2	0
Tinnitus (n = 19)	7	10	2
Deafness (n = 20)	3	17	0
Fullness in ear (n = 11)	5	6	0
Headache (n = 6)	3	2	1
All symptoms together	31	44	6

TABLE V

EVOLUTION OF AUDIOMETRY FINDINGS (n = NUMBER OF EARS) (FIRST SEQUENCE: 41 EARS (TWO EARS WITHOUT READINGS); SECOND SEQUENCE 42 EARS (ONE EAR WITHOUT READINGS)

Air conduction; Mean±SEM; Student 't' test

	Initial values	First sequence			Second sequence		
250 Hz.	46.75±3.54	−10.5 ±4.24	p<0.05		−2.62±3.73		
		HR (n = 20)		p<0.02	PL (n = 21)		NS
	NS	+5.0 ±4.78	NS		−2.86±2.73	NS	
	42.86±3.30	PL (n = 21)			HR (n = 21)		
500 Hz.	46.75±3.70	−11.25±4.09	p<0.02		−3.81±3.57	NS	
		HR		p<0.05	PL		NS
	NS	+2.86±4.49	NS		−4.05±2.03	NS	
	45.24±2.64	PL			HR	(p≃0.06)	
1,000 Hz.	46.75±3.08	−14.0 ±4.03	p<0.01		−0.71±3.57	NS	
		HR		p<0.001	PL		NS
	NS	+6.19±3.58	NS		−5.48±1.86		
	40.95±2.86	PL			HR		
2,000 Hz.	46.25±3.03	−10.0 ±2.62	p<0.002		−1.19±2.36	NS	
		HR		p<0.01	PL		NS
	NS	+0.71±2.47	NS		+3.10±2.20	NS	
	39.52±3.05	PL			HR		
3,000 Hz.	44.25±3.17	−6.75±2.09	p<0.01		−1.67±1.93	NS	
		HR		p<0.002	PL		NS
	NS	+3.10±2.06	NS		+2.14±2.06	NS	
	39.05±3.53	PL			HR		

TABLE VI

EVOLUTION OF AUDIOMETRY FINDINGS (n = NUMBER OF EARS) FIRST SEQUENCE: 41 EARS (TWO EARS WITHOUT READINGS); SECOND SEQUENCE: 42 EARS (ONE EAR WITHOUT READINGS)

Bone conduction; Mean±SEM; Student 't' test

	Initial values	First sequence			Second sequence	
250 Hz.	35.75±3.76	−9.0±3.30	p<0.02		−1.67±3.30	NS
	NS	HR (n = 20)		p<0.05	PL (21)	NS
	31.32±3.48	+3.16±4.40	NS		−5.79±2.89	NS
		PL (n = 19)			HR (19)	(p≃0.06)
500 Hz.	36.0±4.16	−9.25±3.65	p<0.02		−0.48±3.63	NS
	NS	HR		NS (p≃0.10)	PL	NS
	37.37±3.18	+0.26±4.48	NS		−3.42±2.45	NS
		PL			HR	
1,000 Hz.	39.50±3.80	−12.25±3.85	p<0.01		+0.48±3.89	NS
	NS	HR		p<0.01	PL	NS
	35.26±3.83	+4.47±3.99	NS		−5.26±2.37	p<0.05
		PL			HR	
2,000 Hz.	39.75±3.37	−7.0 ±2.47	p<0.02		0.0 ±3.01	NS
	NS	HR		p<0.01	PL	NS
	33.42±3.61	+3.42±2.71	NS		+1.32±1.75	NS
		PL			HR	
3,000 Hz.	41.25±3.40	−6.75±2.18	p<0.01		−0.95±1.97	NS
	NS	HR		p<0.01	PL	NS
	33.42±3.86	+2.89±2.07	NS		+3.68±2.29	NS
		PL			HR	

between the two groups became not quite significant, $p \simeq 0.01$).

The results in the second sequence reflected a similar evolution as found with the symptoms. A further improvement was seen under HR treatment for two frequencies for air conduction (1,000 Hz.: $p < 0.01$; 500 Hz.: $p \simeq 0.06$) and for bone conduction (1,000 Hz.: $p < 0.05$; 250 Hz.: $p \simeq 0.06$). In the placebo group, whereas a deterioration of hearing had been seen at all frequencies in the first sequence, the patients showed a small (never significant) improvement in the second sequence. This again suggested a 'carry-over' effect in these patients following the initial HR treatment for three months. This resulted in a disappearance of significant differences between the two groups at the end of the trial.

Caloric tests

The results of caloric tests showed already significant variations between the two tests performed at the beginning and end of the placebo run-in period. No clear trend was seen during the further duration of the trial.

Tolerability

Tolerability of HR was excellent: there was an even distribution of very minor side-effects in the two treatment periods (eight in the HR periods and nine in the placebo periods). None of these appeared to be clearly drug-related.

Discussion

A very striking placebo effect in the major symptoms of Menière's disease confirms the observations of Thomsen *et al.* (1979). The great majority of patients found an improvement in vertigo, nausea and vomiting during the placebo run-in period. A smaller percentage even showed a reduction of tinnitus, deafness, and 'fullness in the ear'. Since some of the patients then remained totally free of some symptoms (with the exception of deafness) during the remaining six months of the trial, it was necessary to exclude them from the analysis of results for that particular symptom.

A further complicating feature of this study was the appearance of a clear persistence of improvement, beginning during the initial HR sequence, into the second placebo sequence. This was true both for the symptoms and for the audiometric findings.

Taking this into consideration, there was a strong suggestion of a more marked improvement of symptoms during the three-month period of HR treatment in those patients who received HR after the placebo period. The most striking finding was the very clear and statistically significant improvement in hearing under treatment with HR. This was true for both air conduction and bone conduction and for all five frequencies studied.

The mechanism of this effect is not very clear but it may have been related to a reduction of secretion of endolymph or to an improvement in irrigation of the inner ear.

Tolerance of the drug was excellent, as has been found in the many other published studies of this drug in peripheral vascular disease (Bergquist and Hallböök, 1981).

Abstract

A double-blind, placebo-controlled, cross-over trial was undertaken in 39 patients with well-defined Menière's disease. After a one-month placebo run-in period, the patients were assigned, on a randomized basis, to three months' treatment with O-(ß-hydroxyethyl)-rutosides (HR) (2 g./day) followed by three months on placebo, or *vice-versa*.

In spite of a very pronounced placebo effect and a marked tendency to a 'carry-over' effect from the first sequence with HR into the second placebo sequence, there appeared to be a clear trend to a greater symptomatic improvement with HR treatment than with placebo.

The audiometric findings showed a very clear, uniform superiority under HR treatment, for both air and bone conduction and at all five frequencies studied (250, 500, 1,000,

2,000 and 5,000 Hz.) (p values between 0.002 and 0.05). Indeed, whereas there was a worsening of hearing-loss at each frequency under placebo during the first sequence, this was significantly diminished at each frequency under HR treatment.

There were no significant changes in vestibulometry (caloric test) which showed wide variations already during the run-in period.

Tolerance to HR treatment was excellent, the incidence of side-effects being similar to that in the placebo periods.

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