Diuretics for Ménière's disease or syndrome (Review)

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ABSTRACT

Background
Ménière's disease is a disorder characterised by hearing loss, tinnitus and disabling vertigo. Diuretics are used to try and reduce the severity and frequency of episodes but there is little evidence behind this treatment.

Objectives
To assess the effect of diuretic treatment in patients with Ménière's disease.

Search strategy
We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 1 2005), MEDLINE (1966 to 2005), EMBASE (1974 to 2005), CINAHL and the *meta*Register of Controlled Trials (*m*RCT) (up to 2005).

Selection criteria
Randomised controlled trials of diuretic versus placebo in Ménière's patients.

Data collection and analysis
One author identified studies which loosely met the inclusion criteria and full texts were retrieved. Two authors independently applied the inclusion criteria. Seven studies were excluded from the review due to inappropriate study design or absence of randomisation.

Main results
There were no trials of high enough quality to meet the standard set for this review.

Authors' conclusions
There is insufficient good evidence of the effect of diuretics on vertigo, hearing loss, tinnitus or aural fullness in clearly defined Ménière's disease.

PLAIN LANGUAGE SUMMARY

Diuretics for the treatment of Ménière's disease or syndrome

Diuretics (drugs which reduce fluid accumulation in the body) are commonly used in the management of the symptoms of vertigo, hearing loss, tinnitus or aural fullness in patients with Ménière's disease. 'Endolymphatic hydrops' is an increase in the pressure of the fluids in the chambers of the inner ear and is thought to be the underlying cause of Ménière's disease. Diuretics are believed to work by reducing the volume (and therefore also the pressure) of these fluids. The authors of this systematic review carried out an extensive search but could not identify any randomised controlled trials of sufficient quality to include in the review. There is no good evidence about the effect of diuretics on the symptoms of Ménière's disease and further research is needed.

BACKGROUND

Prosper Ménière gave his name to a disorder characterised by recurrent episodes of spontaneous vertigo, fluctuating hearing loss and tinnitus, often with a feeling of fullness in the ear. The disorder may be subdivided into two categories. It is usually idiopathic (i.e. without known cause), in which case it is referred to as Ménière's disease. It may also be secondary to a number of known inner ear disorders, in which case it is referred to as Ménière's syndrome.

Ménière's disease is most common between 40 and 60 years of age, although younger people can also be affected (da Costa 2002; Morales 2003; Takeda 1998; Watanabe 1995). The incidence is estimated to be between 100 and 200 per million new cases per year. Acute episodes of Ménière's tend to occur in clusters with a mean frequency of between 6 and 11 clusters per year, though remission may last several months. Episodes have been observed to occur with increasing frequency over the first few years after presentation and then decrease in association with a sustained deterioration in hearing (Moffat 1997). In most cases, vertiginous episodes eventually cease completely (Silverstein 1989). This fluctuating natural history makes formal evaluation of any treatment effect in Ménière's difficult.

Ménière's is thought to be associated with endolymphatic hydrops, i.e. raised endolymph pressure in the membranous labyrinth of the inner ear (Hallpike 1938). The cause of the hydrops is not known in most cases. Specific disorders affecting the inner ear which are also associated with hydrops include temporal bone fracture, syphilis, hypothyroidism, Cogan's syndrome and Mondini dysplasia.

The disorder is not always easy to diagnose and there is no 'gold standard' diagnostic test. It is almost certainly over-diagnosed by non-specialists. The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) has produced diagnostic guidelines (Alford 1972) which have been revised twice (Ménière's Guide 1995; Pearson 1985), but these are not universally accepted. Nevertheless, they provide a standard which can be applied easily to make the diagnosis in normal clinical practice. In brief, these guidelines now stipulate that a 'definite' diagnosis can only be made on the basis of:

1) at least two spontaneous episodes of rotational vertigo lasting at least 20 minutes;
2) audiometric confirmation of a sensorineural hearing loss;
3) tinnitus and/or a perception of aural fullness.

These criteria exclude most other vestibular conditions, but further investigation is also necessary to exclude other disease processes such as an acoustic neuroma.

Ideally, the aim of treatment is to:

1) reduce the number and severity of acute attacks of vertigo;
2) abort or ameliorate the hearing loss and tinnitus associated with such attacks;
3) alleviate any chronic symptoms (e.g. tinnitus and imbalance);
4) prevent progression of the disease, in particular the loss of hearing and balance function which characterises the disorder.

No treatment modality has been shown to achieve all of these aims. In fact an evidence base for the management of patients with Ménière's disease is sadly lacking. The two main medical treatment modalities are betahistine therapy and diuretics. The effect of betahistine compounds in patients with either Ménière's disease or Ménière's syndrome was assessed in 2001 by a Cochrane systematic review (James 2001). Betahistine is thought to exert its effect by either reducing the endolymphatic pressure through improved circulation in the stria vascularis or inhibiting activity in the vestibular nuclei. The review concluded that there was no evidence that betahistine was effective in Ménière's. The strict criteria used in the review may have excluded studies with patients with Ménière's-type symptoms including vertigo and a further evaluation of the effect of betahistine on such patients is in progress.

The proposed mechanism of action of diuretics in Ménière's disease is an alteration in the electrolyte balance within the endolymph causing a reduction of the endolymph volume and pressure either by increased drainage of endolymph or a reduction in its production.

The different types of diuretic are:

1) Thiazide diuretics, e.g. benzofluazide, hydrothiazide and chlorthalidone - inhibitors of Na^+/Cl^- reabsorption from the distal convoluted tubules of the nephrons;
2) Potassium-sparing diuretics, e.g. amiloride, spironalactone and triamterene - inhibitors of Na+/K+ exchange within collecting ducts;
3) Loop diuretics, e.g. frusemide - inhibitors of co-transporter in the medullary thick ascending limb of the loop of Henle;
4) Carbonic anhydrase inhibitors, e.g. acetazolamide - inhibitors of H+ secretion and resultant promotion of Na+ and K+ excretion.

The main type of diuretic used in Ménière's is thiazide, but a search was made for all diuretic agents.

As in the James 2001 Cochrane review we focused on studies employing strict criteria for the diagnosis of Ménière's to try to address the specific question of the effects of drugs in patients with 'definite' Ménière's disease or syndrome.

OBJECTIVES

We sought to assess the effects of diuretics in patients with either Ménière's disease or Ménière's syndrome. Specifically we assessed

the effect of diuretic treatment on the frequency and severity of attacks, on chronic symptoms such as tinnitus, imbalance and hearing loss and on the progression of these symptoms.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials of diuretic versus placebo. Trials analysed on an intention-to-treat basis were preferred, and where necessary and possible, we planned to reconstruct intention-to-treat analyses.

Types of participants

Patients of any age with Ménière's disease or syndrome. Studies were to be graded on the basis of the robustness of the methods used to diagnose these disorders and this grading was to form the basis of a sensitivity analysis:

Grade I - Studies in which the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) 1995 criteria have been used and only patients with definite and certain Ménière's included in the study.
Grade II - Studies in which clear but less rigorous criteria have been used.

Studies that distinguished patients with Ménière's syndrome but did not use an appropriate criteria were to be considered separately.

Priority was given to trials studying patients who had not received diuretics for any reason in the past.

Types of intervention

Diuretics versus placebo. Other medication may be used concurrently provided it is used equally in each group. We decided to compare diuretics with placebo as no 'gold standard' treatment for Ménière's is available. We excluded any trials with no placebo group as there is a significant placebo effect in Ménière's management.

Trials with a cross-over design were only to be included if data from results before the cross-over were extractable in order to avoid the potential confounding effect of a carry-over phenomenon.

Types of outcome measures

Important outcomes were:

1. Number and severity of acute attacks of vertigo
2. Changes in hearing
3. Severity of tinnitus
4. Changes in perception of aural fullness
5. Functional impairment and disability
6. Overall changes in well-being and quality of life
7. Side effects of the treatment

If disease was bilateral and asymmetrical, we planned to assess outcomes 2, 3 and 4 using the more severely affected ear.

Outcomes were measured in the short or long-term. The prevention of progressive hearing loss is equally important but must be measured over a period of many months or years.

Ménière's is a chronic disease with a fluctuating and episodic pattern of symptoms. Therefore, assessment of long-term effectiveness of any therapy is extremely important. Ideally trials should evaluate both the long-term (> 3 months) effects of both short courses of treatment (2 to 12 weeks), and the effectiveness of long-term (> 3 months) treatment. Long-term outcomes should be assessed at 18 to 24 months and 42 to 48 months after the onset of treatment, as suggested by the AAO-HNS.

The severity of the disease and the time elapsed before treatment could be an important factor in determining response to diuretics and we followed the same staging system as James 2001 to address this issue in more detail.

The AAO-HNS 1995 guidelines for the evaluation of treatment of Ménière's disease are designed to evaluate the long-term effects of specific (usually surgical) intervention. However, like the diagnostic criteria referred to above, they are well defined and rigorous.

In outline:

1) The number of vertiginous episodes per unit time is recorded with and without treatment.
2) Hearing is assessed by four-tone average of pure tone threshold at 0.5, 1, 2 and 3 kHz on audiogram.
3) Functional impairment is assessed with a scale measuring daily tasks.
4) Measures for assessment of tinnitus and perception of aural fullness have not been defined.

Studies were to be categorised on the similarity of their outcome measures to AAO-HNS guidelines. Studies using similar measures were to be graded (I), dissimilar but appropriate measures (II), and those using measures considered inadequate were to be graded (III). This was also to form the basis for a sensitivity analysis.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Ear, Nose and Throat Disorders Group methods used in reviews.

Randomised controlled trials and controlled clinical trials of diuretics versus placebo were identified.

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 1 2005), MEDLINE (1966 to 2005), EMBASE (1974 to 2005),

CINAHL and the *meta*Register of Controlled Trials (*m*RCT). The date of the last search was 2005.

CENTRAL was searched using the terms:

#1 Labyrinth Diseases*:ME (in the case of MeSH terms, the asterisk signifies inclusion of all subheadings)
#2 Endolymph* and hydrop* (asterisk used as a wildcard symbol for free text)
#3 Meniere*
#4 labyrinth*
#5 Vestibul*
#6 Balance*
#7 Tinnitus:ME
#8 tinni*
#9 Cochlear*
#10 Sensorineural*
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 Diuretics:ME
#13 Diuresis:ME
#14 diure*
#15 #12 or #13 or #14
#16 #11 and #15

Alternative search terms for diuretic were thiazide, dyazide, hydrochlorothiazide, Dichlortride®, flunarizine, chlorthalidone, nicotinic acid, triamterene, furosemide, acetazolamide, carbonic anhydrase inhibitor, glycerol and urea. All search strategies were modelled on the CENTRAL version.

The same search strategy was combined with the optimum search strategy formulated by The Cochrane Collaboration for identifying controlled trials to search EMBASE (from 1974 to 2005) and MEDLINE (from 1966 to 2005). Reference lists of identified publications were scanned for additional trials and authors contacted if necessary. In addition, the reference lists of any previous reviews of the subject and the review authors' own files were scanned for relevant studies. Conference proceedings were handsearched for details of further trials and a search for unpublished trials was made by contacting the manufacturers and others for details.

METHODS OF THE REVIEW

Study selection

The initial search was made by one author to identify trials which loosely met the inclusion criteria. Both authors then reviewed the full text articles of the retrieved trials and applied the inclusion criteria independently. Any differences in opinion about which studies to include in the review were resolved by discussion between the two authors. The authors were blind to the names of journals, authors and the study results while applying the criteria for determining which studies to include in the review.

We did not identify any studies suitable for inclusion in this review. If studies which meet the inclusion criteria are found for future updates, the following methods will be applied:

Data extraction

The two authors will independently extract data from the studies using standardised data forms. Data will be extracted so as to allow an intention-to-treat analysis. Where necessary and where data from the study are not provided, the review authors will write to the authors of the study requesting further information.

Quality assessment

The quality of all included trials will be assessed independently by at least two review authors using the same method as James 2001, which is a modification of the method derived by Schulz et al (Schulz 1995). Differences will be resolved by discussion. The selected studies will be assessed for the following characteristics:

1. The certainty of diagnosis of Ménière's ('Types of participants');
2. The adequacy of the randomisation process and of allocation concealment (A: adequate, B: uncertain, C: inadequate);
3. The potential for attrition bias after allocation to study group, i.e. losses of participants to follow up and whether analysis was intention-to-treat;
4. Whether the trial was conducted and outcomes assessed in a double blind manner;
5. The adequacy of compliance and its assessment;
6. The quality of the outcome assessment ('Types of outcomes measures').

Studies will be graded A, B or C for their overall methodological quality. Quality will be used for sensitivity analysis.

Data analysis

Data analysis will be by intention-to-treat. If data are compatible and of sufficient quality (outcome measure categories (I) or (II)), they will be combined to give a summary measure of effect, otherwise data will not be combined. Study quality will be used in a sensitivity analysis. If possible, the effect of different doses of diuretic will be compared. If sufficient data are available subgroup analyses will be carried out, grouping patients by duration and severity of disease.

Study outcomes are likely to be measured in a variety of ways using continuous, discrete and categorical variables. Data may be dichotomised if appropriate. Statistical advice will be sought to determine the best way of presenting and summarising the data.

DESCRIPTION OF STUDIES

Seven trials were identified. Only two were placebo controlled. There were two cross-over trials, neither of which contained data that could be extracted for the period of the study prior to cross-over. One study did not use a placebo but compared a diuretic

with betahistine. No trials met the criteria for inclusion in this review.

Studies were excluded for the following reasons:

Study type
Four studies were not randomised placebo controlled trials. Klockhoff 1974 and Brookes 1984 were observational studies. Corvera 1989 was a retrospective study. Petermann 1982 was a randomised trial but not placebo controlled.

Allocation
Allocation of patients to betahistine or placebo was not randomised in Ralli 1989.

Trial design
Van Deelen 1986 and Klockhoff 1967 were cross-over trials. They could not be used as the data from the first part of the trial could not be extracted. We were unable to contact the authors to obtain the raw data.

Brookes 1984 was an observational study of 14 patients given acetazolamide for varying duration of one week to nine months. A Grade I criteria for diagnosis of Ménière's diagnosis was used. The study was not placebo controlled, nor randomised. Outcome measures were qualitative and there was no long-term evaluation.

Corvera 1989 was a retrospective review of three groups of patients thought to have Ménière's disease; 79 had been given chlorthalidone, 42 acetazolamide, 71 had symptom control only. Diagnosis was not based on the AAO-HNS guidelines and the criteria for diagnosis were not specified. The study was not placebo controlled, randomised or assessed in a double blind manner. Initial hearing loss appeared to be much greater in the symptom control group. Only hearing loss and not vertigo, tinnitus or functional impairment was assessed. All frequencies were averaged together which means that changes in low frequency may have been masked.

Klockhoff 1967 was a randomised controlled double blind trial of 30 patients. A Grade II criteria for diagnosis of Ménière's disease was used. There was an initial two-month observation period then patients were given a placebo or hydrochlorothiazide for four months. There was then an observation period and then placebo or drug for four months. Data for the period before the cross-over could not be extracted and it was not possible to exclude the carry-over phenomenon.

Klockhoff 1974 was an observational study of 34 patients with a Grade II criteria for diagnosis of Ménière's disease. All patients were given chlorthalidone for varying time periods depending on symptoms. The trial was not randomised or placebo controlled. Outcomes were measured as for Klockhoff 1967. The analysis of results was poor as the paper only describes individual patient improvement, with no statistical analysis. It was not possible to determine whether the patients would have improved symptomatically independently of the chlorthalidone. A further group of 220 patients also received chlorthalidone but they had incapacitating vertigo with no mention of Ménière's.

Petermann 1982 was a randomised controlled double blind trial of betahistine dihydrochloride versus hydrochlorothiazide in 32 patients. There was no placebo. The authors used a Grade II criteria for Ménière's diagnosis. It is uncertain how randomisation and concealment were performed. There was also no long-term follow up of results and patients were only assessed for the three-month duration of each intervention.

Ralli 1989 was not a randomised, double blind or controlled study. Twenty-five patients were given acetazolamide and observed for five hours. Follow up was not adequate for a therapeutic trial. A further nine patients were given a placebo but this was not conducted as a double blind randomised controlled trial.

Van Deelen 1986 was a double blind cross-over placebo controlled trial. There was no Grade II criteria for Ménière's diagnosis. Randomisation was unspecified. The trial was rejected because data for each part of the study could not be extracted. There was no observation gap between the two interventions therefore the carry-over phenomenon could not be avoided. There was also no long-term follow up of results. Each intervention was only assessed for the duration of the intervention which was 17 weeks.

METHODOLOGICAL QUALITY

No studies met the inclusion criteria for the review.

RESULTS

The search strategy identified seven trials studying the treatment of Ménière's disease with diuretics. None of these trials could be included in this review.

DISCUSSION

The outcome of treatment of Ménière's disease is difficult to assess. Although there are strict criteria established by the AAO-HNS for the diagnosis of Ménière's disease, they are often not adhered to. Outcome measures are rarely assessed according to AAO-HNS criteria. Also, because of the long duration of treatment required, and long period of follow up required to assess any benefit, high quality trials are difficult to set up and execute.

Consequently, we found no high quality evidence evaluating the effectiveness of diuretics in Ménière's disease or syndrome. There were no double blind randomised placebo controlled trials using the AAO-HNS criteria for diagnosis and outcome measure evaluation, or of sufficient length of treatment and follow up, to be included. We found no trials with a low risk of methodological

bias that used the highest level of diagnostic criteria and outcome measures (i.e. overall quality grade A - 'Methods of the review').

The effect of diuretics on vertigo, hearing loss, tinnitus or aural fullness in clearly defined Ménière's disease cannot currently be evaluated.

Despite the lack of high quality evidence, some studies have reported an improvement in patients' vertigo whilst using diuretics. No study considered for this review described any side effects from the use of diuretics. The generally documented side effects include polyuria, thirst, constipation, mild stomach problems, impotence, hypokalaemia, hypercalcaemia, impaired glucose tolerance, gout, hyperlipidaemia and skin rashes. However, the low dose diuretics used for Ménière's disease appear to be well tolerated and are relatively inexpensive. Some patients may still be willing to try them.

AUTHORS' CONCLUSIONS

Implications for practice

There is no good evidence for or against the use of diuretics in Ménière's disease or syndrome.

Implications for research

A large randomised clinical trial is required to establish the efficacy of diuretics in Ménière's disease or syndrome. The AAO-HNS guidelines provide a standardised protocol for diagnosis and assessment that would form an ideal basis for future trials of diuretics.

POTENTIAL CONFLICT OF INTEREST

None known.

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** Indicates the major publication for the study*

TABLES

Characteristics of excluded studies

Study	Reason for exclusion
Brookes 1984	ALLOCATION Not randomised, not placebo controlled.
Corvera 1989	ALLOCATION Not randomised, not placebo controlled. Not assessed in a double blind manner.
Klockhoff 1967	ALLOCATION Randomised controlled double blind trial of 30 patients. PARTICIPANTS Grade II criteria for Ménière's disease. INTERVENTIONS Initial two-month observation period then patients given placebo or hydrochlorothiazide for four months, then observation period then placebo or drug for four months. OUTCOMES Data before cross-over not extractable. Cannot exclude carry-over phenomenon.
Klockhoff 1974	ALLOCATION Not randomised, not placebo controlled.
Petermann 1982	ALLOCATION Randomised controlled double blind cross-over trial. Uncertain how randomisation and concealment was performed. PARTICIPANTS Grade II criteria for Ménière's diagnosis. INTERVENTIONS Betahistine dihydrochloride versus hyrdochlorothiazide 32 patients. No placebo.

	OUTCOMES Trial rejected because data for each part of the study is not extractable. There was no observation gap between the two interventions therefore the carry-over phenomenon cannot be avoided. There was also no long-term follow up of results; patients were only assessed for the three-month duration of each intervention.
Ralli 1989	ALLOCATION Not randomised, double blind or controlled study.
Van Deelen 1986	ALLOCATION Double blind cross-over placebo controlled trial. Randomisation unspecified. PARTICIPANTS There was no Grade II criteria for Ménière's diagnosis. OUTCOMES Trial rejected because data for each part of the study was not extractable. There was no observation gap between the two interventions therefore the carry-over phenomenon cannot be avoided.

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Diuretics [*therapeutic use]; Meniere Disease [*drug therapy]; Syndrome; Tinnitus [drug therapy]

MeSH check words

Humans

COVER SHEET

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Authors	Thirlwall AS, Kundu S
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