Intratympanic gentamicin for Ménière's disease or syndrome (Review)

Pullens B, van Benthem PP

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Intratympanic gentamicin for Ménière's disease or syndrome

Bas Pullens[1], Peter Paul van Benthem[2]

[1]ENT Surgery, University Medical Centre Utrecht, Utrecht, Netherlands. [2]ENT Surgery, Gelre Ziekenhuizen, Apeldoorn, Netherlands

Contact address: Bas Pullens, ENT Surgery, University Medical Centre Utrecht, Heidelberglaan 100, Utrecht, 3584 CX, Netherlands. bpullens78@yahoo.com.

Editorial group: Cochrane Ear, Nose and Throat Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2011.
Review content assessed as up-to-date: 29 June 2010.

Citation: Pullens B, van Benthem PP. Intratympanic gentamicin for Ménière's disease or syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD008234. DOI: 10.1002/14651858.CD008234.pub2.

ABSTRACT

Background

Ménière's disease is characterised by three major symptoms: vertigo, deafness and tinnitus, which may be accompanied by aural fullness, all of which are discontinuous and variable in intensity. While discontinuous, these symptoms are synchronous. Intratympanic application of gentamicin, an ototoxic aminoglycoside, is a relatively new ablative treatment for vertigo in Ménière's disease with promising results.

Objectives

To assess the effectiveness of intratympanic gentamicin in the treatment of vertigo in 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); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ISRCTN and additional sources for published and unpublished trials. The date of the most recent search was 30 June 2010.

Selection criteria

All randomised or quasi-randomised controlled trials of intratympanic gentamicin versus placebo, or versus another treatment for Ménière's disease.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We contacted study authors for further information.

Main results

We identified two trials, involving 50 participants, which fulfilled the inclusion criteria. Both of these trials are prospective, double-blind, placebo-controlled randomised clinical trials on the effect of intratympanic gentamicin on vertigo complaints. After assessing the risk of bias of both studies, we concluded that one had a greater risk of bias and deemed the other to be of higher quality. Both of these trials found a significant reduction in vertigo complaints in the gentamicin group when compared to the placebo group. Due to clinical heterogeneity we could not perform a meta-analysis. One study described an increase in hearing loss in four patients (25%) treated with gentamicin while the other described no increase in hearing loss. No other adverse effects were noted by either study.

Authors' conclusions

Based on the results of the two included studies, intratympanic gentamicin seems to be an effective treatment for vertigo complaints in Ménière's disease, but carries a risk of hearing loss.

PLAIN LANGUAGE SUMMARY

Intratympanic gentamicin for Ménière's disease or syndrome

Ménière's disease is characterised by three major symptoms: rotational dizziness (vertigo), hearing loss and ringing in the ears (tinnitus), sometimes accompanied by aural fullness. Intratympanic gentamicin is a relatively new therapy with promising results. Gentamicin is an antibiotic which damages the inner ear and the balance organ when it is applied behind the ear drum. This treatment may decrease the spells of vertigo in Ménière's disease. In this review we assess the effectiveness of this kind of treatment for Ménière's disease. Two randomised controlled trials, including a total of 50 patients, were identified which fulfilled the review inclusion criteria. Both of these found a beneficial effect of intratympanic gentamicin therapy for Ménière's disease, although the size of the effect differed between the two trials. Based on these findings, we conclude that intratympanic gentamicin may be an effective treatment for vertigo complaints in Ménière's disease, but it carries a risk of increasing hearing loss. Further research is needed to clarify the effect of intratympanic gentamicin on vertigo in Ménière's disease and the risk of inducing or increasing hearing loss.

BACKGROUND

Description of the condition

Ménière's disease is an incapacitating disease in which recurrent attacks of vertigo are accompanied by hearing loss, tinnitus and/or aural fullness. The attacks of vertigo may follow each other with intervals of days, weeks or even months. While the attacks are discontinuous, these symptoms are synchronous. Usually, the attacks become less severe and disappear after two to eight years in 60% to 80% of sufferers (Portmann 1980; Silverstein 1989), with profound lasting hearing loss and tinnitus, although there is great variability in the presentation and natural course of the disease. When no known cause of the disease is identified, the term Ménière's *disease* is applicable. When the symptoms are secondary to a known disease (e.g. meningitis), the term Ménière's *syndrome* is used.

Few articles have been published on the epidemiology of Ménière's disease. Great variation exists in the published reports of the incidence and prevalence of Ménière's disease, ranging from 17 cases per 100,000 population in Japan (Nakae 1984) to 46 cases per 100,000 population in Sweden (Stahle 1978). There seems to be a slight female preponderance, with up to 1.3 times more women affected than men. The disease is more common in adults in their fourth and fifth decade of life (Kotimaki 1999; Sajjadi 2008). The frequency of bilateral disease is unclear. Published reports vary greatly between 2% and 78% (Balkany 1980). In a large population study by Kitahara in Japan, bilaterality of disease was noted in 9.1% of patients in their first year of experiencing symptoms. This increased steadily to 41.5% after 20 years of disease (Kitahara 1991).

In 1861 Prosper Ménière first recognised that this disorder originated from the inner ear (the membranous labyrinth), but wrongly attributed the cause to haemorrhage (Meniere 1861). In 1938 Hallpike and Yamakawa independently described a hydrops (i.e. accumulation of fluid) of the endolymphatic system in patients with Ménière's disease (Hallpike 1938; Yamakawa 1938). In 1965 Kimura introduced an experimental model in which an endolymphatic hydrops was produced in guinea pigs after surgical obliteration of the endolymphatic sac and duct (Kimura 1967). Endolymphatic hydrops caused by an abnormality in the absorption of endolymph at the endolymphatic sac remains the most promising theory to explain the symptoms of Ménière's disease. Other explanations for the cause of an endolymphatic hydrops, such as a hypoplasia of the vestibular aqueduct (Egami 1978; Yamamoto 1992), a genetic predisposition (Morrison 1995), or a viral aetiology (Vrabec 2003), have been suggested.

Currently no 'gold standard' diagnostic test for Ménière's disease exists. Diagnostic criteria vary among practitioners who mostly diagnose Ménière's disease based upon the patient's history, neurotologic and audiologic evaluation and imaging. In 1972 the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) produced diagnostic guidelines (Alford 1972), which were revised in 1985 (Pearson 1985) and 1995 (Monsell 1995b). According to these guidelines Ménière's disease is 'definite' when at

least two spontaneous episodes of vertigo occur for at least 20 minutes, sensorineural hearing loss of at least 20 decibels (dB) is objectified and tinnitus or aural fullness in the affected ear is experienced. Further investigation has to be performed to exclude any other disorder (Monsell 1995b). When patients match the AAO-HNS criteria, but symptoms are secondary to a known cause, they are classified as having Ménière's syndrome.

A number of different treatment modalities have been identified for this disease, ranging from dietary measures (e.g. a low-salt diet) and medication (e.g. betahistine (Serc®), diuretics) to extensive surgery (e.g. endolymphatic sac surgery). Although a large number of studies have been conducted on therapy for Ménière's disease (see the Cochrane Reviews of betahistine and diuretics: Burgess 2006; James 2001), an effective evidence-based therapy has never been established. Ménière's disease has a fluctuating natural course with remissions and exacerbations. Spontaneous remission is not uncommon, which makes evaluation of treatment difficult. The AAO-HNS therefore advises a follow-up period of at least two years to evaluate therapy (Coelho 2008; Durland 2005; Ghossaini 2006; Odkvist 2001).

In general, there are two types of interventions for Ménière's disease: those that aim to modulate the disease in terms of reducing the severity and frequency of the attacks, and those that target a single symptom (usually vertigo) by ablating the vestibular end organ. Intratympanic gentamicin aims to control vertigo attacks by (partially) ablating the vestibular end organ.

Description of the intervention

Schuknecht et al first published on the use of intratympanic aminoglycosides (streptomycin) in Ménière's disease in the 1950s (Schuknecht 1957). Streptomycin was later replaced by gentamicin, another type of aminoglycoside antibiotic, in order to reduce the risk of hearing loss (gentamicin is deemed more vestibulotoxic than ototoxic, possibly preserving hearing). In the last couple of decades, intratympanic injection of gentamicin has become a popular treatment option for Ménière's disease. The aim of this therapy is to chemically damage or ablate the diseased labyrinth in order to stop the fluctuating malfunction of the labyrinth which causes the symptoms of Ménière's disease, and to create a lasting situation of hypofunction for which the brain can compensate. This chemical ablation of the labyrinth has some advantages over the classic surgical ablation (labyrinthectomy, vestibular or cochleovestibular nerve section): it can be performed in the outpatient clinic under local anaesthesia, so no major surgery is necessary and gentamicin is more vestibulotoxic than ototoxic, so it may be possible to preserve hearing.

Although gentamicin is usually applied into the middle ear, great differences exist in the method of application, the number of applications and the amount of gentamicin used. This can be largely categorised into five different groups:

1. multiple daily dosing in which three daily doses of gentamicin are given;
2. weekly dosing in which weekly injections are given, usually for four weeks;
3. low-dose technique in which one or two injections are given with repeat treatment only for recurrent vertigo;
4. continuous microcatheter delivery; and
5. titration technique in which daily or weekly doses are given until onset of vestibular symptoms, change in vertigo symptoms, or hearing loss occurs.

No consensus exists on the best dosing schedule to minimise hearing damage, but many authors argue that intermittent dosing with long intervals between two injections to check whether hearing loss has occurred is a safer approach in preserving hearing (see Agreements and disagreements with other studies or reviews) (Carey 2004; Chia 2004; Longridge 2005).

How the intervention might work

Gentamicin is placed in the tympanic cavity through the tympanic membrane. The method of application varies and includes the use of grommets, paracentesis or inner ear wicks, amongst others. It is thought that the gentamicin permeates the perilymph and the endolymph of the inner ear through the round and oval window membranes, where it damages the vestibular hair cells. This causes a situation of constant hypofunction of the diseased labyrinth, which results in a steady state to which the brain can adapt, without the fluctuating vertigo of Ménière's disease. However, the use of intratympanic gentamicin carries the distinct risk of inducing hearing loss (Carey 2004; Schuknecht 1957).

As described above, a number of different dosing schedules are used for intratympanic gentamicin treatment. Although numerous articles have been published on the use of each of these techniques, there is no agreement in the otolaryngologic community on the best technique to secure the greatest amount of vertigo control with the lowest risk of associated hearing loss. While some authors propose complete chemical ablation (usually using multiple daily dosing), others state that complete ablation is not necessary for the control of vertigo, possibly with better preservation of hearing (Chia 2004; Diamond 2003).

Why it is important to do this review

Ménière's disease has a fluctuating natural course with remissions and exacerbations. Spontaneous remission is not uncommon, which makes evaluation of treatment difficult. Studies on therapy for Ménière's disease should be done in a randomised controlled trial (RCT) setting because of this fluctuating natural course. Although a number of reviews have been published, none have been restricted to RCTs. Furthermore, the appropriate dosing schedule for the best clinical result with the least amount of

hearing loss has yet to be determined and the frequency of occurrence of sensorineural hearing loss as an adverse effect of treatment needs to be established. Since Ménière's disease itself can be accompanied by increasing hearing loss, it seems paramount that this should be investigated in a randomised, (placebo-)controlled trial set-up (Chia 2004; Diamond 2003; Longridge 2005).

OBJECTIVES

To assess the effectiveness and safety of the use of intratympanic gentamicin in managing the symptoms of episodic vertigo in Ménière's disease. We will also assess the effect on hearing loss and tinnitus/aural fullness.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials.

Types of participants

Patients suffering from Ménière's disease not otherwise controlled by conservative therapy, and without a history of surgical intervention. Studies which have used the AAO-HNS criteria for Ménière's disease or syndrome, and which only include patients with "definite" or "certain" Ménière's disease, were graded 'I'. Studies in which clear but less rigorous criteria were used were graded 'II'. Studies in which less clear criteria were used were graded 'III' (AAO-HNS 1995; James 2001).

Types of interventions

We considered any type of intratympanic installation of gentamicin in this review. The mode of installation and amount of gentamicin had to be specified and compared with a placebo or alternative intervention.

Types of outcome measures

Primary outcomes

- Control of vertigo, as suggested by the AAO-HNS 1995.

The AAO-HNS Committee on Hearing and Equilibrium proposed the "control of vertigo" as a main objective outcome measure when assessing therapy in Ménière's disease. The number of vertigo attacks in the interval between 18 and 24 months after treatment (Y) is divided by the number of vertigo spells for the period of six months prior to the treatment (x) and multiplied by 100. The resulting number indicates the extent of "control of vertigo". The AAO-HNS further divides the control of vertigo into classes, where Class A (CoV = 0) is complete control and class B (CoV 1 to 40) is substantial control. A minimum duration of follow up of at least two years is therefore advised, however we also considered studies with shorter periods of follow up for this review. Assessment of control of vertigo by any other outcome measure (e.g. Visual Analogue Scale (VAS) score or Dizziness Handicap Inventory (DHI)) is also acceptable.

Secondary outcomes

- Loss or gain of hearing.
- Severity of tinnitus.
- Perception of aural fullness.
- Complications and adverse events.
- Quality of life.
- Adverse events.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the last search was 30 June 2010.

Electronic searches

We searched the following databases from their inception for published, unpublished and ongoing trials: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 2); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; ISRCTN; ClinicalTrials.gov; ICTRP (International Clinical Trials Registry Platform) and Google.
We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2, Box 6.4.b. (Handbook 2009)). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We scanned reference lists of identified studies for further trials. We searched PubMed, TRIPdatabase, NHS Evidence - ENT and Audiology, and Google to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their reference lists for additional trials.

Data collection and analysis

Selection of studies

We scanned the initial search results 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. We resolved any differences in opinion about the inclusion of studies by discussion.

The two authors independently used titles, keywords and (where available) abstracts of the identified citations to exclude trials which clearly did not meet the inclusion criteria of the review. If one of the authors concluded that the trial might possibly meet the criteria, we obtained the full paper for further study. We then assessed hard copies of the articles passing this initial screening to determine whether they met the inclusion criteria. The results of the two independent selections were compared. Again, we resolved any disagreements by discussion.

Data extraction and management

Two authors extracted data jointly. There was no blinding of journal or author names and affiliations.

We extracted the following data where available:

1. type of protocol used (titration, fixed-dose, low-dose, etc.) (when a titration protocol was used, the method by which the end of therapy was assessed needed to be described);
2. concentration of gentamicin;
3. number of injections and/or total amount of gentamicin;
4. mode of application.

Assessment of risk of bias in included studies

We assessed the quality of the selected studies using the Cochrane Collaboration's tool for assessing risk of bias. This tool addresses the following domains: sequence generation, allocation concealment, selective outcome reporting, blinding, incomplete outcome data and other sources of bias. The two authors judged these domains by answering the questions posed in table 8.5.a of the *Cochrane Handbook for Systematic Reviews of Interventions* (see below), where an answer 'yes' indicates low risk of bias, 'no' indicates high risk of bias and 'unclear' indicates an uncertain risk of bias. These results were incorporated into 'Risk of bias' tables in RevMan 5 (RevMan 2008).

We also judged two extra domains: the certainty of diagnosis of Ménière's (see also 'Types of participants') and the quality of outcome assessment (see 'Types of outcome measures'). This is a modification following an earlier review by James and colleagues (James 2001). We have adapted the 'Risk of bias' tool to include also the grading allocated for AAO-HNS diagnosis of Ménière's disease. For the 'other sources of bias' domain, we gave special attention to the correct or incorrect follow-up period for Ménière's disease as described by the AAO-HNS (AAO-HNS 1995) (correct being a follow-up period of at least two years).

Dealing with missing data

When critical data were missing from an included study, we contacted the principal investigator and requested the missing data.

Assessment of heterogeneity

We assessed the included studies for methodological and statistical heterogeneity. We quantified heterogeneity using the I^2 statistic. When studies were sufficiently homogeneous, we had planned to use a meta-analysis with a fixed-effect model to pool the data and a random-effects model when a certain amount of heterogeneity existed, however the data from the included studies were not pooled.

Data synthesis

If we identify further studies for future updates of this review, we will use the following methods for data synthesis:

Data analysis will be by intention-to-treat. If data are compatible and of sufficient quality, they will be combined to give a summary measure of effect, otherwise data will not be combined. We will use study quality in a sensitivity analysis. If possible, we will compare the effect of different doses of gentamicin. If sufficient data are available we will carry out subgroup analyses.

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

We will produce tables of comparison (if possible) and will include the following outcomes:

1. reduction in spells of vertigo or reduction in vertigo complaints;
2. loss or gain of hearing.

In addition, we will calculate multivariate regression models. If subgroup analysis and multivariate analysis require further information, we will contact authors of studies.

Subgroup analysis and investigation of heterogeneity

If further studies are included in future updates of this review, we will use the following methods for subgroup analysis:

If possible, we will carry out a subgroup analysis comparing the following modalities:

1. type of protocol used: if possible, the different protocol types (titration, fixed-dose, low-dose, etc.) will be compared;
2. gentamicin: if possible we will compare different concentrations;
3. number of injections and/or total amount of gentamicin, as above;
4. mode of application: if possible we will compare the Silverstein MicroWick, intratympanic injection through a paracentesis, or through a ventilation tube.

Sensitivity analysis

If sensitivity analysis is feasible in future updates we will compare the effect of inclusion and exclusion of studies of different qualities.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

We retrieved a total of 248 references from the searches: 148 of these were removed in first-level screening (i.e. removal of duplicates and clearly irrelevant references), leaving 100 references for further consideration. We evaluated the abstracts of these studies. We retrieved seven intervention studies which loosely met the inclusion criteria in full text. The search also identified four reviews which we also retrieved in full text. One of the intervention studies was published in Turkish and we sought help from the Cochrane ENT Group to translate this article (Akkuzu 2006).

Of the seven intervention studies, only two met the inclusion criteria for this review and could be included (Postema 2008; Stokroos 2004). The reasons for exclusion of the five other studies are shown in the 'Characteristics of excluded studies' table (Akkuzu 2006; De Stefano 2007; Enrique-Gonzaleza 2008; Quaranta 2001; Silverstein 1999).

Included studies

The studies by Postema 2008 and Stokroos 2004 were included in this review.

Trial design

Both studies were prospective, randomised, double-blind, placebo-controlled trials. The follow-up period in Postema 2008 was 12 months after treatment; in Stokroos 2004 the follow-up period was variable and was stated to be "at least 6 months". Both reported vertigo and hearing loss as outcome measures. Stokroos 2004 reported the caloric response as an additional outcome measure; Postema 2008 described tinnitus and aural fullness as other outcome measures.

Participants

Both studies used patients diagnosed with Ménière's disease according to the AAO-HNS criteria (grade I, see 'Types of participants'). Ménière's syndrome was not discussed in either study. Stokroos 2004 included 22 patients in their study, of which 12 received gentamicin and 10 received placebo, according to the 'Results' section. However, it is stated in the 'Material and methods' section of the paper that only 10 patients were given an intratympanic injection of either gentamicin or placebo. This statement is not clarified further in the text of the study, so we contacted the author (R.J. Stokroos) about this. He stated that the total study group consisted of 22 participants, of whom 12 received gentamicin. A power analysis was performed with a reduction of 50% of vertiginous spells as a clinically relevant therapeutic effect; this showed that a group of 16 to 22 patients was needed.

Postema 2008 had a study group of 28 patients, of which 16 were enrolled in the active treatment group. They state that power analysis showed that at least 20 patients had to participate to consider the average reduction in vertigo to be significant. They did not state what difference of means was considered clinically relevant.

In the study by Stokroos 2004 conservative/medical treatment had to be proven unsuccessful for at least six months to be included in the study. Postema 2008 only included patients with Ménière's disease whose electronystagmography showed a caloric response and in whom conservative medical treatment with betahistine was unsuccessful.

In the Stokroos 2004 study, the two groups were compared for mean age at the start of the study. There was no significant difference. In the Postema 2008 study, the groups were matched for age and hearing loss of the diseased and contralateral ear. Other comparisons were not given.

Intervention

Stokroos 2004 used a 30 mg/ml buffered (pH 6.4) solution of gentamicin. The placebo was the buffer solution only. The solution was injected using a paracentesis technique; no grommet was inserted. The amount of solution injected was not stated. The application protocol was described in detail; applications were repeated every six weeks until either control of symptoms was achieved or one of the stop criteria was met. The stop criteria included a cumulative dose of gentamicin $\geq$ 360 mg, > 6 months after the last

injection, or an increase in hearing loss after one of the injections, amongst others. This means that each patient in the active group and each patient in the placebo group received a different number of injections and therefore a different amount of placebo or gentamicin.

Postema 2008 used 0.4 ml of 30 mg/ml gentamicin in the active group. The placebo was not specified. Four weeks before the start of the injections, a middle ear ventilation tube was introduced into the tympanic membrane. Once a week an injection of gentamicin or placebo was given through the tube to a total number of four injections (= four weeks). After these injections the follow-up period started. Further details on the injection protocol (positioning of the patients, amount of time the gentamicin/placebo was in the middle ear) were not given.

Outcome measures

Stokroos 2004 did not report the outcome measures in the 'Material and methods' section. In the 'Results' section, they noted results in terms of the number of vertiginous attacks per year before and after treatment and the text refers to the control of vertigo as proposed by the AAO-HNS. It is unclear, however, how this is calculated since the follow up is only six months after treatment in some cases. As secondary outcome measures, the cumulative caloric response in the treated ear before and after treatment was given, as well as hearing function in the form of the extended Fletcher index (the average hearing loss at the frequencies 500, 1000, 2000 and 4000 Hz). The number of applications was given as mean ± SD. The way the other numerical data are given is not described, but it appears to be by mean value ± standard deviation (SD).

Postema 2008 reported the outcome measures in their 'Subjects and methods' section. The subjects used a form to score vertigo complaints, tinnitus and aural fullness on a four-point scale: severe (three points), moderate (two points), mild (one point) and none (0 points). Besides these outcome measures, hearing was evaluated throughout the study with the extended Fletcher index; the average hearing loss in dB at 0, 5, 1, 2 and 4 kHz. During the study data were collected at eight time points starting at the moment of insertion of the myringotomy tube up until 12 months after the last application. All numerical data were given in mean ± SD.

Excluded studies

We excluded five studies from the review (see 'Characteristics of excluded studies'). None of these were RCTs. We identified two ongoing studies (see 'Characteristics of ongoing studies').

Risk of bias in included studies

The risk of bias in the included studies is described below and in the 'Characteristics of included studies' table.

Allocation

Postema 2008 and Stokroos 2004 were both prospective, randomised, double-blind, placebo-controlled trials.

In Stokroos 2004 randomisation was performed by the hospital pharmacist, who was the only person who knew whether placebo or gentamicin was given before the end of the study period. The method of randomisation was not described. As stated in the 'Results' section, 12 of the 22 patients enrolled were assigned to the active treatment group. These groups were compared for mean age at the start of the study; the difference was not statistically significant. There was no mention of comparison for other factors; a summary with demographic and prognostic factors (e.g. duration of disease, number of vertigo attacks prior to the start of the study) to permit assessment of the degree to which allocation was balanced was not given. It is noteworthy that the number of vertiginous attacks before treatment differed greatly between the two groups (74 ± 114 in the active treatment group compared to 25 ± 31 in the placebo group). We contacted the authors for clarification. They stated that the differences in frequency of attacks were not statistically significant, before and after correction for the outlying value.

It is stated in the 'Material and methods' section that "in 10 patients with a diagnosis of MD ... a paracentesis was done followed by application of placebo, or gentamicin." In the 'Results' section it is stated that 22 patients were included in the study. This difference in the number of patients was not clarified in the text, so we contacted the authors for clarification. It became apparent that indeed a total number of 22 patients were included in the trial and were analysed.

In Postema 2008 the method of randomisation and allocation sequence generation is not given. Sixteen of the 28 patients were treated with gentamicin. It is stated in the 'Results' section that the groups were matched for age and hearing loss of the diseased and contralateral ear. Other comparisons were not given.

Blinding

Stokroos 2004 stated that the study was double-blind. It is stated further that the hospital pharmacist was the only person who knew whether placebo or gentamicin was given before the end of the study period. The method of blinding was not described in detail. As a placebo the buffer solution, used to buffer the gentamicin solution to a pH of 6.4, was used.

Postema 2008 stated that the study was double-blind and that the double-blind code, known only by the hospital pharmacist, was broken at the final visit at 12 months follow up. The method of blinding was not described. The placebo was not described.

Incomplete outcome data

Stokroos 2004 did not mention loss to follow up or incomplete outcome data. It is unclear how the number of vertigo attacks per

year (see "outcome measures") is calculated when some participants had a follow-up period of six months.

Postema 2008 did not mention loss to follow up. They reported that "a complete data set could not be obtained" for two subjects in the placebo group. Whether this led to loss to follow up, or exclusion of the study, is unclear. We contacted the authors for clarification and it became clear that these subjects were lost to follow up and were analysed in the study group to which they were allocated according to the intention-to-treat principle.

Selective reporting

In Stokroos 2004 the authors state in the 'Results' section that all patients in the gentamicin group were completely relieved of vertigo complaints after therapy. However, they mention in the 'Discussion' section that one of the patients had a recurrence of vertigo attacks one to two years after intratympanic gentamicin injection, contradicting the earlier statement of complete success in the therapeutic group. We contacted the authors for clarification. They stated that by using a titration model (applications until vestibular control is achieved) there is less damage to the vestibular end-organ, but a greater chance of recurrent vestibular complaints. The a priori chance of this recurrence is estimated by the author (Professor Stokroos) to be 4% to 6%. This, however, is not depicted in the study results.

In a follow-up retrospective study on patients who received gentamicin treatment for Ménière's disease by the same study group, the authors report complete control of vertigo in 61.4% of patients, and substantial control of vertigo in 19.3% of patients (De Beer 2007).

Other potential sources of bias

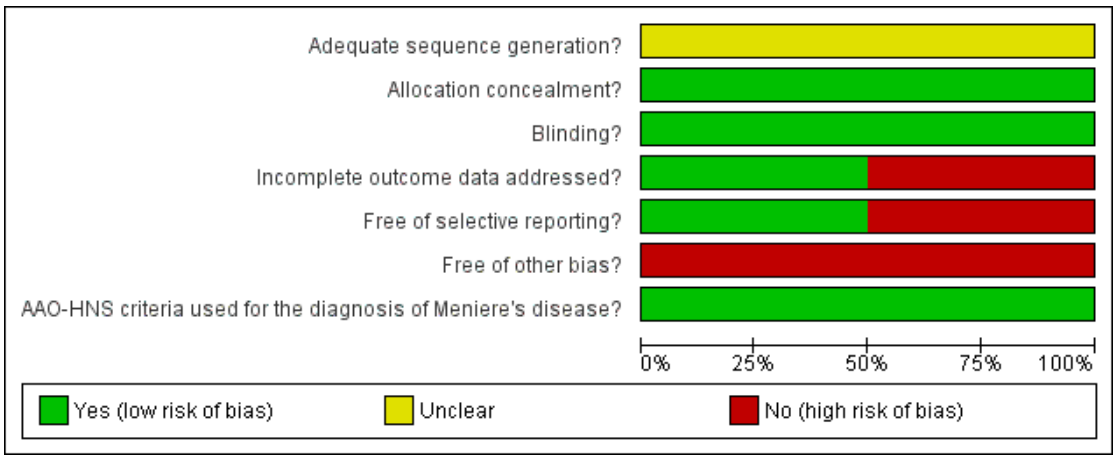
Follow up

In Stokroos 2004 the follow up is different for each patient. They used a protocol in which they continued to inject gentamicin on a six-weekly basis until the complaints disappeared for at least six months or until a total of 12 injections or 360 mg of gentamicin was given. The authors furthermore stated that the follow-up period varied between six and 28 months. This means that the participants did not receive the same amount of gentamicin, or placebo, and that the follow-up period differed between participants.

Postema 2008 used a follow-up period of 12 months. The follow-up period recommended by the AAO-HNS is two years.

For a summary of the risk of bias assessment see the methodological quality graph (Figure 1).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Effects of interventions

Vertigo complaints

In Stokroos 2004 the number of vertiginous attacks per year decreased from 74 ± 114 before treatment to zero after treatment

in the gentamicin group. This was a significant reduction (P = 0.002). In the placebo group, a significant reduction of vertiginous attacks from 25 ± 31 before treatment to 11 ± 10 after treatment was found (P = 0.028). As mentioned before, a recurrence of vertiginous attacks occurred in one patient one to two years after treatment with gentamicin. This finding is not reflected in the 'Results' section of the paper.
The number of applications was 1.5 ± 0.51 in the gentamicin group versus 2.8 ± 2.7 in the placebo group.
In Postema 2008 a reduction of vertigo score from 2.1 ± 0.8 (mean ± SD) to 0.5 ± 0.6 was found in the gentamicin group. In the placebo group it was stated that the vertigo score did not change (2.0 ± 0.8 before versus 1.8 ± 1.0 after treatment). Although the P value was not given, it is stated that the vertigo score after one year of treatment was significantly lower in the gentamicin group when compared to the placebo group. What the study group consider a clinically relevant reduction of vertigo complaints remains, however, unclear.

Hearing

In Stokroos 2004 there was no significant change in hearing in the gentamicin group (60 ± 18.7 dB before versus 54 ± 20 dB after treatment, P = 0.17) or in the placebo group (53 ± 16.5 dB before versus 58.8 ± 20 dB after treatment, P = 0.24). It is stated that "hearing was reported unchanged by all subjects, i.e. no deafness or significant hearing loss occurred".
In Postema 2008 the average increase in hearing loss was 8.1 ± 18.1 dB in the gentamicin group; for the placebo group it was 0.0 ± 0.7 dB. No P value was given for this finding. 'Figure 1' in the text shows a graph that depicts individual hearing loss per patient; one patient experienced an increase in hearing loss of 60 dB in the gentamicin group. Two patients experienced an increase of 20 dB and one patient of 30 dB in the gentamicin group. Increases of this magnitude did not occur in the placebo group. It is noteworthy, however, that another patient experienced an improvement in hearing of 20 dB in the gentamicin group.

Tinnitus

In Postema 2008 neither therapy significantly changed the tinnitus scores. In Stokroos 2004 tinnitus was not an outcome parameter.

Aural fullness

In Stokroos 2004 aural fullness was not an outcome parameter.
In Postema 2008 perceived aural fullness decreased in the gentamicin group (1.7 ± 1.0 before versus 0.9 ± 1.1 after study) but did not change in the placebo group (1.8 ± 1.0 before versus 1.8 ± 1.1 after treatment). It is stated that the aural fullness score after one year of follow up was significantly lower in the gentamicin group when compared to the placebo group (P value not given). They described the relationship between aural fullness and vertigo score and described a possible relationship at times when vertigo scores were low. Calculation of the Pearson's correlation coefficient gives r = 0.41.

Other

Stokroos 2004 discussed caloric response as an outcome parameter. They found no significant change in cumulative caloric response after gentamicin or placebo therapy.
Complications were not mentioned by either study, nor were adverse effects (apart from hearing loss). Quality of life was not an outcome parameter in either study.

DISCUSSION

Summary of main results

Both studies included in this review are prospective, double-blind, placebo-controlled randomised clinical trials on the effect of intratympanic gentamicin on vertigo complaints in Ménière's disease. Both studies found a significant reduction of vertigo after gentamicin therapy in comparison to the placebo treatment.
Stokroos 2004 conclude that the vertiginous attacks completely disappeared after gentamicin therapy, while the attacks significantly reduced in the placebo group.
Postema 2008 also described a decrease of vertigo score in the gentamicin group: nine out of 16 patients did not have any vertigo complaints one year after treatment. In this study there was no decrease of vertigo complaints in the placebo group.
No significant change in hearing loss was reported in Stokroos 2004. Hearing loss increased slightly (average 8.1 ± 18.1 dB) in the gentamicin group in Postema 2008 when compared to the placebo group. However, when regarding the individual hearing scores (in figure 1 of the paper), four patients (25%) had an increase in hearing loss of 20 dB or greater in the gentamicin group, with one patient experiencing an increase in hearing loss of 60 dB.

Overall completeness and applicability of evidence

Both included studies adequately address the questions posed in this review. Both are double-blind, randomised controlled trials on the effect of intratympanic gentamicin on vertigo complaints, studying a total number of 50 patients. Although both studies differ in set-up, they both found a significant reduction in vertiginous complaints in Ménière's disease after gentamicin therapy. However, the actual size of the effect varies greatly between the two included studies. The Stokroos 2004 study describes the largest effect of the intervention with a decrease in vertigo in the placebo

group. The Postema 2008 study describes a smaller effect on vertigo complaints with no noteworthy effect in the placebo group.
An explanation for the difference in effect size for the gentamicin group between the two studies could be the different outcome parameters: Stokroos 2004 uses amount of vertigo attacks per year while Postema 2008 uses a visual analogue scale (VAS) score for vertigo complaints. One could argue that in using an ablative procedure such as intratympanic gentamicin injection residual dizziness complaints are picked up using a VAS score, but are not given in the classic control of vertigo outcome (number of attacks per year). Furthermore, there are some methodological issues with the Stokroos 2004 study as discussed under 'Quality of the evidence' (see below) which could explain the large decrease of vertigo complaints effect in both the treatment group and the placebo group. This is further emphasised by their own follow-up retrospective descriptive study (De Beer 2007) in which complete control of vertigo was achieved in 61.4% of the patients treated with intratympanic gentamicin.
In terms of hearing loss, there are four patients (25%) in the Postema 2008 study with increased hearing loss over 15 dB in the active group compared to no hearing loss in the placebo group. One of these patients experienced an increase of 60 dB which should be considered a major complication. Stokroos 2004 describes no significant hearing loss in their study. The reason for this rather large difference could be that Stokroos 2004 used less gentamicin (1.5 ± 0.51 injections versus four injections) and/or had a larger time interval between two injections (six weeks versus one week) than Postema 2008. This, however, is only speculation.
In the Stokroos 2004 study, a rather large and statistically significant decrease of vertigo attacks is described in the placebo group. Whether this reflects the natural history of the disease with remissions and exacerbations, or a placebo effect, remains unclear.
Given the clinical and methodological heterogeneity, we sought help to assess the advisability of performing a meta-analysis (see 'Acknowledgements'). We concluded that the clinical heterogeneity was too great to perform a meta-analysis; there was clinical heterogeneity concerning the number of injections, the interval between injections, the amount of gentamicin used and the outcome parameters. Also, there was methodological heterogeneity in trial design and quality.

Quality of the evidence

There are some questions regarding the methodology of the Stokroos 2004 study for a number of reasons. Firstly, there is a big difference in the number of vertiginous attacks per year before treatment between the gentamicin group (74 ± 114) and placebo group (25 ± 31). Given the large standard deviation, it seems inappropriate to use mean as a measure of central tendency when the distribution is not normal. The author (R.J. Stokroos) was contacted on this and he stated that there was no significant difference between the two groups, either before or after correction for the outlying value, implying balanced randomisation. However, there may have been inadequate statistical power to detect clinically significant differences and a type III error occurred.
Second, they used a protocol in which gentamicin injections were repeated every six weeks until vertigo disappeared for at least six months or one of the exclusion criteria was met (> 360 mg/12 applications, or > 6 months after last application). This means that if a patient experienced recurrence of vertigo within six months after the last injection, a new injection was given up to a maximum of 12 injections. Given the fact that some patients had a follow-up period of only six months, this type of protocol comprises a 'self-fulfilling prophecy'. Furthermore, it means that all patients had a different follow-up period and a different number of injections, indicating that the intervention might have been different between and within the two different groups. While the beneficial effects of gentamicin could be overestimated in this way, this could also explain the decrease of vertigo attacks in the placebo group. Additionally, a recurrence of vertigo complaints one to two years after gentamicin treatment is mentioned in the 'Discussion' section. This finding is not included in the results after therapy (see also 'Selective reporting'). A follow-up retrospective descriptive study by De Beer 2007 described complete control of vertigo in 61.4% of the patients treated with intratympanic gentamicin.
The Postema 2008 study seems to have been adequately set up, although the follow-up period was less than that advised by the AAO-HNS. As a primary outcome parameter, a four-point subjective symptom scale was used to express vertigo complaints. While control of vertigo is the outcome parameter of choice according to the AAO-HNS, this scale seems to be a subtle tool with which to address vertigo complaints as it also includes dizziness complaints other than the typical vertigo attacks characteristic of Ménière's disease (AAO-HNS 1995). This could be one of the possible explanations for the smaller effect on dizziness complaints in the Postema 2008 study: while the typical vertigo attacks could have disappeared after gentamicin treatment, the patient could still experience complaints of dizziness, possibly due to unilateral labyrinthine hypofunction.
Postema 2008 does not state what size of effect is deemed clinically relevant on which to base the power calculations for the number of participants. When using 90% power for an analysis, however, a minimum difference of means of 1.12 is significant with these numbers of participants. The fact that Postema et al. found a difference in means of 1.3 between the two treatment groups indicates that they had enough power to demonstrate a clinically relevant effect.
Postema 2008 describe a possible relationship between a low vertigo score and a low aural fullness score based on a Pearson's correlation coefficient of r = 0.41. We find this kind of coefficient hard to interpret, however, and a coefficient of r = 0.41 is not particularly indicative for a strong correlation.
We conclude that of the two studies, the Postema 2008 study is of higher quality.

Potential biases in the review process

We used an extensive search strategy, which included more than 14 databases and was subject to no language or publication restrictions, to capture all trials relevant to this review, both published and unpublished. It is possible that studies may have been missed, but unlikely. We were able to contact the primary investigators of both included studies for additional data and information.
The first author of this review (BP) is performing a double-blind randomised controlled trial on intratympanic gentamicin treatment for Ménière's disease at the University Medical Centre of Utrecht, and this has been noted in the 'Declarations of interest' section. We are not aware of any other potential biases in the review process.

Agreements and disagreements with other studies or reviews

A number of reviews have been published on this subject. However, none were restricted to RCTs.
Chia 2004 included a total of 27 studies in their review in which they performed a meta-analysis. There appears to be great clinical, methodological and statistical heterogeneity between the included studies: all descriptive studies involving gentamicin treatment for Ménière's disease (retrospective and prospective) were included in this review, in which a subgroup analysis was performed based on the different protocols used. The authors conclude that gentamicin treatment seems effective in the treatment of Ménière's disease and that the titration method offers the best and most complete vertigo control.
Cohen-Kerem 2004 included 15 prospective and retrospective cohort studies. They concluded that intratympanic injection of gentamicin appears to be effective in treating vertigo complaints and suggest that it is safer to avoid the short, high-dose regimen. They clearly point out the need for an appropriately set up randomised controlled trial.
Diamond 2003 concluded that gentamicin treatment is effective in reducing vertigo complaints. They too point out the need for an appropriately set up randomised controlled trial.
Herraiz 2010, a Spanish article on intratympanic dugs (corticosteroids and gentamicin) for Ménière's disease, also describes a beneficial effect of intratympanic gentamicin on vertigo attacks and includes the Stokroos 2004 study amongst other, mostly descriptive retrospective studies. The Postema 2008 study is not included in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Intratympanic gentamicin treatment for Ménière's disease seems to be an effective therapy in terms of reducing vertigo complaints. Although the Stokroos 2004 study described the largest effect, it is considered of poorer quality than Postema 2008 due to methodological issues. The Postema study is of higher quality but had only one year of follow up.

In the Postema 2008 study, four patients (25%) experienced an increase in hearing loss over 15 dB after gentamicin injection. One of these four patients experienced an increase in hearing loss of 60 dB after gentamicin injections. In the Stokroos 2004 study, no significant hearing loss occurred. This could form an argument that the use of low-dosage gentamicin, with large intervals between injections, is safer in terms of minimising hearing loss. Possible adverse events are not mentioned in either study.

Based on these two studies, we conclude that intratympanic gentamicin can be an effective treatment for vertigo in Ménière's disease, with a potential risk of increased hearing loss. Until further data are published (see 'Implications for research'), we recommend low-dosage gentamicin with large intervals between injections.

Implications for research

Despite an extensive literature search for intervention studies using intratympanic gentamicin for Ménière's disease, only two studies with a total of 50 patients could be included in this review. More data, obtained in a randomised controlled fashion, are needed to clarify the possible beneficial effect of intratympanic gentamicin on vertigo in Ménière's disease, taking into account the natural fluctuating course of this disease with exacerbation and remission.

While the AAO-HNS recommends the number of pure vertigo attacks as an outcome measure, we feel that including other forms of dizziness complaint as an outcome measure (by, for example, a VAS score) could be helpful in determining residual balance complaints after gentamicin injection.

It is imperative that more data become available on the risk of hearing loss associated with intratympanic gentamicin. While most studies report mean difference in hearing loss of an entire group, we feel that recording the number of patients experiencing a significant increase in hearing loss (e.g. 15 dB or more) seems more appropriate. Given that the risk of a significant increase in hearing loss seems quite large (25% in the Postema 2008 study) and the fact that Ménière's disease itself has a natural course of increasing hearing loss, it is paramount that this should be investigated in a randomised, controlled study. Questions remain concerning the amount of gentamicin needed for optimal vertigo control with a minimum risk of hearing loss. A dose-response study seems ideal to answer these questions.

ACKNOWLEDGEMENTS

The authors would like to thank Maroeska Rovers of the Julius Centre for Health Sciences and Primary Care for her help regarding methodological issues, especially in assessing the possibility of performing a meta-analysis.

The authors would like to thank Dr. Postema and Professor Stokroos for their help in answering the questions regarding their studies.

Finally, the authors would like to thank the Cochrane ENT Group, especially Jenny Bellorini for all her help with in the review process and Ece Yilmaz who translated the article by Akkuzu et al.

REFERENCES

References to studies included in this review

Postema 2008 *{published data only}*
Postema RJ, Kingma CM, Wit HP, Albers FW, Van Der Laan BF. Intratympanic gentamicin therapy for control of vertigo in unilateral Meniere's disease: a prospective, double-blind, randomized, placebo-controlled trial. *Acta Oto-Laryngologica* 2008; **128**(8):876–80. [PUBMED: 18607963]

Stokroos 2004 *{published data only}*
Stokroos R, Kingma H. Selective vestibular ablation by intratympanic gentamicin in patients with unilateral active Meniere's disease: a prospective, double-blind, placebo-controlled, randomized clinical trial. *Acta Oto-Laryngologica* 2004;**124**(2): 172–5. [PUBMED: 15072419]

References to studies excluded from this review

Akkuzu 2006 *{published data only}*
Akkuzu B, Ozgirgin N, Ozluoglu LN. Intratympanic treatment in Meniere's disease: the effect of gentamicin and dexamethasone on vertigo control and hearing [Meniere hastalginda intratimpanik tedavi: Gentamisin ve deksametazonun vertigo kontrolu ve isitme uzerine etkisi]. *Kulak Burun Bogaz Ihtisas Dergisi* 2006;**16**(5): 193–9. [PUBMED: 17124437]

De Stefano 2007 *{published data only}*
De Stefano A, Dispenza F, De Donato G, Caruso A, Taibah A, Sanna M. Intratympanic gentamicin: a 1-day protocol treatment for unilateral Meniere's disease. *American Journal of Otolaryngology* 2007;**28**(5):289–93. [PUBMED: 17826528]

Enrique-Gonzaleza 2008 *{published data only}*
Enrique-Gonzaleza A, Sanchez-Ferrandiz N, Perez-Fernandez N. Disability in patients with Meniere's disease following the use of two different treatment modalities: betahistine and intratympanic gentamicin. *Revue de Laryngologie Otologie Rhinologie* 2008;**129**(4-5):249–54. [PUBMED: 19408504]

Quaranta 2001 *{published data only}*
Quaranta A, Scaringi A, Aloidi A, Quaranta N, Salonna I. Intratympanic therapy for Meniere's disease: effect of administration of low concentration of gentamicin. *Acta Oto-Laryngologica* 2001;**121**(3):387–92. [PUBMED: 11425206]

Silverstein 1999 *{published data only}*
Silverstein H, Arruda J, Rosenberg SI, Deems D, Hester TO. Direct round window membrane application of gentamicin in the treatment of Meniere's disease. *Otolaryngology - Head and Neck Surgery* 1999;**120**(5):649–55. [PUBMED: 10229588]

References to ongoing studies

Agarwal 2011 *{unpublished data only}*
Agarwal K, Bronstein A. Transtympanic gentamicin vs. steroids in refractory Meniere's disease. http://clinicaltrials.gov/ct2/show/NCT00802529. [: NCT00802529]

Pullens 2011 *{unpublished data only}*
Pullens B, Van Rooy I, Bruintjes TJD, Klis JFL. Intratympanic gentamicin therapy for Ménière's: a comparison of two regimes. EudraCT database. [: 2006–005913–37]

Additional references

AAO-HNS 1995
Committee on Hearing and Equilibrium. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Menière's disease. American Academy of Otolaryngology - Head and Neck Foundation, Inc. *Otolaryngology - Head and Neck Surgery* 1995;**113**(3):181–5.

Akkuzu 2006
Akkuzu B, Ozgirgin N, Ozluoglu LN. Intratympanic treatment in Meniere's disease: the effect of gentamicin and dexamethasone on vertigo control and hearing [Meniere hastalginda intratimpanik tedavi: Gentamisin ve deksametazonun vertigo kontrolu ve isitme uzerine etkisi.]. *Kulak Burun Bogaz Ihtisas Dergisi* 2006;**16**(5): 193–9. [PUBMED: 17124437]

Alford 1972
Alford BR. Menière's disease: criteria for diagnosis and evaluation of therapy for reporting. Report of subcommittee on equilibrium and its measurement. *Transactions of the American Academy of Ophthalmology and Otolaryngology* 1972;**76**:1462–4.

Balkany 1980
Balkany TJ, Sires B, Arenberg IK. Bilateral aspects of Meniere's disease: an underestimated clinical entity. *Otolaryngologic Clinics of North America* 1980;**13**(4):603–9.

Burgess 2006
Burgess A, Kundu S. Diuretics for Ménière's disease or syndrome. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [Art. No.: CD003599. DOI: 10.1002/14651858.CD003599.pub2]

Carey 2004
Carey J. Intratympanic gentamicin for the treatment of Meniere's disease and other forms of peripheral vertigo. *Otolaryngologic Clinics of North America* 2004;**37**(5):1075–90.

Chia 2004
Chia SH, Gamst AC, Anderson JP, Harris JP. Intratympanic gentamicin therapy for Meniere's disease: a meta-analysis. *Otology & Neurotology* 2004;**25**(4):544–52.

Coelho 2008
Coelho DH, Lalwani AK. Medical management of Meniere's disease. *Laryngoscope* 2008;**118**(6):1099–108.

Cohen-Kerem 2004
Cohen-Kerem R, Kisilevsky V, Einarson TR, Kozer E, Koren G, Rutka JA. Intratympanic gentamicin for Meniere's disease: a meta-analysis. *Laryngoscope* 2004;**114**(12):2085–91. [PUBMED: 15564826]

De Beer 2007
De Beer L, Stokroos R, Kingma H. Intratympanic gentamicin therapy for intractable Meniere's disease. *Acta Oto-Laryngologica* 2007;**127**(6):605–12. [PUBMED: 17503229]

Diamond 2003
Diamond C, O'Connell DA, Hornig JD, Liu R. Systematic review of intratympanic gentamicin in Meniere's disease. *Journal of Otolaryngology* 2003;**32**(6):351–61.

Durland 2005
Durland WF Jr, Pyle GM, Connor NP. Endolymphatic sac decompression as a treatment for Meniere's disease. *Laryngoscope* 2005;**115**(8):1454–7.

Egami 1978
Egami T, Sando I, Black FO. Hypoplasia of the vestibular aqueduct and endolymphatic sac in endolymphatic hydrops. *Otolaryngology* 1978;**86**(2):327–39.

Ghossaini 2006
Ghossaini SN, Wazen JJ. An update on the surgical treatment of Meniere's diseases. *Journal of the American Academy of Audiology* 2006;**17**(1):38–44.

Hallpike 1938
Hallpike CS, Cairns H. Observations on the pathology of Menière's syndrome. *Proceedings of the Royal Society of Medicine* 1938;**31**: 1317–31.

Handbook 2009
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Herraiz 2010
Herraiz C, Miguel Aparicio J, Plaza G. Intratympanic drug delivery for the treatment of inner ear diseases [Via intratimpanica en el tratamiento de patologia de oido interno]. *Acta Otorrinolaringologica Espanola* 2010;**61**(3):225–32. [PUBMED: 20452879]

James 2001
James AL, Burton MJ. Betahistine for Meniere's disease or syndrome. *Cochrane Database of Systematic Reviews* 2001, Issue 1. [Art. No.: CD001873. DOI: 10.1002/14651858.CD001873]

Kimura 1967
Kimura RS. Experimental blockage of the endolymphatic duct and sac and its effect on the inner ear of the guinea pig. A study on endolymphatic hydrops. *Annals of Otology, Rhinology and Laryngology* 1967;**76**(3):664–87.

Kitahara 1991
Kitahara M. Bilateral aspects of Meniere's disease. Meniere's disease with bilateral fluctuant hearing loss. *Acta Oto-laryngologica. Supplementum* 1991;**485**:74–7.

Kotimaki 1999
Kotimaki J, Sorri M, Aantaa E, Nuutinen J. Prevalence of Meniere disease in Finland. *Laryngoscope* 1999;**109**(5):748–53.

Longridge 2005
Longridge NS. Meta-analysis of intratympanic gentamicin. *Otology & Neurotology* 2005;**26**(3):554.

Meniere 1861
Ménière P. Memoire sur les lesions de l'oreille interne donnant lieu à des symptômes de congestion cerebrale apoplectiforme. *Gazette Medicale de Paris* 1861;**16**:597–601.

Monsell 1995b
Monsell EM. New and revised reporting guidelines from the Committee on Hearing and Equilibrium. American Academy of Otolaryngology - Head and Neck Surgery Foundation, Inc. *Otolaryngology - Head and Neck Surgery* 1995;**113**(3):176–8.

Morrison 1995
Morrison AW. Anticipation in Meniere's disease. *Journal of Laryngology and Otology* 1995;**109**(6):499–502.

Nakae 1984
Nakae K, Komatuzaki K. Epidemiological study of Meniere's disease. *Pract Otol (Kyoto)* 1984;**69**:1783–8.

Odkvist 2001
Odkvist L. Pressure treatment versus gentamicin for Meniere's disease. *Acta Oto-Laryngologica* 2001;**121**(2):266–8.

Pearson 1985
Pearson BW, Brackmann DE. Committee on Hearing and Equilibrium guidelines for reporting treatment results in Meniere's disease. *Otolaryngology - Head and Neck Surgery* 1985;**93**(5): 579–81.

Portmann 1980
Portmann G. The old and new in Meniere's disease - over 60 years in retrospect and a look to the future. *Otolaryngologic Clinics of North America* 1980;**13**(4):567–75.

RevMan 2008
The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2008.

Sajjadi 2008
Sajjadi H, Paparella MM. Meniere's disease. *Lancet* 2008;**372** (9636):406–14.

Schuknecht 1957
Schuknecht HF. Ablation therapy in the management of Meniere's disease. *Acta Oto-Laryngologica. Supplement* 1957;**132**:1–42.

Silverstein 1989
Silverstein H, Smouha E, Jones R. Natural history vs. surgery for Meniere's disease. *Otolaryngology - Head and Neck Surgery* 1989; **100**(1):6–16.

Stahle 1978
Stahle J, Stahle C, Arenberg IK. Incidence of Meniere's disease. *Archives of Otolaryngology* 1978;**104**(2):99–102.

Vrabec 2003
Vrabec JT. Herpes simplex virus and Meniere's disease. *Laryngoscope* 2003;**113**(9):1431–8.

Yamakawa 1938
Yamakawa K. Uber die pathologische Veranderung bei einem Menière-Kranken. *Proceedings of the 42nd Annual Meeting of the The Oto-Rhino-Laryngological Society of Japan* 1938;**44**:2310–2.

Yamamoto 1992
Yamamoto E, Mizukami C, Ohmura M. Investigation of the external aperture of the vestibular aqueduct in Meniere's disease by three-dimensional image analysis. *Acta Otolaryngologica* 1992;**112** (1):31–5.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Postema 2008

Methods	Prospective, randomised, double-blind, placebo-controlled trial
Participants	28 patients with Ménière's disease according to the AAO-HNS criteria
Interventions	Weekly injection of 0.4 ml of 30 mg/ml gentamicin versus weekly injection of placebo. The placebo was not specified. A total of 4 injections were given. The injections were applied through a ventilation tube.
Outcomes	Vertigo, hearing loss, aural fullness and tinnitus
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The methods of randomisation were not given. While groups were matched for age and hearing loss, other comparisons were not given.
Allocation concealment?	Yes	The method of randomisation was not given, but it is stated that this was a double-blind, randomised trial in which the hospital pharmacist was the only person who knew whether placebo or gentamicin was given before the end of the study
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	2 patients were lost to follow up. Their data were analysed according to the intention-to-treat principle.
Free of selective reporting?	Yes	None known
Free of other bias?	No	The follow-up period was shorter than the 2-year period advised by the AAO-HNS
AAO-HNS criteria used for the diagnosis of Meniere's disease?	Yes	Grade I

Stokroos 2004

Methods	Prospective, randomised, double-blind, placebo-controlled trial
Participants	22 patients with Ménière's disease according to the AAO-HNS criteria
Interventions	Buffered gentamicin 30 mg/ml injections every 6 weeks until the vertigo complaints disappear. A buffer solution alone was used as a placebo.
Outcomes	Vertigo, hearing loss and caloric response
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The method of randomisation or sequence generation was not described and there seems to be a large difference between the two 2 groups
Allocation concealment?	Yes	It is stated that the hospital pharmacist was the only person who knew whether placebo or gentamicin was given before the end of the study
Blinding? All outcomes	Yes	See above
Incomplete outcome data addressed? All outcomes	No	It is unclear how the number of vertiginous attacks per year is calculated when some participants had only 6 months follow up
Free of selective reporting?	No	One patient had a recurrence of vertigo complaints after gentamicin treatment. This is not mentioned in the 'Results' section
Free of other bias?	No	The follow-up period seems insufficient and is different for each participant, as is the number of injections. The set-up of this trial raises questions regarding the methodology and risk of bias. Using a protocol in which injections are repeated every 6 weeks until the vertigo has disappeared for at least 6 months could lead to a 'self-fulfilling prophecy' when the minimum follow-up period in some participants is only 6 months.

Stokroos 2004 (*Continued*)

AAO-HNS criteria used for the diagnosis of Meniere's disease?	Yes	Grade I

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akkuzu 2006	Allocation: There was no randomisation, blinding or concealment of allocation
De Stefano 2007	Allocation: No concealment of allocation, no blinding, no randomisation
Enrique-Gonzaleza 2008	Allocation: No concealment of allocation, no randomisation, no blinding
Quaranta 2001	Allocation: There was no randomisation, blinding or concealment of allocation
Silverstein 1999	Allocation: No control group, no randomisation, blinding or concealment of allocation

Characteristics of ongoing studies *[ordered by study ID]*

Agarwal 2011

Trial name or title	Transtympanic gentamicin vs. steroids in refractory Ménière's disease
Methods	Randomised controlled trial
Participants	Patients with Ménière's disease
Interventions	Methylprednisolone versus gentamicin
Outcomes	Vertigo complaints
Starting date	April 2009
Contact information	Adolfo M Bronstein, Imperial College London, UK
Notes	http://clinicaltrials.gov/ct2/show/NCT00802529

Pullens 2011

Trial name or title	Intratympanic gentamicin for Meniere's disease: a comparison of two regimes
Methods	Randomised, placebo-controlled trial
Participants	Patients with Ménière's disease
Interventions	Placebo versus 2 x gentamicin versus 4 x gentamicin
Outcomes	Vertigo
Starting date	July 2009
Contact information	B Pullens, ENT Surgery, University Medical Centre Utrecht, Utrecht, Netherlands
Notes	-

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)	CINAHL (EBSCO)
#1 MeSH descriptor Endolymphatic Hydrops explode all trees #2 meniere* #3 endolymphatic near hydrops #4 labyrinth near hydrops #5 labyrinth near syndrome #6 aural near vertigo #7 labyrinth near vertigo #8 cochlea near hydrops #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) #10 MeSH descriptor Gentamicins explode all trees #11 (gentamicin* OR gentamycin* OR garamycin* OR genticin* OR gentavet* OR gmyticin* OR myticin* OR gentamycol*) #12 (sisomicin* OR sisomycin* OR sizomycin* OR sissomycin* OR dehydrogentamicin* OR rickamicin* OR extramycin* OR siseptin* OR pathomycin*) #13 (sch13475 OR (sch near 13475)) #14 "antibiotic 6640" #15 (netilmicin* OR certomycin* OR netromycin* OR netrocin* OR netromicin* OR netillin*) #16 (sch20569 OR (sch near 20569)) #17 (#10 OR #11 OR #12 OR	#1 "Endolymphatic Hydrops" [Mesh] OR meniere* [tiab] OR (ENDOLYMPHATIC [tiab] AND HYDROPS [tiab]) OR (LABYRINTH [tiab] AND HYDROPS [tiab]) OR (LABYRINTH [tiab] AND SYNDROME [tiab]) OR (aural [tiab] AND vertigo [tiab]) OR (labyrinth [tiab] AND vertigo [tiab]) OR (cochlea [tiab] AND hydrops [tiab]) #2 Gentamicins [Mesh] OR (gentamicin* [tiab] OR gentamycin* [tiab] OR garamycin* [tiab] OR genticin* [tiab] OR gentavet* [tiab] OR gmyticin* [tiab] OR myticin* [tiab] OR gentamycol* [tiab] OR sisomicin* [tiab] OR sisomycin* [tiab] OR sizomycin* [tiab] OR sissomycin* [tiab] OR dehydrogentamicin* [tiab] OR rickamicin* [tiab] OR extramycin* [tiab] OR siseptin* [tiab] OR pathomycin* [tiab] OR sch13475 [tiab] OR (sch [tiab] AND 13475 [tiab]) OR "antibiotic 6640" [tiab] OR netilmicin* [tiab] OR certomycin* [tiab] OR netromycin* [tiab] OR netrocin* [tiab] OR netromicin* [tiab] OR netillin* [tiab] OR sch20569 [tiab] OR (sch [tiab] AND 20569 [tiab])	1 meniere disease/ 2 (meniere* or (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).tw. 3 1 or 2 4 gentamicin/ 5 (gentamicin* or gentamycin* or garamycin* or genticin* or gentavet* or gmyticin* or myticin* or gentamycol* or sisomicin* or sisomycin* or sizomycin* or sissomycin* or dehydrogentamicin* or rickamicin* or extramycin* or siseptin* or pathomycin* or sch13475 or (sch and "13475") or "antibiotic 6640" or netilmicin* or certomycin* or netromycin* or netrocin* or netromicin* or netillin* or sch20569 or (sch and "20569")).tw. 6 4 or 5 7 6 and 3	S1 (MH "Meniere's Disease") S2 TX meniere* or (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops) S3 S1 or S2 S4 (MH "Gentamicins") S5 TX gentamicin* or gentamycin* or garamycin* or genticin* or gentavet* or gmyticin* or myticin* or gentamycol* or sisomicin* or sisomycin* or sizomycin* or sissomycin* or dehydrogentamicin* or rickamicin* or extramycin* or siseptin* or pathomycin* or sch13475 or (sch and "13475") or "antibiotic 6640" or netilmicin* or certomycin* or netromycin* or netrocin* or netromicin* or netillin* or sch20569 or (sch and "20569") S6 S4 or S5 S7 S3 and S6

(*Continued*)

#13 OR #14 OR #15 OR #16) #18 (#9 AND #17)	#3 #1 AND #2		
Web of Science	**BIOSIS Previews (Ovid)**	**CAB Abstracts (Ovid)**	**ISRCTN (mRCT)**
#1 TS=(meniere* OR (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)) #2 TS=(gentamicin* or gentamycin* or garamycin* or genticin* or gentavet* or gmyticin* or myticin* or gentamycol* or sisomicin* or sisomycin* or sizomycin* or sissomycin* or dehydrogentamicin* or rickamicin* or extramycin* or siseptin* or pathomycin* or sch13475 or (sch and "13475") or "antibiotic 6640" or netilmicin* or certomycin* or netromycin* or netrocin* or netromicin* or netillin* or sch20569 or (sch and "20569")) #3 #2 AND #1	#1 TS=(meniere* OR (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)) #2 TS=(gentamicin* or gentamycin* or garamycin* or genticin* or gentavet* or gmyticin* or myticin* or gentamycol* or sisomicin* or sisomycin* or sizomycin* or sissomycin* or dehydrogentamicin* or rickamicin* or extramycin* or siseptin* or pathomycin* or sch13475 or (sch and "13475") or "antibiotic 6640" or netilmicin* or certomycin* or netromycin* or netrocin* or netromicin* or netillin* or sch20569 or (sch and "20569")) #3 #2 AND #1	1 (meniere* or (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).tw. 2 (gentamicin* or gentamycin* or garamycin* or genticin* or gentavet* or gmyticin* or myticin* or gentamycol* or sisomicin* or sisomycin* or sizomycin* or sissomycin* or dehydrogentamicin* or rickamicin* or extramycin* or siseptin* or pathomycin* or sch13475 or (sch and "13475") or "antibiotic 6640" or netilmicin* or certomycin* or netromycin* or netrocin* or netromicin* or netillin* or sch20569 or (sch and "20569")).tw. 3 gentamicin/ 4 2 OR 3 5 1 AND 4	meniere% AND (gentamicin OR gentamycin OR garamycin OR genticin OR gentavet OR gmyticin OR myticin OR gentamycol OR sisomicin OR sisomycin OR sizomycin OR sissomycin OR dehydrogentamicin OR rickamicin OR extramycin OR siseptin OR pathomycin)

WHAT'S NEW

Last assessed as up-to-date: 29 June 2010.

Date	Event	Description
7 March 2011	Amended	Amendment made to the review abstract.

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 3, 2011

CONTRIBUTIONS OF AUTHORS

Bas Pullens wrote the protocol. Peter Paul van Benthem initiated the review and revised the protocol. They both performed the study selection. Bas Pullens performed the data extraction and writing up.

DECLARATIONS OF INTEREST

The first author of this review (Pullens) is performing a double-blind, randomised controlled trial on intratympanic gentamicin treatment for Ménière's disease at the University Medical Centre of Utrecht.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*administration & dosage]; Ear, Middle; Gentamicins [*administration & dosage; adverse effects]; Meniere Disease [*drug therapy]; Randomized Controlled Trials as Topic; Syndrome; Vertigo [*drug therapy]

MeSH check words

Humans