The modern management of Ménière's disease

BY JOHN S PHILLIPS

In this article, **John Phillips** considers the evolution of management options for Ménière's disease. Treatment options past and present are discussed, together with an insight into future developments regarding the role of intratympanic steroids.

Ménière's disease can be the source of both fascination and frustration for anyone involved in the care of affected patients due to the enigmatic manner in which this condition presents and the challenges it poses for the management of those affected by its symptoms. Prosper Ménière first described the triad of symptoms bearing his name in 1861. To date a tremendous amount has been written about this condition, but we still do not fully understand the underlying mechanisms responsible for producing its symptoms and this has significantly hampered the development of definitive specialised treatments. Prosper Ménière initially recommended a number of treatments including tonics, debilitants, iron compounds, bitters, soda water (with and without ice), irritant applications, blistering plasters, rubefacient lotions, Croton oil, antimonial ointment, leeches, sulphur waters and Turkish baths, but fortunately medicine has moved on significantly since the 19th Century. Many treatments are available that are directed towards providing symptomatic relief by destroying the inner ear, but this often has consequences in the short term for the hearing and longer term implications when patients develop bilateral disease. As such, interest in developing non-destructive treatments has evolved over the last few decades. However, as often is the case for conditions of unknown aetiology, new treatments come and go. Initial enthusiasm and excitement is often followed by disappointment once a formal dispassionate appraisal of outcome by modern strict research criteria ensues. Both the diagnosis and treatment of Ménière's disease has been the subject of evolving trends in medicine. The once popular procedure of electrocochleography, amongst other tests, has become less favoured for the diagnosis of Ménière's disease[1]. For a number of decades the efficacy of endolymphatic sac surgery has been questioned, particularly since the publication of the Danish sham trial. Betahistine continues to be a frequently prescribed drug for the treatment of Ménière's disease, however the efficacy of this medication remains contentious and a matter for open debate. Support for the administration of diuretics remains lacking. The Meniett device has been identified by a number of systematic reviews of prospective data to fail to provide a positive effect [2]. It has also been reported that hearing levels deteriorate in patients who use this therapy [2]. Barriers to conducting adequately robust research into Ménière's disease include being able to provide adequate blinding and following the condition up for a sufficient period of time to separate symptomatic improvement from the natural history whereby the balance improves and the hearing deteriorates as the condition 'burns out'.

Over the last two decades, there has been increasing use of, and research into, intratympanic remedies for a number of inner ear pathologies, including Ménière's disease. Targeted drug delivery to the inner ear allows the application of a drug at higher than normal concentrations without subjecting the recipient to potential systemic side-effects. For patients with Ménière's disease, a variety of preparations have been administered via the eardrum, including steroids, such as dexamethasone and methylprednisolone; aminoglycosides, such as gentamicin and streptomycin; antiviral agents, such as ganciclovir; and other medications, such as prostaglandin analogues. Over the past decade, there has been increased support for intratympanic steroid therapy, especially

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in situations where there is a fear of damaging any remaining serviceable hearing. Intratympanic gentamicin is certainly an effective treatment for Ménière's disease, but the concerns regarding the application of a destructive treatment remain. Furthermore it has been recently proposed that simple intratympanic gentamicin is ineffective in about 10% of patients [3].

Interest in the role of steroids for the treatment of inner ear diseases originates from work performed by McCabe in the late 1970s. Since then work supporting the theory that Ménière's disease is an immune-mediated disorder of the endolymphatic sac has strengthened the proposed role of steroids for the treatment of Ménière's disease. The elevation of immune complexes, autoimmune responses to type II collagen, autoimmune responses to other inner ear antigens, focal inflammation within the endolymphatic sac, IgG deposits within the endolymphatic sac, autoantibodies to the endolymphatic sac and many other specific and non-specific determinants of immune-mediated disease have all been demonstrated in patients with Ménière's disease [4]. Furthermore, experimental studies have identified glucocorticoid receptors within a variety of crucial inner ear structures, particularly the cochlea, vestibular tissues and spiral ligament.

A Cochrane review appraising the evidence for the effectiveness of intratympanic dexamethasone has been supportive of this treatment modality [4]. Although conducted in a high quality manner, the review included only one long-term, double-blinded placebo-controlled trial [5]. One explanation for the paucity of supportive research may be a consequence of the difficulties performing Ménière's disease research for the reasons already outlined above. In his study, Garduño-Anaya described the perfusion of dexamethasone solution 4mg/ml into the middle ear daily over a five-day period; but many other treatment regimes are undertaken [5]. Garduño-Anaya identified a significant improvement in vertigo control, as well as some improvement in tinnitus, hearing loss and aural fullness in the dexamethasone group compared with the control group at two years' follow-up [5]. In part encouraged by this work, a pharmaceutical company in the United States have patented a sustained-release formulation of dexamethasone called OTO-104. Initial short-term evidence from phase 1 studies have been encouraging with data suggesting a dose-dependent response for a variety of dexamethasone concentrations [6]. Phase 2 studies have been completed in the USA and are ongoing in the UK. Further studies are planned for North America and Europe in 2016.

Whilst in many respects, the management of Ménière's disease has failed to progress despite the advent of new medications, devices and surgical procedures, there is currently hope with regard to more recent developments in the field of delivering intratympanic steroid therapies. One cannot be completely confident of the future role of this mode of therapy, particularly when we reflect on the history of other treatments that were once heralded as potential 'cures' before being dismissed as being ineffective. However, investigation via more robust methods of scientific enquiry will allow us to determine whether intratympanic steroid therapies are truly effective, and if proven to be the case, we will posses some firm data to substantiate these claims. As is the case in many areas of medical research, despite the true aetiology of Ménière's disease currently being elusive, the success of a particular intratympanic treatment for Ménière's disease may have profound implications for our understanding of the fundamental mechanisms of this condition.

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Declaration of competing interests

John Phillips is a member of the scientific advisory committee for Otonomy. John Phillips is currently the chief investigator for the current ongoing UK OTO-104 trial. John Phillips has been reimbursed for costs incurred whilst speaking at international meetings.

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