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Furosemide Distinguishes Central and Peripheral Tinnitus

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Abstract: The response of patients with tinnitus to the suppressive effects of IV furosemide is about 50%. Since furosemide is a drug without known effects on the central nervous system but with well documented effects in the auditory periphery, we hypothesized that it suppressed tinnitus of peripheral origin and that the response rate was due to that selectivity. To test this hypothesis we recruited 14 patients with unilateral tinnitus who had previously undergone either a labyrinthectomy or acoustic neuroma removal in the complaint ear. Tinnitus in these patients would most likely be of central origin. The first 12 patients tested were negative in response to IV furosemide as compared to the 50% response rate already documented. The last two patients had acoustic neuromas removed and were positive to IV furosemide, meaning that their tinnitus was suppressed. Examination of the case records of these latter two patients revealed that their cochlear portion of the VIIIn had been spared during surgery. We therefore suggest that IV furosemide selectively suppresses tinnitus of peripheral etiology.

INTRODUCTION

The side effects of a drug may be constrained or its selectivity enhanced if the drug acts only on a process unique to the target system. However, this is generally difficult to achieve but in the case of loop diuretics (such as furosemide, bumetanide, and ethacrynic acid), those agents seem to act only in the inner ear and the kidney. In the case of the inner ear, the loop diuretics and not other diuretics powerfully reduce the endocochlear potential (EP), a fact which is unique to the human inner ear.

There is direct correlation between reduction in EP and reduction in VIIIn firing rates.[1] Although it is not known whether in human tinnitus the VIIIn firing rates are increased, some authors have demonstrated that salicylate administration in doses presumed to cause tinnitus produces increased firing rates in the VIIIn afferent and efferent cochlear neurons.[2,3] Therefore, agents such as furosemide which decrease firing rates through an effect on the endocochlear potential (EP) might prove to be a palliative in tinnitus.

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Our first test of furosemide was by intravenous injection at an 80 mg level in a population of 40 patients with known tinnitus. These patients were injected with either furosemide or another diuretic, one without effects known to the human inner ear. We used two diuretics rather than a placebo so that we could simulate the urge to urinate. This way the patients were not able to distinguish furosemide from the other diuretic used. Since the patients were not informed as to which drug they had been given and since both produced frequent urination, the effectiveness of furosemide could be assessed without bias. We measured the changes in the severity or loudness of the patient's tinnitus after the administration of the diuretics using two different methods: 1) by a self-rating or subjective scale, and 2) by audiometric loudness matching procedures. Of the 40 patients in this trial, 20 reported a suppression of their tinnitus with furosemide (a lessening of the severity and/or loudness of their tinnitus) (Fig.1).

The next step was to determine if furosemide would work when given orally and what the effective dosage would be. To do this 12 of the 20 patients whose tinnitus was suppressed by furosemide were given various dosages of oral furosemide. It is important to emphasize that these patients were already positive to an IV furosemide injection. If the response to the IV furosemide challenge was negative, no oral furosemide was indicated. All 12

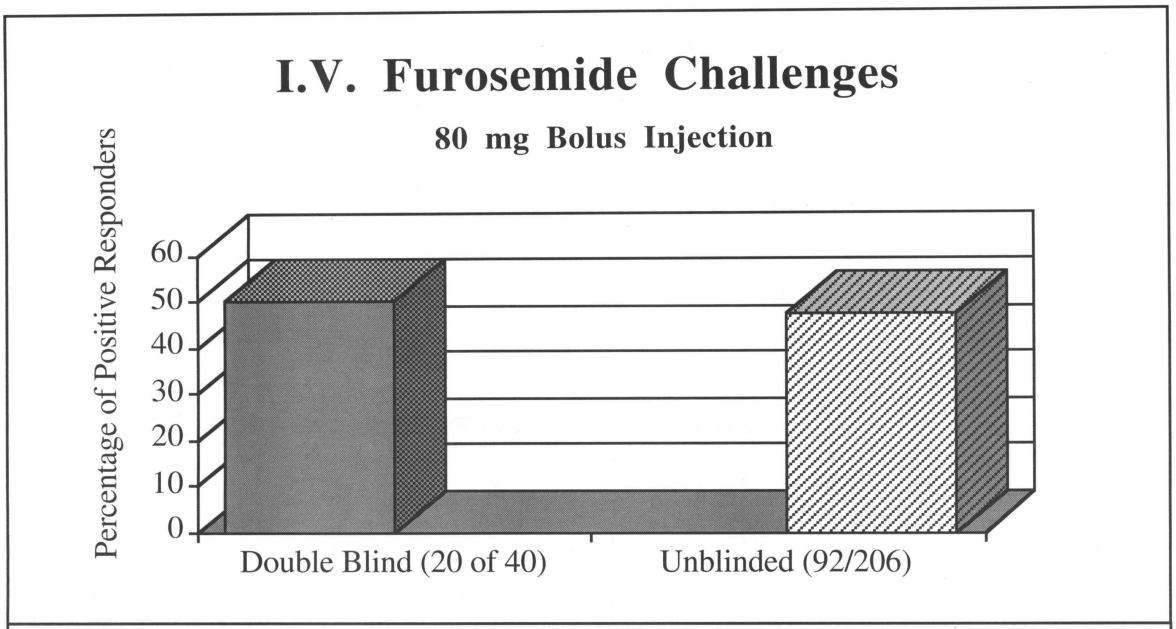

Figure 1. Furosemide challenge-80 mg administered intravenously over a two minute period. Both a subjective evaluation and tinnitus loudness matching done for the next 20 minutes. Unblinded tinnitus clinic patients were referred for the challenge.

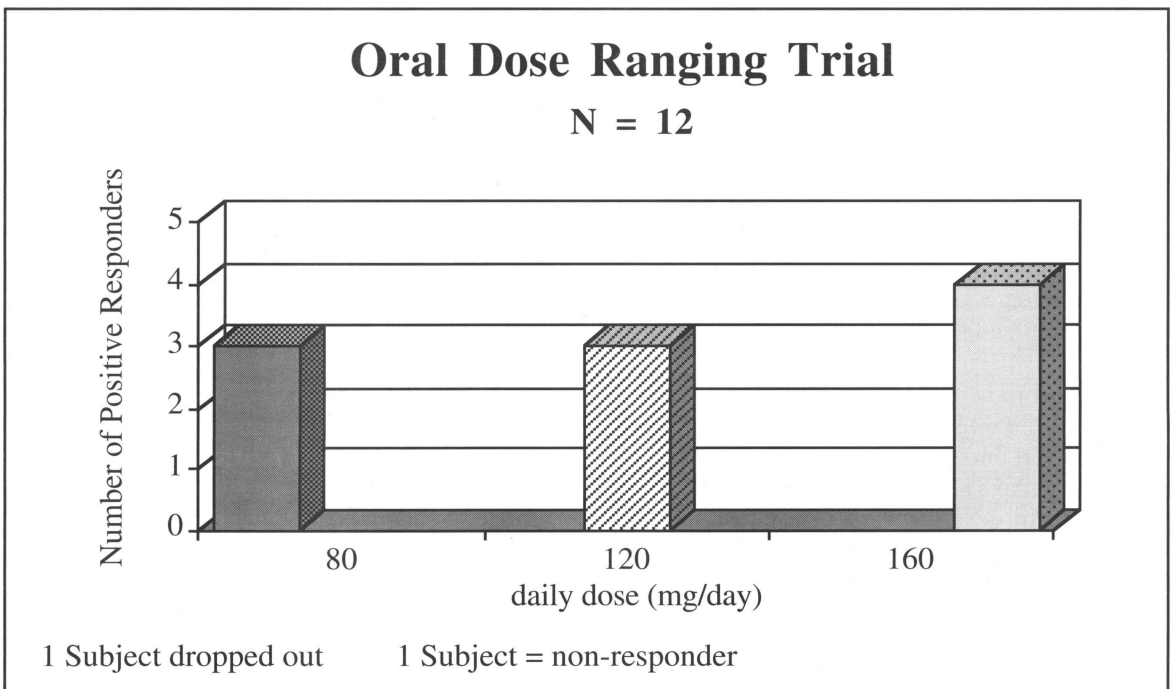

Figure 2. Furosemide was administered at 40 mg tablets two, three, or four times a day for five days. All patients were started on 80 mg per day if there was no response the dose was increased after five days to 120 mg and again after five days to 160 mg if indicated.

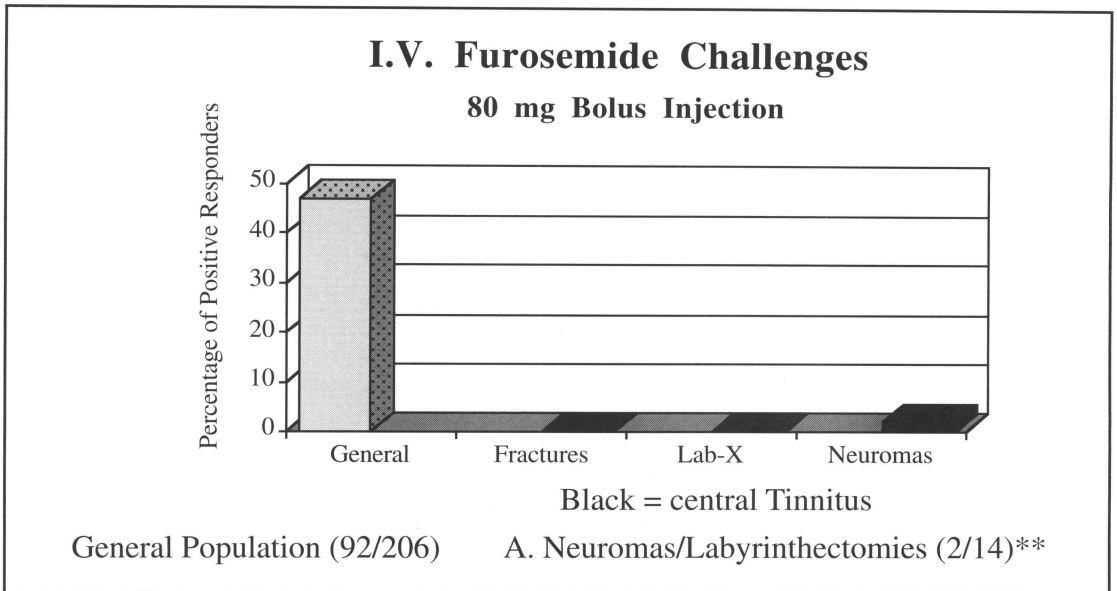

Figure 3. The two patients who were positive to furosemide challenge had normal hearing prior to their surgery for acoustic neuromas. The difference between the general population and the central tinnitus patients and their responses to furosemide were significant ($P<0.05$ by Fisher's exact test).

patients were started on 80 mg per day (two 40 mg tablets per day) for five days. Three of the twelve patients responded at this dose level. For the remaining patients, the dose was increased to 120 mg (three 40 mg tablets per day) for five days. An additional three patients responded at this dose. The remaining six patients were given a 160 mg (four 40 mg tablets per day) for five days and four of these six patients responded at that level. Therefore, a total of 10 of the 12 original patients were positive for oral furosemide (Figure 2).

In fact, one of the patients dropped out of the trial so that it could be said that 10 of 11 patients enjoyed suppression of their tinnitus by oral furosemide. Having realized the suppressive effect from the intravenous drug, these patients approached the oral medication with a more positive attitude and with the hope that their tinnitus would be relieved. This positive attitude or belief that this drug was going to have a beneficial effect on their complaint is very important, and may even bias some patient's reports on the effectiveness of the medication. On the other hand, using the injection to pre-select patients for trial with oral furosemide insures that only those patients who are actually sensitive to this medication will be given oral furosemide.

Since our early trials in the mid 1980's, over 800 patients have come to the Tinnitus Clinic at Tulane University Medical Center. Of these 180 have received the IV furosemide challenge, and of these 85 reacted positively to it and were given prescriptions for oral furosemide. As can be seen from the numbers of our original response rate of about 50% has held up over the years (Figure 3). Furosemide has essentially no effects in the brain and therefore probably has effects only on tinnitus that comes from the inner ear and not from the brain (i.e. peripheral tinnitus). It is possible that 50% of tinnitus sufferers have tinnitus that comes from the brain or a more central origin. However, the conventional wisdom is that most tinnitus comes from the inner ear.

MATERIAL & METHODS

We recognize that patients who have tinnitus that appears to be coming from an ear that has no serviceable hearing represent a very special kind of tinnitus sufferer. If our idea that furosemide only works on peripheral types of tinnitus was true then furosemide should have no effect if given to patients who have tinnitus in a completely deaf ear. Fourteen patients were identified with tinnitus coming from an ear that had a previous destructive surgery or temporal bone fracture (Figure 4).

These 14 patients were given an injection of furosemide as reported above and 12 of 14 (86%) reported no change in their tinnitus as predicted. However, two patients (14%) reported an improvement in their tinnitus complaint following the injection. This improvement was documented using a subjective rating scale in which the patient was asked to rate the amount of change in either the perceived loudness or the severity of their tinnitus

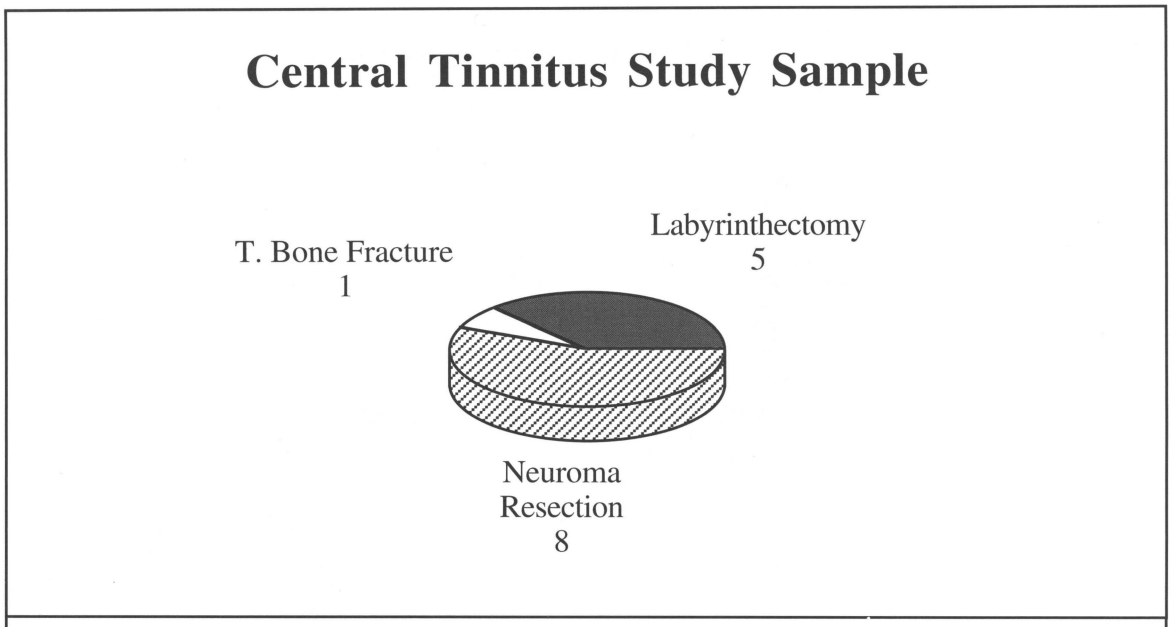

Figure 4. Distribution of patients in the central tinnitus population

following the bolus injection. We previously reported that subjective rating changes do correspond with changes in audiometric loudness matches during IV challenges.[4] The 14% positive response rate is to be contrasted with an improvement rate of about 50% among randomly tested subjects who are complaining of tinnitus of apparent peripheral or inner origin.

DISCUSSION

The patients with presumed central tinnitus who responded positively to IV furosemide were patients with acoustic neuroma whose cochlear portion of the VIIIn was left intact during surgery and who had normal hearing sensitivity prior to surgery. It may be that these tumors were producing cochlear side effects such as tinnitus resulting in a condition referred to as "the disconnected ear".[5] Several authors have been able to document presence of transiently evoked otoacoustic emissions, distortion product otoacoustic emissions, and electrocochleography in patients with a profound sensorineural hearing loss secondary to a large acoustic neuroma.[5-9] They interpreted their results to indicate an intact and functional cochlea in the presence of neural pathology. Numerous other investigators have confirmed the presence of intact cochlear function in the presence of VIIIn pathology.[5,7,9-13] The fact that only two of eight postoperative acoustic neuroma subjects responded positively to furosemide may be a result of individual tumor morphology.[8] Unfortunately, at the time that our two acoustic neuroma patients underwent the postoperative IV furosemide challenge we did not have emissions equipment available which we believe is necessary to validate their cochlear status.

Given the fact that both of these patients had documented normal hearing sensitivity prior to resection of their tumors, it is possible that their positive responses to furosemide resulted from cochlear-based effects of the acoustic neuromas. It has been hypothesized that tinnitus might result from "deafferentation hypersensitivity" secondary to acoustic neuroma removal.[14] As has been reported in a similar way with regard to electrical stimulation of the cochlear promontory, tinnitus of central neural origin may be suppressed with electrical promontory stimulation. Tinnitus of presumed neural origin (as in acoustic neuroma) cannot be suppressed.[15] In retrospect, it may be that labyrinthectomized patients and those having suffered a transverse temporal bone fracture are not pathophysiologically equivalent to postoperative acoustic neuroma patients. Labyrinthectomies and transverse temporal bone fractures both directly affect cochlear morphology and functional status. Acoustic neuroma resection, however, may leave cochlear morphology and functional status unaffected. Although they may share absence of hearing as a common denominator, the mechanism for tinnitus generation among these three etiologies may not be the same and therefore their response to peripherally orientated treatments may not be the same. This may very well explain the positive response to furosemide seen in two patients with tinnitus of presumed central origin.

CONCLUSIONS

1) IV furosemide challenge seems to distinguish tinnitus of central vs. peripheral etiology.

2) The ability of furosemide to distinguish these forms of tinnitus may prove useful in helping the surgeon to decide whether or not to perform VIIIn section or labyrinthectomy in the treatment of intractable tinnitus.

3) In the armamentarium for the medical treatment of tinnitus, furosemide may be useful in the palliation of tinnitus of peripheral origin whereas other drugs may be useful for tinnitus of central origin (e.g. Benzodiazepines, and vigabatrin).

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