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Calcium antagonists in the treatment of sudden deafness

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Summary. In the treatment of patients with sudden deafness, we found no significant difference between an oral calcium antagonist (nifedipine) and intravenous naftidrofuryl given concomitantly with vitamin A, vitamin E, and zinc. This prospective randomized study in 50 patients again shows that recovery to useful hearing levels tends to be spontaneous and independent of the type of medical treatment given. Irrespective of their capability to prevent contractions of cerebral vascular smooth muscle induced by neurotransmitter and vasoconstrictor substances and of their rheological properties, currently available calcium antagonists of the nifedipine type are unable to enhance hearing recovery at the present time.

Key words: Calcium antagonists – Treatment – Sudden deafness

Introduction

Sudden sensorineural hearing loss (SHL) may result from vascular dysfunction of the inner ear. In the past, most treatments have been used in an attempt to improve cochlear blood flow. More recently, the clinical effectiveness of calcium antagonists has been shown in the management of central and peripheral vasospastic syndromes. Such findings have indicated that these drugs might be useful in the treatment of SHL.

At the present time, more than a dozen available drugs have been described as "calcium antagonists". These agents represent a very heterogeneous group of preparations, which have dissimilar pharmacodynamic and pharmacokinetic properties acting at different sites. Of primary interest are the class A calcium antagonists [3], or the 4–5 didydropyridines, such as nifedipine, nimodipine, diltiazem, and verapamil. The class B antagonists are less potent and less specific, and include such drugs as cinnarizine and flunarizine (Fig. 1). Their common denominator is a reduction of calcium ions needed to maintain or induce specific cellular activities [6].

The calcium antagonists interfere with the excitation-induced inward displacement of calcium ions. The so-called "potential sensitive" or slow channels are their primary target, and to a lesser degree the "receptor-operated" channels of the smooth muscle [6]. Other pharmacological properties of the calcium antagonists include local anesthetic activity, alpha-adrenergic blocking activity, antihistaminic effects, phosphodiesterase inhibition, calmodulin inhibition, Ca^{++}-ATPase stimulation, and inhibition of oxidative phosphorylation [6].

Clinical trials have shown that calcium antagonists exhibit great organ and tissue selectivity and that even within one chemical group there are large differences between analogues in the intensity and localization for the effects produced. Moreover, various calcium antagonists will exert different effects in vessels of different anatomical origins [6]. In general, the calcium antagonists prevent vascular smooth muscle contractions induced by neurotransmitter and vasoconstrictor substances [12]. The calcium antagonists also exhibit rheological properties by stabilizing the thrombocyte membrane [7]. During ischemia, calcium antagonists counteract the depletion of the intracellular ATP-pool and prevent deleterious calcium overload of the cell during reperfusion [3]. As a result of these pharmacological properties, the calcium antagonists make theoretically ideal drugs to use in therapeutic trials in patients with SHL.

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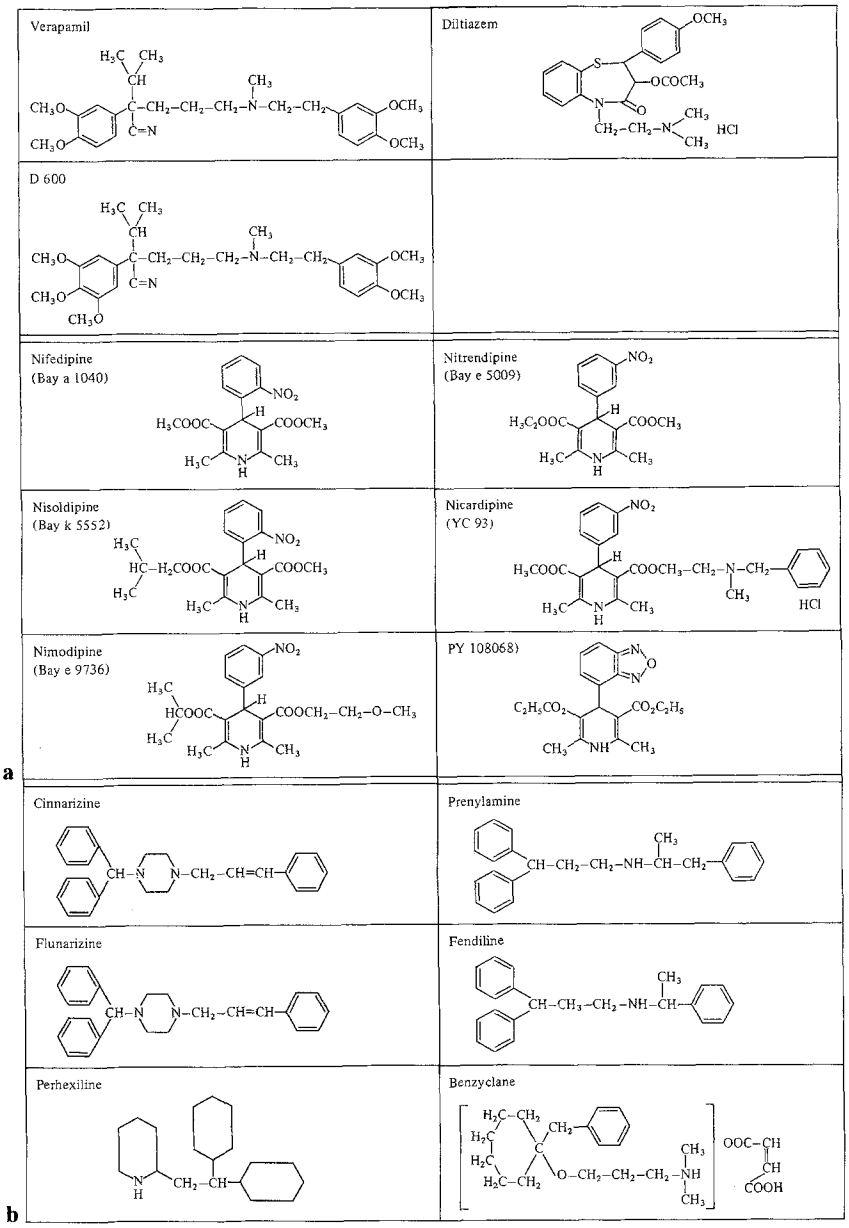

Fig. 1a, b. Structures of selected calcium antagonists. **a** Potent and specific calcium channel blockers. **b** less potent and less specific antagonists

Materials and methods

In a prospective randomized study, 50 patients (26 males, 24 females) with SHL without vestibular involvement were critically evaluated between January 1984 and December 1984. All patients had complete histories and physical examinations, a medical consultation, laboratory studies, mastoid and chest X-rays, sequential audiograms and a vestibular examination including a caloric test. Viral studies were not included. The patients were then stratified into two groups. Group 1 ($n = 25$) was treated with 60 mg nifedipine given orally daily and 500 ml parenteral normal saline. Group 2 received i.v. 600 mg naftidrofuryl in 500 ml normal saline each day, as well as oral 200 mg naftidrofuryl, 30,000 IU vitamin A, 70 mg vitamin E, and 50 mg zinc.

Results

The mean age of the patients in group 1 was 46.9 ± 19.7 years. There were 12 left and 13 right ears involved. Concomitant findings in these patients included hypertensive heart disease ($n = 4$), gout ($n = 1$), diabetes ($n = 2$), and preceding upper respiratory infections (URI; $n = 3$). The interval between SHL and therapy was 8.3 ± 7.6 days, and the mean duration of therapy was 16.2 ± 6 days. In group 2, the mean age of the patients was 46 ± 16.4 years. There were 11 left and 14 right ears involved. Concomitant findings were hypertensive heart disease ($n = 5$),

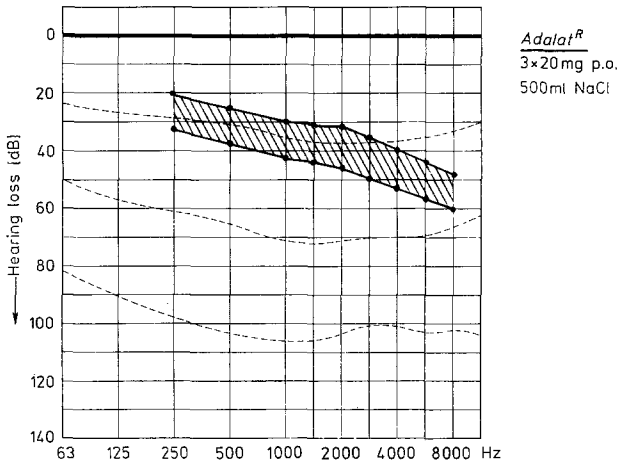

Fig. 2. Hearing loss and recovery *(dotted line)* after treatment with the calcium antagonist nifedipine (Adalat)

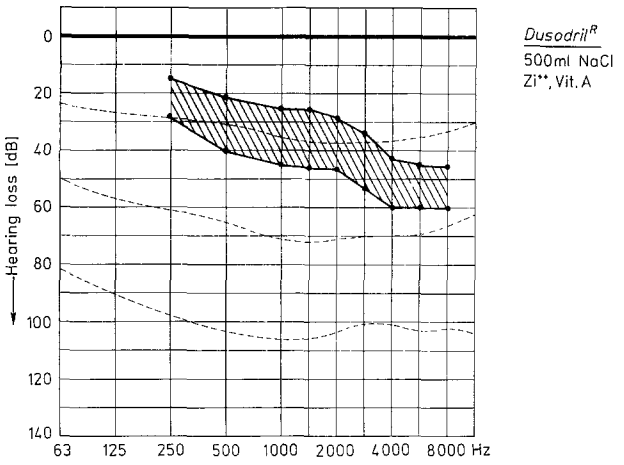

Fig. 3. Hearing loss and recovery *(dotted line)* after treatment with naftidrofuryl (Dusodril)

hypothyroidism ($n = 1$), diabetes ($n = 2$), and preceding URI ($n = 3$). The interval between therapy and SHL was 7.3 ± 8.6 days, and the mean duration of therapy was 16.7 ± 4.9 days. There was no complete deafness of the involved ear in either group after SHL.

The average hearing recovered in group 1 for 500, 1000, and 2000 Hz was 11.8 ± 10.79 dB, and in group 2 was 17.1 ± 18.9 dB. However, the difference in recovery between the two groups was not significant ($t = 1.147$). The average hearing loss and recovery for all frequencies is shown for the patients treated with nifedipine in Fig. 2, and for the patients treated with naftidrofuryl in Fig. 3. Statistical analysis using the *t*-test, U-test (Wilcoxon) or the H-test (Kruskal and Wallis) for all frequencies revealed no significant difference for the recovery rate between either group of patients.

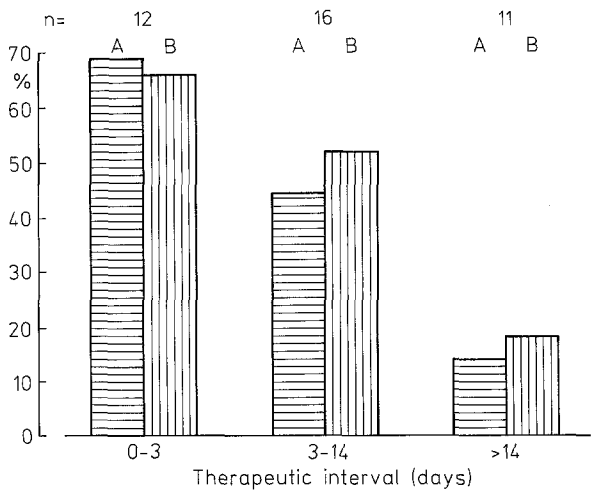

Fig. 4. Bar-gram showing recovery of hearing immediately after therapy (**A**) and 6–24 months later (**B**) (without any further medication being given) as a function of the interval between initial hearing loss and when therapy was actually given

Discussion

In a previous prospective study, we examined the effect of a low-molecular dextran and sodium bicarbonate therapy in patients with SHL [11]. We concluded that the age of the patient had no influence on immediate recovery, but hearing levels were prone to deteriorate within 2 years in older patients. As shown in Fig. 4, early treatment resulted in better recovery ($P < 0.05$) and patients with more severe damage to the cochlea recovered best when treated early. Nevertheless, this study showed that recovery was a function of time. Additionally, some individuals recovered without any further treatment within 6–24 months. We compared our recovery statistics with those published by other authors. Haug et al. [5] recommended stellate ganglion block as treatment for SHL, while Fisch [2] advised carbogen inhalations. Other methods included the use by Otto and Kellerhals [10] of low-molecular dextrans and the administration of nimodipine and pentoxifylline by Handrock and Berghaus [4]. None of the treatment regimens used was better than the ones we evaluated and all fall within the range of spontaneous recovery rates previously reported [1, 2, 8, 9, 12, 13].

Certain questions remain unanswered. We are currently unable to explain why calcium antagonists of the nifedipine type lack any beneficial effect in patients with SHL and why the recovery rates were even slightly worse than in controls. There are several possible explanations. One possibility is that treatment was started too late after cochlear damage had occurred. Another explanation is that nifedipine

has no beneficial effect on cochlear microcirculation. Nifedipine has a well-documented lowering effect on blood pressure in patients with hypertension, but normotensive patients in our study were not affected. However, there is also a slight chance that high doses of nifedipine interfere with membrane permeability during the bioelectrical phenomenon of acoustical stimulation, or exert a negative effect on efferent synaptic transmission.

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