ings, or both. Once, however, this dangerous period had passed patients remained relatively free of sores until 10-15 years after injury. Older patients are known to be at greater risk of developing sores,¹⁵ but we have shown that the duration of the paralysis is also important. Thus a 40 year old patient who has been paralysed for 15 years and is suffering from urinary tract infection, osteoporosis, immobility, obesity, and atrophy of the tissues due to continuous sitting is plainly not as fit as the 40 year old who first becomes paralysed at this age.

The social state of the patient is another important factor. In our series of patients with chronic sores 50 were single and 25 married, which contrasts with the pattern recorded at this unit in 1964.¹⁶ The single paraplegic patient is particularly at risk, and some of our patients who had remained well for 15 years developed sores when the spouse or caring relative died or became ill themselves.

Many patients admitted to hospital with chronic sores might have avoided admission if appropriate advice had been given. Most had developed their severe sores after prolonged sitting because their medical and nursing attendants misguidedly thought that sores were caused by going to bed and would heal if the patient sat in a chair. Other patients had been told that as the sore was on the sacrum there would be no direct pressure on it and they could continue to sit. Medical attendants were often unaware of the risks that shearing strains place on the skin over the sacrum when patients sit in a chair or transfer from bed to chair.

Twenty seven patients developed their sores while in hospital and, although it may be argued that all were ill before they were admitted, eight developed their sores after admission for social reasons. Thus inadequate nursing care may have contributed to the development of their sores. Versluysen reported that 90 out of 283 patients admitted to an orthopaedic ward as an emergency after an accident or with non-urgent conditions developed sores, 68 of them within 14 days.¹⁵ The reasons why patients develop sores in hospital have been attributed to poor routine care in district general hospitals, where patients may be left lying on their backs and not turned.¹¹ It is not surprising,

therefore, that paraplegic patients develop sores, because they cannot turn themselves; furthermore, because their skin is numb they are unable to appreciate that they have developed a sore and do not complain of pain. Clearly, all the medical staff who are responsible for the management of these patients must be aware of the factors which predispose to the development of sores and ensure that routine nursing care takes these into account. Similarly, both the patients and those responsible for looking after them at home must be well briefed so that the risks of developing this distressing complication may be minimised.

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β Blockers and loss of hearing

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Abstract

Loss of hearing in a 43 year old man during treatment with metoprolol was dose related and disappeared within a few months after the drug had been stopped. The hearing impairment was of mixed type, with an air bone gap without any disorder of the middle ear observable by conventional clinical methods. Similar scattered reports from international sources on loss of hearing during treatment with β blockers are also presented.

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Introduction

β Adrenoceptor blocking drugs play a great part in the treatment of common cardiovascular diseases such as angina pectoris and hypertension.¹ The efficiency and limitations of these drugs are well known. One side effect, however, seems to have been forgotten since a thorough report appeared on practolol and deafness.² Here we report loss of hearing during treatment with metoprolol and discuss similar scattered reports from international sources.

Patient and methods

A 29 year old man was admitted to hospital in 1969 for hypertension and glucosuria. Blood pressure was 160/120 mm Hg despite treatment with chlorthalidone 50 mg daily during the previous two months. Intra-arterial blood pressure was normal, and glucosuria disappeared when the drug was stopped. In 1970 he was investigated further. X ray films of the heart were normal. Angiography showed minor, possibly hypertensive, changes of the intrarenal arteries. Fundoscopic examination and tests for phaeochromocytoma and primary hyper-

aldosteronism yielded normal results. He was again discharged without treatment.

In 1977 his blood pressure was permanently raised, and increasing doses of propranolol (up to 480 mg daily) were prescribed (figure). Propranolol was replaced by metoprolol in December 1977. Blood pressure was well under control but he himself increased the dosage of the drug to get rid of palpitations of the heart. In 1978 he noticed loss of hearing and short attacks of dizziness. The drug was stopped in March 1982, after which he noticed a gradual improvement in hearing during the following months.

Pure tone audiometry was performed with clinical audiometers of the type Madsen OB 70 until 1981, thereafter of the type Madsen Micro-5. They were equipped with matched TDH-39 earphones with MC 41/AR cushions calibrated according to ISO-R389-1964. Measurements of bone conduction were performed with Radioear B-70 bone telephone, calibrated according to standards adopted by the Swedish Technical Audiological Society. Speech audiometry was performed with word lists³ presented from a tape recorder (Revox A77) and passed through the speech channel of the audiometer. Acoustic impedance was measured with a Grason-Stadler 1723 middle ear analyser with a probe tone frequency of 220 Hz at 90 db sound pressure level.

The concentration of metoprolol was determined by modified high pressure liquid chromatography according to Pritchard *et al.*,⁴ Yee *et al.*,⁵ and Scales and Copsey.⁶ Hydroxylation capacity was determined by measuring debrisoquine and 4-hydroxydebrisoquine concentrations in a urine sample.⁷

Results

The first hearing test was performed in 1970 and showed normal hearing except for a slight sensorineural high tone loss of hearing. A second pure tone audiogram in October 1978 showed a bilateral, symmetrical, quite extensive loss of hearing of mainly conductive type. In November 1980 pure tone audiometry showed loss of hearing combined type bilaterally, somewhat more pronounced on the right side. Speech audiometry accorded with pure tone audiometry and tympanometry, and stapedius reflex thresholds were normal bilaterally (85-95 db). Pure tone audiometry in February 1979 (200 mg metoprolol), November 1980 (400 mg), and October 1982 (drug free) showed dose related loss of hearing. A pure tone audiogram in March 1983 confirmed normal hearing except for the sensorineural high tone loss of hearing already seen in 1970.

In a provocation test (28 November to 12 December 1983) he received metoprolol 100 mg twice daily. During provocation the thresholds were within the normal range but raised 5-10 db. The same results were found 10 days after provocation, but after another three weeks the thresholds were the same as before provocation. During provocation he experienced some dizziness but no loss of hearing. A positive Romberg's test with a tendency to fall forwards and an abnormal finger to nose test on the right side could be shown but not at a second examination four weeks after the provocation.

Hydroxylation capacity was within the normal range, and plasma metoprolol concentrations measured on the same day as the hearing test was performed during provocation were even found to be low (maximal concentration = 66 ng/ml).

Discussion

In our patient varying loss of hearing appeared during treatment with metoprolol and disappeared when the drug was stopped. With one exception the extent of loss of hearing was related to the dose of metoprolol. The exception was in October 1978, when the daily dose was 200 mg. One explanation of the quite extensive loss of hearing on this occasion might have been that he was taking a higher dose than had been prescribed; it might alternatively have been a delayed effect of the higher dose (600 mg daily) that had been taken about one month earlier. The rather slow return to normal of the thresholds after the provocation test supports the second theory. The raised thresholds during provocation were for each frequency close to the methodological error. As, however, the thresholds for almost all frequencies were raised, the slight loss of hearing may be assumed to have been real.

The combination of a mainly conductive loss of hearing with

Relation between daily dose of β blocker, blood pressure, and timing of hearing tests in a patient with reversible loss of hearing. (Arrows indicate timing of pure tone audiometry measurements.)

normal impedance audiometry is difficult to explain. Air bone gap was observed regularly when audiometry showed loss of hearing. Furthermore, speech audiometry showed well preserved discrimination ability indicating a normal or close to normal cochlear function in the midfrequencies.

Loss of hearing of mixed type during treatment with practolol has been reported in some cases,² but often due to serous otitis media. In our patient, however, serous otitis media was excluded by impedance audiometry and otomicroscopy. Some kind of arthropathy in the joints of the ossicular chain might have caused the peculiar audiometric results. Arthritis has been observed in connection with the use of β blockers,⁸ and arthritic changes in the joints of the middle ear bones have been reported,⁹ although not certainly connected with loss of hearing. β Blockers have been reported to unmask or precipitate myasthenia gravis and to produce diplopia in otherwise neurologically normal patients.¹⁰ Dysfunction of the stapedius muscle in our case would not be shown by the tests performed. Dysfunction of the stapedius muscle of the kind seen in myasthenia gravis¹¹ would not, however, cause loss of hearing.

Even though a computer based search for references (Medline) was a failure, our patient's case is evidently not unique. At the time when practolol was much prescribed several cases of loss of hearing were reported to the British Committee on Safety of Medicines, and 36 cases of deafness and tinnitus were reported in 1964-82 during treatment with various β blocking drugs (Weber, unpublished findings, 1984). With the exception of some cases associated with practolol, there are only two reports of hearing loss during treatment with β blockers in the files of the Swedish Adverse Drug Reactions Advisory Committee. One is on a 59 year old man who was treated with propranolol 40 mg daily for angina and hypertension. Impaired hearing was noticed on admission 40 days later, and after another three weeks he was also suffering from vertigo. Hearing acuity slowly improved during the three months after the drug had been stopped. The second report is on a 60 year old man, who was treated initially with propranolol, chlorthalidone, and hydralazine for hypertension. After several months propranolol was replaced by metoprolol. About four months later he suddenly experienced right ear tinnitus, and hearing tests showed neurogenic loss of hearing. No more details are given.

During the search for further references we found a case report¹² on a 57 year old man with coronary heart disease who had developed sudden deafness during concomitant treatment with nadolol (a non-selective β blocker), aspirin, and occasional flurazepam.

The mechanism, or mechanisms, by which β blocking drugs exert their effect on hearing ability does not seem to be easily explained by their different pharmacological properties. Impaired hearing during β blocking treatment also seems to be quite rare. We, however, were not aware of the connection between drug treatment and loss of hearing until the treatment was stopped, which suggests that this side effect is probably underreported today. We think this relation merits further investigation.

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Influence of non-steroidal anti-inflammatory drugs on diuretic treatment of mild to moderate essential hypertension

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Abstract

In an open triple crossover study in 10 patients with mild to moderate essential hypertension the influence was investigated of adding indomethacin 50 mg, naproxen 250 mg, or sulindac 200 mg, each twice daily for four weeks, to diuretic treatment with hydrochlorothiazide 50 mg a day.

After two weeks' treatment with indomethacin a slight increase in blood pressure was observed, whereas both sulindac and naproxen tended to enhance the antihypertensive effect of hydrochlorothiazide. After treatment for four weeks, however, the effects of all three drugs on blood pressure appeared to be blunted. Furthermore, body weight increased significantly during treatment with indomethacin but not during treatment with naproxen or sulindac. No significant changes were found for various biochemical variables, including concentrations of plasma electrolytes and serum creatinine and albumin, plasma renin activity, plasma aldosterone concentration, and 24 hour urinary excretion of sodium and potassium, with the exception, however, of an increase in plasma potassium concentration during treatment with indomethacin.

These observations suggest that the interaction of indomethacin, naproxen, and sulindac with diuretic treatment in mild to moderate essential hypertension is transient and of minor clinical importance.

Introduction

Although several investigations have shown that inhibition of the synthesis of prostaglandins in the kidney by non-steroidal anti-inflammatory drugs can blunt the natriuretic response during

diuretic treatment, particularly in states of high angiotensin II concentrations,¹⁻⁶ published findings have agreed less on whether non-steroidal anti-inflammatory drugs can influence, in a clinically important way, the antihypertensive effect of thiazide diuretics. Several authors have reported attenuation of the effect of thiazide diuretics and other antihypertensive drugs on blood pressure as a result of indomethacin treatment in patients with hypertension.⁷⁻¹¹ For instance, when indomethacin was added to various antihypertensive drugs an increase of 14/6 mm Hg in supine blood pressure was observed⁸ and even of 13/9 mm Hg in patients treated with only thiazide diuretics.⁷ On the other hand, Steiness found only a slight (and not significant) increase in blood pressure during treatment with indomethacin but an additional decrease during treatment with sulindac.¹² As sulindac is supposed to have less effect on renal prostaglandin synthesis than any other non-steroidal anti-inflammatory drug,^{13,14} it might have advantages in hypertensive patients receiving diuretics who need non-steroidal anti-inflammatory drugs for osteoarthritis or other rheumatic diseases.

Here we report the results of the treatment of 10 patients with essential hypertension with hydrochlorothiazide alone and hydrochlorothiazide in combination with indomethacin, naproxen, or sulindac.

Patients and methods

Ten patients (eight men, two women), aged 21-65 (mean (SD) 48.4 (11.3)) years, with essential hypertension, were selected from the outpatient clinic for study. We included patients with untreated supine diastolic blood pressure greater than 85 mm Hg. None of the patients had secondary hypertension, signs or symptoms of congestive heart failure, aortic valve dysfunction, or history of peptic ulcer. All patients gave their informed consent, and the local ethics committee approved the protocol.

The trial was designed as an open triple crossover study lasting for 28 weeks. After a washout period of four to eight weeks, in which all other antihypertensive treatment was stopped, treatment with hydrochlorothiazide 50 mg a day was started. Then, successively, indomethacin 50 mg twice daily, naproxen 250 mg twice daily, and sulindac 200 mg twice daily were added for four weeks in random sequence, and always with an intermediate washout period of four weeks in which hydrochlorothiazide alone was continued.

Every two weeks the patients visited the outpatient clinic for measurement of supine and standing blood pressure, pulse rate, and

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