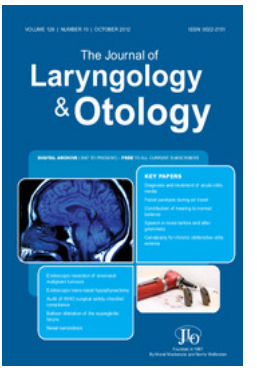

Bromocriptine-associated ototoxicity

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Bromocriptine-associated ototoxicity*

by

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Abstract

Three patients treated with bromocriptine for chronic hepatic encephalopathy showed audiometric evidence of bilateral sensori-neural hearing-loss. Audiometrically, the hearing improved in all three patients when the bromocriptine dosage was reduced, thus suggesting that this drug may produce a reversible ototoxicity.

Introduction

Bromocriptine (2-bromo-alpha-ergocryptine) is a dopamine agonist which has been used successfully to treat Parkinsonism (Calne *et al.*, 1978; Parkes, 1979; Teychenne *et al.*, 1982), acromegaly (Sachdev *et al.*, 1981; Moses *et al.*, 1981; Quabbe, 1982), prolactinomas (Archer *et al.*, 1982; Editorial, 1982) and other 'non-functioning' pituitary tumours (Johnston *et al.*, 1981), mastodynia (Durning and Sellwood, 1982) and chronic hepatic encephalopathy (Morgan *et al.*, 1980). Early side-effects include nausea, dizziness and postural hypotension. Their occurrence can be largely circumvented by slow introduction of the drug. Psychiatric disturbances and erythromelalgia are associated with prolonged use of the drug in high doses, but occur infrequently.

We report the occurrence of a reversible ototoxic effect in three patients treated with bromocriptine for chronic hepatic encephalopathy.

Case Reports

Case 1

TSE, a male aged 52 years, presented in 1974 with alcoholic cirrhosis complicated by variceal bleeding and hepatic encephalopathy. He settled well with conservative management, but still showed evidence of encephalopathy when discharged from hospital. Over the next two years his mental state remained poor despite abstinence from alcohol, protein restriction to 40 g./day and lactulose 40 ml./day. In October 1976 bromocriptine was introduced and increased over eight weeks to a maintenance dose of 20 mg. daily. His clinical condition improved remarkably and at three months there was no subjective or objective evidence of encephalopathy.

In November 1977 he installed new stereophonic equipment at home. Over the next 15 months sound engineers visited repeatedly because the patient, an accomplished musician, complained that the equipment blunted the tonal differences between instruments and blurred top soprano and tenor notes. In May 1979, at the suggestion of a sound engineer, he asked to have his hearing tested. The audiogram showed bilateral sensori-neural hearing-loss, most marked in the high frequency range and suggestive of drug ototoxicity (Fig. 1a). His plasma bromocriptine concentration 90 minutes after a 5 mg. dose was 2.4 ng/ml, which is within the normal therapeutic range. His plasma albumin was 42 g./l. (reference range 35 to 55). The patient refused to stop bromocriptine but agreed to reduce the dose to 10 mg. daily over the next

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three months under careful supervision. Little loss of efficacy was observed. Subjective improvement in hearing was first noted in September 1979 and confirmed by an audiogram in December 1979 (Fig. 1b). Further subjective improvement occurred and was confirmed in audiograms performed in March and September 1980. Since that time his hearing has remained stable on bromocriptine 10 mg. daily and an audiogram performed in June 1983 showed no further significant change (Fig. 1c).

Case 2

NT, a male aged 25 years, presented in 1967 with cryptogenic cirrhosis and uncontrollable variceal haemorrhage; an emergency porto-caval shunt was performed. In 1970 hepatic encephalopathy was noted which responded reasonably well to protein restriction 40 g./day and lactulose 20 to 40 ml./day. However, his condition later deteriorated so that in the 12 months from March 1976 he was admitted on six occasions with hepatic pre-coma. In March 1977 bromocriptine was introduced and increased over six weeks to a maintenance dose of 15 mg. daily. A dramatic improvement in his clinical condition followed. He observed no change in his hearing, but a screening audiogram in April 1980 showed slight symmetrical, bilateral sensori-neural hearing-loss, particularly at high frequencies, consistent with drug ototoxicity (Fig. 2a). His plasma bromocriptine concentration 90 minutes after a 5 mg. dose was 1.8 ng./ml. which is within the normal therapeutic range. His plasma albumin was 44 g./l. The patient and his family refused to stop bromocriptine and were only persuaded to reduce the dosage to 10 mg. daily in November 1981 when a repeat audiogram showed no change. Very little loss of efficacy was noted when the drug dosage was reduced but the repeat audiogram in June 1983 showed a slight but definite improvement (Fig. 2b).

Case 3

AL, a male aged 59 years, presented in 1969 with hepatitis B associated cirrhosis complicated by recurrent variceal haemorrhage. A porto-caval shunt was performed following which he developed hepatic encephalopathy. He initially responded to protein restriction 40 g./day and lactulose 40 ml./day, but the improvement was ill-sustained. In April 1977 he started treatment with bromocriptine, achieving a maintenance dose of 15 mg. daily. His clinical condition improved remarkably. He had not observed any change in his hearing, but a screening audiogram performed in April 1980 showed bilateral, sensori-neural hearing-loss consistent with drug ototoxicity (Fig. 3a). His plasma bromocriptine concentration 90 minutes after a 5 mg. dose was 3.3 ng/ml. which is within the normal therapeutic range. His plasma albumin was 40 g./l. Bromocriptine was reduced to 10 mg. daily, with little loss of efficacy, and a repeat audiogram in August 1980 (Fig. 3b) showed deterioration in the right ear but some improvement in the left ear. The patient died suddenly in September 1980 following a myocardial infarction.

Discussion

All three patients described showed bilateral high frequency hearing-loss whilst on treatment with bromocriptine. None of the patients were taking drugs known to be ototoxic, nor was there evidence that they had done so previously. There was no history of excessive exposure to noise nor of previous ear problems. Reduction of the dose of bromocriptine was followed by improvement in the audiograms in two of the patients in both ears and in the other patient in one ear. It seems reasonable to suggest that the drug was responsible for the reversible ototoxicity.

The doses of bromocriptine used to treat chronic hepatic encephalopathy are modest compared with those used in Parkinsonism (Calne *et al.*, 1978; Parkes, 1979), acromegaly (Sachdev *et al.*, 1981) and in the treatment of prolactinomas (Archer *et al.*, 1982). Despite the fact that many patients have been exposed to much higher doses of bromocriptine for as long or longer than the patients reported here, no previous reports of bromocriptine-associated ototoxicity exist. It is possible that the ototoxicity may go un-noticed, as only one of our three patients experienced subjective hearing-loss and he was an accomplished musician; the other two were asymptomatic and their hearing-loss was only detected on audiometry. Alternatively, bromocriptine-associated ototoxicity may only occur in patients in whom the drug is used to treat chronic hepatic encephalopathy; this latter would seem more likely.

Bromocriptine is incompletely absorbed from the gastro-intestinal tract, metabolised in the liver and mainly excreted in the bile. In plasma it is 90 to 96 per cent bound to albumin. In theory bromocriptine metabolism might be disturbed in

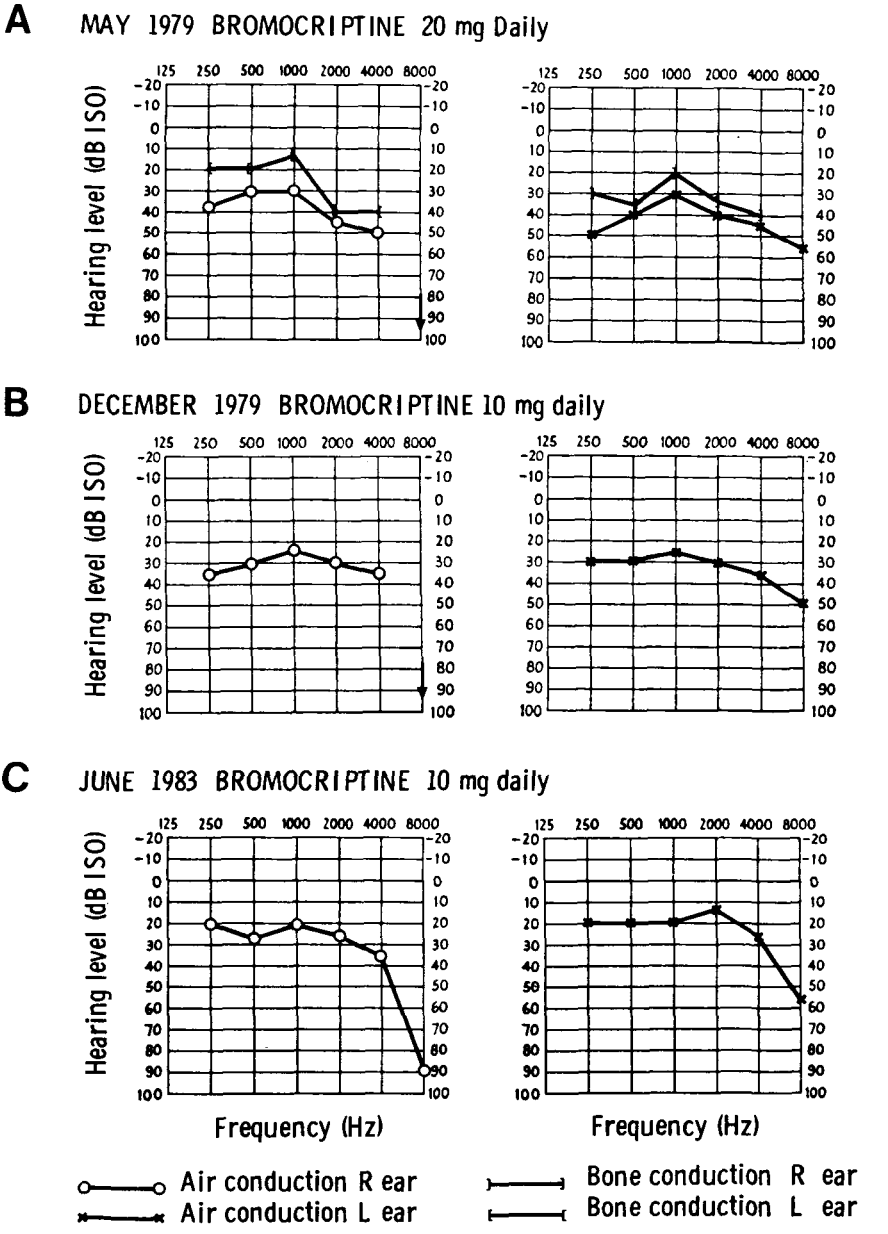

FIG. 1

Serial audiograms in patient TSE.

(a)—May 1979, bilateral high frequency sensori-neural hearing-loss while taking bromocriptine 20 mg. daily.

(b)—December 1979, improvement in hearing-loss six months after reduction of bromocriptine dosage to 10 mg. daily.

(c)—June 1983, sustained improvement in hearing on maintenance bromocriptine 10 mg. daily.

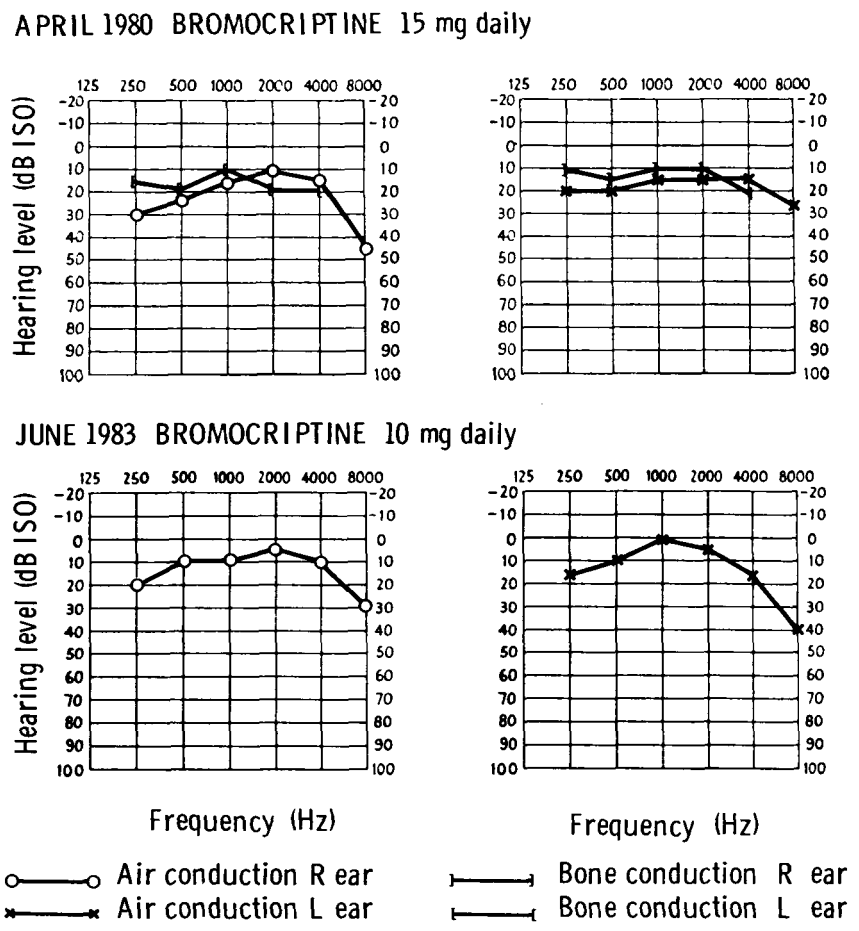

FIG. 2

Serial audiograms in patient NT.
(a)—April 1980, symmetrical, bilateral sensori-neural hearing-loss while taking bromocriptine 15 mg. daily.
(b)—June 1983, improvement in hearing-loss following reduction of bromocriptine dosage to 10 mg. daily in November 1981.

patients with liver disease perhaps leading to higher plasma concentrations for a given dose of drug. However, plasma bromocriptine concentrations were within the normal therapeutic range in all three patients and none was hypoalbuminaemic.

The mechanism by which the ototoxicity arises must of necessity be speculative. Other drugs which may cause reversible ototoxic effects include diuretics, especially ethacrynic acid and frusemide; anti-protozoal agents, notably quinine and chloroquine; and salicylates. In all these instances, the damage is thought to be brought about by vasoconstriction of the small vessels in the microvasculature of the cochlea (Hawkins *et al.*, 1967). Indeed histopathological damage to the stria vascularis has been seen in guinea-pigs (Quick and Duvall, 1970), cats (Johnsson and Hawkins, 1972) and a human subject (Arnold *et al.*, 1981) following the use of loop diuretics. The ototoxicity occurring with bromocriptine may also have a vascular origin.

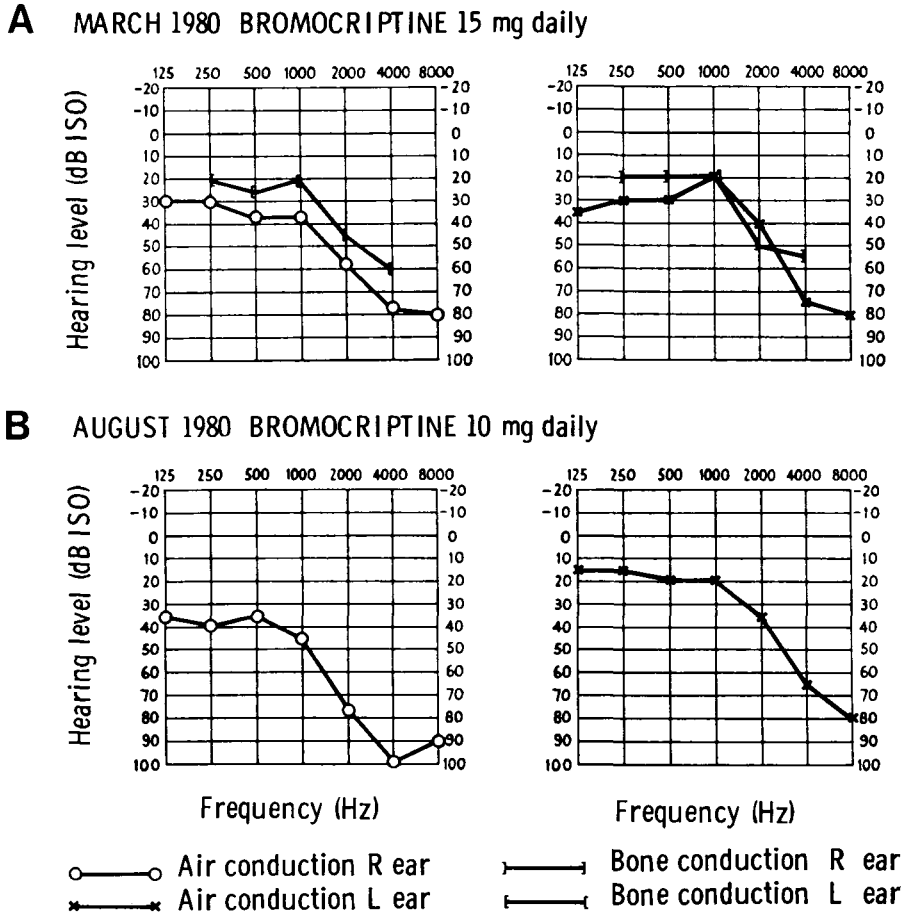

FIG. 3

Serial audiograms in patient AL.
(a)—March 1980, bilateral high frequency sensori-neural hearing-loss whilst on bromocriptine 15 mg. daily.
(b)—August 1980, improvement in hearing-loss in the left ear five months after reduction of bromocriptine dosage to 10 mg. daily.

Patients on long-term treatment with bromocriptine should be screened for potential ototoxicity and if necessary the drug dosage reduced. Pre-treatment audiometry and regular screening during therapy should be contemplated, especially in patients with chronic hepatic encephalopathy.

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Professor Dame Sheila Sherlock kindly allowed us to study and to report these patients who were under her care. Dr. W. Maclay of Sandoz Pharmaceuticals kindly arranged measurement of the plasma bromocriptine concentrations.

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