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Medicine in the Elderly

Cognitive impairment associated with beta-blockade in the elderly

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Summary: We report the cases of three elderly patients presenting with insidious mental impairment whilst receiving both lipophilic and hydrophilic beta-adrenoceptor blocking agents (propranolol and atenolol respectively). In each case marked improvement occurred on drug withdrawal. Two of our cases probably had early senile dementia of the Alzheimer's type and continued to exhibit signs of mild mental impairment, but the third was restored to normal functioning. We found no evidence of impaired perfusion to suggest a vascular basis for the effect or of depression. We believe that beta-blockade may cause or exacerbate mental impairment in the elderly.

Introduction

Cerebral side effects have long been recognized as a complication of beta blockade, particularly by the lipophilic agents, such as propranolol. Reported adverse events include insomnia, nightmares, sedation and psychosis. These drugs, and particularly the hydrophilic agents such as atenolol, are often considered to be safe in the elderly.[1] We report three cases of insidious cognitive impairment from an assessment clinic for the elderly, in whom marked improvement occurred on drug withdrawal. This effect was seen not only with propranolol but also with atenolol.

Case reports

Case 1

A 70 year old man presented with memory impairment which had become gradually more severe over a 3 year period. He had suffered an uncomplicated myocardial infarct 7 years previously. He had been treated for 3 years with propranolol 60 mg/day for an essential tremor, but received no other medication.

He was unable to give any useful history, all of which was provided by his wife. He was disorientated in time (he knew the decade, but not year or month) and his Mini Mental State (MMS)[2] score was 21 out of 30. He was unable to subtract serial 3s from 100 more than twice and required continuous prompting during undressing.

He was in atrial fibrillation with a ventricular rate of 55/minute and blood pressure was 130/70 mmHg. He was well-perfused, not in heart failure and showed no neurological abnormality. His full blood count, urea and electrolytes and vitamin B12 were all normal.

In view of his bradycardia the propranolol was discontinued. Over the following few days his mental state steadily and dramatically improved. On review one month later he was able to answer questions without hesitation and knew the year and month, although still not the day of the week. Detailed questioning confirmed continuing impairment of short-term memory, an MMS score of 25 and he was now able to undress efficiently. Atrial fibrillation persisted with a ventricular rate of 60/minute and blood pressure was unchanged. His improved mental state has persisted after 12 months of follow-up.

Case 2

A 66 year old man presented with a 12-month history of loss of memory for recent events. He had lost his ability to solve the Daily Telegraph crossword and his sense of direction had deteriorated such that he was unable to go out walking alone. He had suffered a minor myocardial infarct 11 years previously and subsequently from mild stable angina. This and moderate hypertension had been treated successfully, and apparently uneventfully, with atenolol 50 mg daily for many years.

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He was fully orientated with an MMS score of 25. He was unable to subtract 3 from 100 more than three times and had extreme difficulty with the simplest of calculations. No other abnormalities were found on examination and the blood pressure was 160/80 mmHg. The investigations listed for case 1 were all normal.

Two months later his condition was unchanged and the atenolol was replaced by a calcium antagonist in view of our experience with case 1. Four weeks later he reported that over the subsequent few days he had become much sharper mentally and was once more successfully solving his crossword. His wife complained, however, that despite this improvement he was still apt occasionally to get lost whilst out walking alone. He was now able to subtract 7 serially from 100 (his MMS score returning to 30) and perform simple arithmetic calculations without error. His blood pressure remained under good control.

After 8 months of follow-up his improved mental performance has been maintained.

Case 3

A 73 year old part-time builder with a long history of hypertension complained of palpitations on exertion. His bendrofluazide treatment was changed to atenolol 50 mg once daily. The palpitations settled but he complained of lethargy and difficulty estimating work. When the atenolol was withdrawn this resolved and the blood pressure remained satisfactory at 150/95 mmHg, without recurrence of the palpitations.

Several months later he sustained a small inferior myocardial infarction. Following this he complained again of palpitations and his blood pressure rose to 160/110 mmHg. Atenolol 50 mg once daily was recommenced, satisfactorily controlling his blood pressure, but not the palpitations. He again complained of difficulty with calculations and became withdrawn from social contact. There were no features of depression and his MMS score was normal, but he performed calculations falteringly.

A 24-hour electrocardiogram showed episodes of paroxysmal supraventricular tachycardia. The atenolol was stopped and nifedipine and amiodarone successfully controlled hypertension and palpitations respectively. His ability to estimate work and perform calculations was entirely restored and has remained so after 6 months of follow-up.

Discussion

The improvement in mental function in these 3 cases after beta-blocker withdrawal is consistent with an adverse drug reaction. Lack of evidence of cerebrovascular disease or cardiovascular insufficiency during drug treatment makes altered cerebral perfusion an unlikely explanation. There was no evidence of any other causes of reversible mental impairment, but it is likely that our first 2 cases have early senile dementia of the Alzheimer's type.

The rapid transport of lipophilic beta-blockers into the central nervous system may facilitate the recognition of adverse reactions in short-term clinical trials. Hydrophilic agents pass into the central nervous system more slowly and this may make a causal association with adverse effects more difficult to establish, since symptoms with a delayed or protracted onset are notoriously difficult to detect even with post-marketing surveillance systems (such as the Yellow Card Scheme). The Committee on Safety of Medicines (CSM) has received many reports of such symptoms as confusion, somnolence and impaired concentration associated with the use of both hydrophilic and lipophilic beta-blockers over the last 26 years (A.W.M. Scott, Personal communication). The CSM does not, however, include in its dictionary of adverse drug effects a category such as 'pseudodementia' or 'insidious mental impairment'.

Most trials examining the side effects of beta-blockers have been performed in younger patients with uncomplicated hypertension or ischaemic heart disease. Much of the data have been conflicting. Currie *et al.* have recently demonstrated cognitive impairment with both lipophilic (propranolol) and hydrophilic (atenolol) agents over a 4-hour period in young, healthy men.[3] The same group also found modifications of the electroencephalogram consistent with a central sedative effect with both drugs.[4] Conversely Gengo and others have claimed that older patients with uncomplicated hypertension should not be expected to suffer significant lethargy or impairment of mental performance due to atenolol or metoprolol.[5] However, extrapolating from the pharmacokinetic and pharmacodynamic data obtained from brief clinical trials, to the behaviour of a drug in routine clinical use is difficult,[6] particularly for older patients with multiple diseases and receiving chronic drug therapy.

A growing population of patients treated appropriately with beta-blockers for many years is now entering late life. We believe that a study is now indicated formally to examine mental function on beta-blocker withdrawal in patients such as ours. Until then we would recommend that beta-blockers be gradually withdrawn where possible in patients presenting with mental impairment.

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