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Reversible Dysphasia and Statins

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This paper presents a case of reversible dysphasia occurring in a patient prescribed atorvastatin in combination with indapamide. A milder dysphasia recurred with the prescription of rosuvastatin and was documented on clinical examination. This resolved following cessation of rosuvastatin. The case highlights both a need for a wider understanding of potential drug interactions through the CYP 450 system and for an increased awareness, questioning and reporting of drug side-effects.

Key Words: Dysphasia; Statins; Drug Interactions

INTRODUCTION

Statins are a very widely used class of medication and controlled studies have demonstrated clear benefits with respect to cardiac disorders and also stroke and cognitive function. Because of this there are moves toward their use in primary prevention of atherosclerosis (1). However they are not without side effects. The literature includes numerous reports of cognitive dysfunction (2) even though their occurrence was not borne out as a general effect in the controlled trials (e.g.3). However the previously published reports have not mentioned aphasia or dysphasia as a specific side effect except as part of a much wider and more serious problem (4).

Despite this a general search of the internet does provide several allegations of language problems occurring with statin use. The evidence provided in association with these allegations is either absent or poor. However as at the 30th March 2011 the Australian register of drug adverse reactions records six cases of aphasic disturbance with atorvastatin, one with rosuvastatin and two with simvastatin (Goodwin, personal communication). These numbers include the presently reported case.

This case is presented as a reasonably well documented occurrence of dysphasia associated with the use of atorvastatin and rosuvastatin and a consideration of some of the factors that might be involved in both the genesis of the syndrome and the absence of documented reports.

CASE DESCRIPTION

Mrs. X. Y. a 58-yr-old Caucasian woman, presented for medico-legal examination on the 14th of April 2010 with regard to a compensation claim involving allegations of harassment at work producing anxiety and depression. At the time of her initial presentation for treatment her general practitioner had noted that her blood pressure was higher than usual and had prescribed the statin Lipitor (atorvastatin) 10 mg per day together with indapamide 2.5 mg per day.

A few days later Mrs. X. Y. reported that she had developed problems in "word finding" in that her speech would be interrupted because she would be unable to find a word to describe an object. Mrs. X. Y. had ceased the Lipitor after a few days and said that her symptoms had resolved quite quickly. She had seen her doctor four weeks later and the doctor had noted "Had symptoms of haziness and confusion with the Lipitor tablets so patient had stopped them. Nil symptoms since then. Claims it may have been due to her anxiety. Unlikely above symptoms due to Lipitor" At this point Mrs. X. Y. had been commenced on Crestor (rosuvastatin) 5 mg daily while continuing on indapamide.

Four weeks later at her medico-legal assessment Mrs. X.Y. was noted to have clear but intermittent difficulty in word finding. She was also tense and tearful at times. She was a little perfectionistic but there was no evidence of any psychotic symptoms. There were no gross neurological abnormalities.

Mrs. X. Y. was reviewed two weeks later. At this point she had stopped the rosuvastatin and her speech was fluent and clear. Mrs. X. Y. was continuing to take indapamide 2.5 mg per day.

A review of Mrs. X. Y.'s investigations indicated that a the time she had been prescribed Lipitor her total cholesterol was 6.1 mM (HDL 1.27, LDL 3.77), trigycerides 2.34 mM and fasting glucose 5.8 mM. Electrolytes and liver function tests did not show any specific abnormality. An exercise ECG carried out two weeks after the prescription of atorvastatin was normal.

DISCUSSION

The immediate inference from the above observations is that

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Mrs. X. Y. had developed dysphasia as a direct side effect of the use of simvastatin. That this is likely to have been a generic statin effect is supported by the recurrence of milder symptoms on rosuvastatin and their remission on its cessation. Using the method of attribution recommended by Naranjo and colleagues (5) it would rate at 9 (definite adverse reaction).

The greater effect resulting from the rosuvastatin is likely to reflect the co-incident prescription of indapamide as both drugs are metabolised through the CYP 450 3A4 pathway whereas rosuvastatin is metabolised via the CYP 450 2C9 pathway (6, 7).

However a larger question is why speech should be selectively affected. There is clear evidence that aphasia can be included in the syndrome of mitochondrial encephalopathy (MELAS) (8) but in this case there is no history of other mitochondrial dysfunction such as muscle weakness. Wagstaff and colleagues (2) suggest that inhibition of membrane synthesis may affect the neuronal membrane. This is supported by Baker and Tarnopolsky (9) who also suggest that decreased ubiquinone (Co-enzyme Q10) synthesis may lead to decreased ATP production and reduced free radical scavenging, and by Ihara and colleagues who report that the cerebral pathology occurring in their MELAS patients reflected damage at a cellular rather than vascular level (6). It may be that speech requires a selective increase in neuronal metabolism and is therefore a vulnerable function.

A genetic vulnerability may also be hypothesised. This has already been studied in relation to statin induced myopathy (10). Slow CYP 450 metabolisers are likely to have proportionately higher blood levels and there may also be a genetically determined increased sensitivity to lower ubiquinone levels within the mitochondria in some patients (11).

Given the history of the episodes in this patient and the comments written in the attending practitioners notes it would seem that other episodes of similar syndromes may be more common than reported. I subsequently have had one further patient retrospectively report transient cognitive symptoms on a statin. The patient had stopped the medication and did not advise their doctor.

Accad (12) notes that one of the problems in the use of statins is the immediacy of side effects and the long delay of benefits. However another problem would seem that there tends to be a "one size fits all" approach and that because of the substantial overall benefits of statin use significant side effects are masked in large trials. Some greater attention to the group reporting side effects may demonstrate significant markers such as CYP 450 slow metabolising that would allow prediction of the at risk group as well as defining specific genetic abnormalities in cerebral lipid metabolism such as those reported by Hollingworth and colleagues (13). Also this particular case draws attention to a need for greater awareness of possible drug interactions through the CYP 450 system amongst primary care physicians.

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