Unexpected outcome (positive or negative) including adverse drug reactions

Possible association between statin use and bowel dysmotility

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3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) are a class of drug that has been proven to be effective in lowering serum lipid levels. Although generally well-tolerated side effects from this class of drug have been noted to include liver dysfunction, renal failure and myopathy. Statins are also known to effect nitric oxide levels through upregulation of nitric oxide synthase. There is some evidence to imply that nitric oxide acts on inhibitory nerves in the colon to produce impaired motility. The authors present a case of recurrent colonic dilatation and volvulus which was initially treated with a sigmoid colectomy. Unfortunately symptoms persisted and a trial of the omission of statins was undertaken resulting in symptomatic relief. Following admission into hospital, statins were inadvertently restarted which caused the symptoms to reoccur. The statin was discontinued and upon review several months later the patient reported symptomatic benefit.

BACKGROUND

Colonic dilatation and volvulus are important surgical conditions and an underlying predisposing cause should be sought such as adhesions and obstructing lesions.¹ Drug induced causes are rarely considered but are particularly pertinent if the patient is otherwise well and malignancy has been excluded. It is important that clinicians should consider unusual drug reactions as a possible explanation.

CASE PRESENTATION

We present the case of a 70-year-old gentleman who has a background history of psoriasis for which he takes methotrexate. He was admitted 14 times in 6 years following recurrent episodes of abdominal discomfort and a persistent sensation that he was unable to open his bowels fully. During each admission abdominal radiographs revealed a sigmoid volvulus. Colonoscopy, CT and barium enema did not reveal a mechanical cause. The patient underwent a laparoscopic sigmoid colectomy and made a good post-operative recovery. His symptoms initially improved but returned 2 years later. Investigations were repeated but were again found to be normal. At this time it was considered that methotrexate might be a factor, however a trial without the medication did not alter his symptoms. The only other medication that the patient was known to take was simvastatin 40 mg on line. This medication was started 8 years ago, approximately 6 months prior to the onset of his symptoms. A trial of omission was then initiated. Following the discontinuation of the medication, the patient's symptoms markedly improved and he was able to open his bowels daily with no discomfort. There had been no change in lifestyle or any other treatment administered during this period. Unfortunately following the admission into hospital for investigation of weakness, he was inadvertently restarted on a statin. Unfortunately his symptoms reoccurred and abdominal radiographs confirmed dilated loops of large bowel. The statin was discontinued and ezetimibe started. The patient was reviewed several months later, at which time he continued to report

a beneficial effect from the discontinuation of the statins. He reported that both the frequency and ease with which he opened his bowels to have improved.

INVESTIGATIONS

The preoperative abdominal radiographs revealed dilated loops of large bowel with no small bowel dilatation. Colonoscopy revealed distended colon but no overt cause and preoperative CT demonstrated features suggestive of megacolon. Barium enema did not reveal a mass lesion. The histology of the resected bowel segment revealed non-specific changes. Postoperatively the plain abdominal radiograph showed distension of large bowel loops, which were less prominent following the discontinuation of statins.

DIFFERENTIAL DIAGNOSIS

The first presentation bowel dysmotility is rare in the older subgroup, but neurological, biochemical and muscular causes could be considered.¹⁻³ The patient had no abdominal surgery apart from his laparoscopic sigmoid colectomy.

OUTCOME AND FOLLOW-UP

Resolution of the patient's symptoms occurred following the discontinuation of the statins. The patient will be seen regularly in clinic and hyperlipidaemia will be treated using alternative agents.

DISCUSSION

The effects of all pharmacological agents upon the large and small bowel are reported to account for 20–40% of all reported side effects.² These side effects can have a profound impact upon a patient's quality of life and ultimately compliance. The side effects of statins include diarrhoea and constipation, although no pathophysiological explanation is provided by the manufacturer. There are various mechanisms that have been postulated by which statins

Table 1 The Naranjo adverse drug reaction probability scale

The Naranjo adverse drug reaction probability scale. To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+2
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	+2
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
			Total	6

are thought to induce myotoxicity. Such theories include blocking mevalonic acid production, depleting coenzyme Q10 and inducing selenoprotein dysfunction.⁴ Another possible mechanism by which statins can have this effect may be related to nitric oxide levels. There is some evidence to imply that nitric oxide acts on inhibitory nerves in the colon to produce impaired motility.⁵⁻⁷ The levels of nitric oxide are increased as a consequence of the upregulation of endothelial nitric oxide synthase caused by statins in some patients. The authors hypothesise that this mechanism could provide a scientific explanation for the clinical observation noted in this patient.

We were unable to identify any reported cases following a MEDLINE database search of statins having an effect on bowel motility in a similar manner.

Although there was a long interval between spontaneous clinical presentations with sigmoid volvulus, the patient experienced chronic and persistent gut dysmotility with difficulty in opening his bowels on a daily basis. Although there are millions of people who use this class of medication, it would be expected that this form of adverse reaction would be well reported. However, constipation is a well-known side effect officially reported in 34 cases⁸ and it is feasible that the mechanism by which this is induced by statins is the same. However, in our patient the symptoms were persistent, a sigmoid volvulus was present and the colonic dilatation was not due to the presence of faecal loading. There was also one reported case of small bowel obstruction from simvastatin.⁸

The assessment of the probability of an adverse drug reaction is difficult. The Naranjo adverse drug reaction probability scale is commonly used in clinical practice.⁹ Implementation of this probability scale yielded a score of 6, which correlates to a probable adverse drug reaction association (table 1).

Although it can be said that there are a number of diseases that can cause symptoms as those experienced by

our patient, one must consider why the discontinuation of statins led to symptomatic benefit in the absence of any other confounding factors.

Learning points

- ▶ Statins may alter nitric oxide levels due to enzymatic upregulation and thus effect bowel motility.
- ▶ Clinicians should be aware that in patients who present with distended bowel, drug induced reactions may be a precipitating factor.
- ▶ Other more common causes of distended bowel and volvulus must be investigated before an assumption that the condition was induced by any medication.

Competing interests None.

Patient consent Obtained.

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