Telmisartan-induced sprue-like enteropathy: a case report

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SUMMARY

A possible case of sprue-like enteropathy (SLE) induced by the use of telmisartan is reported. Telmisartan is an angiotensin-receptor II blocker (type 1) used for the treatment of hypertension. Several cases of SLE associated with olmesartan and other drugs of the same group have been reported. In all cases, SLE resolved following therapy withdrawal. We describe the case of an 80-year-old woman who presented with diarrhoea and abdominal pain. In the past 5 years she had been treated with telmisartan 40 mg once a day for hypertension, so we hypothesised that symptoms might be caused by telmisartan. After treatment discontinuation, diarrhoea disappeared. Three causality algorithms were applied and revealed a possible or likely causal relationship. At present, the patient remains asymptomatic. There is a causal relationship between the use of telmisartan and SLE. This association should be taken into account by physicians when prescribing and reviewing drug therapies.

BACKGROUND

Sprue-like enteropathy (SLE) is characterised by the presence of chronic diarrhoea, weight loss and villous atrophy similar to that associated with celiac disease.¹ In 2013, the Food and Drug Administration issued a warning about the association of olmesartan with this adverse event.² Isolated cases of SLE related to the use of valsartan, losartan and irbesartan have also been reported.^{3–4} Thus, SLE might be an adverse event associated with a drug class rather than with a specific drug, more specifically, to angiotensin II receptors blockers (ARB), which are commonly used for the treatment of hypertension. Symptoms associated with the use of these drugs are characterised by late onset. Clinical symptoms and histological alterations resolved after treatment discontinuation.^{5–6}

Herein, we present the case of a woman with hypertension treated with telmisartan, who presented with diarrhoea and a substantial weight loss. The patient did not meet the criteria for a diagnosis of celiac disease and symptoms resolved after treatment withdrawal.

Thereby, we consider it relevant to describe this case and enhance the possibility that SLE might be an adverse event associated with the drug class.

CASE PRESENTATION

We report the case of a Caucasian 80-year-old woman diagnosed with hypertension, diabetes mellitus 2, dyslipidaemia, mild aortic stenosis, asthmatic bronchitis, osteoporosis and a history of breast cancer 11 years ago. In January 2016, she

started to have diarrhoea episodes and intermittent abdominal pain, with three to six stools of variable consistency per day and urge incontinence. She did not have symptoms of rectal bleeding. A weight loss of 3 kg in a year was observed.

The patient had been prescribed telmisartan 40 mg daily for hypertension since 2012. Her usual treatment included omeprazole, insulin glargine, metformin, calcium associated with colecalciferol, simvastatin, acetaminophen, lorazepam, mirtazapine and timolol in combination with travoprost.

INVESTIGATIONS

In the case reported here, a differential diagnosis of celiac disease was not performed despite compatibility of symptoms. No duodenal biopsy was performed to test villous atrophy before and after treatment discharge. In consequence, an analysis of causality between telmisartan and enteropathy was undertaken including Naranjo Scale⁷ (table 1), Karch Lasagna algorithm⁸ (table 2) and the WHO-UMC system for standardised case causality assessment⁹ (table 3). The causality was classified as *possible* by Naranjo scale and as *probable* by Karch Lasagna and WHO-UMC.

TREATMENT

Initially, symptoms were suspected to be caused by lactose intolerance. She was recommended a lactose-free diet but she did not follow it. The medications including lactose as an excipient (telmisartan, mirtazapine and lorazepam) were not withdrawn either.

As the lactose intolerance could not be confirmed, the clinical pharmacist reviewed her medication to determine if the symptoms could be secondary to some of the drugs she used. On suspicion that the causative drug of diarrhoea was telmisartan, the pharmacist proposed the drug discontinuation and replacing it with amlodipine.

OUTCOME AND FOLLOW-UP

One month after the discontinuation of telmisartan, diarrhoea and the other symptoms resolved. Six months after stopping treatment with telmisartan and switching to amlodipine, she remained asymptomatic.

This adverse event was reported to the regional centre of pharmacovigilance.

DISCUSSION

Enteropathy associated with telmisartan is an adverse event characterised by diarrhoea, weight loss, vomiting, fatigue and abdominal pain.⁴

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Table 1 Naranjo adverse–reaction probability scale

QUESTION	YES	NO	DO NOT KNOW	SCORE
Are there previous conclusive reports on this reaction?	+1	0	0	1
Did the adverse event appear after the suspected drug was administered?	+2	–1	0	2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
Did the adverse event reappear when the drug was re-administered?	+2	–1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	–1	+2	0	0
Did the reaction reappear when a placebo was given?	+1	0	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	0
TOTAL SCORE				4

DOUBTFUL, 0.; POSSIBLE, 1–4; PROBABLE, 5–8; SCORING, DEFINITE: >9.

According to the European Medicines Agency database Eudra-Vigilance, 1691 cases of SLE have been reported to be associated with olmesartan, two with valsartan, two with telmisartan and one with candesartan.¹⁰ After a literature review, only three case reports of telmisartan-induced SLE were found.^{4 11 12}

The mechanism underlying ARB-associated enteropathy is still unclear.¹ The late onset of symptoms from the start of treatment suggests that it is an immune-mediated sensitivity.¹³ Solano-Iturri et al¹⁴ postulated that it could be the result of an immune injury, with an increased CD8 +T cell count and IL-15 overexpression in epithelial cells. Both, clinical and histological alterations resolved after drug discontinuation.¹⁵ Factors such as age, sex

Table 2 Karch Lasagna algorithm

QUESTION	DEFINITE	PROBABLE	POSSIBLE	CONDITIONAL
Reasonable time sequence (+2)	YES	YES	YES	YES
Previous knowledge about the adverse reaction (+2)	YES	YES	YES	NO
The adverse reaction improve when the drug was discontinued (+2)	YES	YES	YES/NO	YES/NO
The adverse event reappear when the drug was re-administered (0)	YES	?	?	?
Another alternative explanation (–1)	NO	NO	YES	NO
TOTAL SCORE		6		

CONDITIONAL, 1–3 DOUBTFUL: 0.; POSSIBLE, 4–5; PROBABLE, 6–7; SCORING, DEFINITE: ≥8.

Table 3 WHO–UMC causality categories

Assessment criteria	Causality term
Event or laboratory test abnormality, with plausible time relationship to drug intake. Cannot be explained by disease or other drugs. Response to withdrawal plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognised pharmacological phenomenon). Rechallenge satisfactory, if necessary.	CERTAIN
Event or laboratory test abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs. Response to withdrawal clinically reasonable. Rechallenge not required.	PROBABLE/ LIKELY
Event or laboratory test abnormality, with reasonable time relationship to drug intake. Could also be explained by disease or other drugs. Information on drug withdrawal may be lacking or unclear.	POSSIBLE
Event or laboratory test abnormality. More data for proper assessment needed, or Additional data under examination.	CONDITIONAL/ UNCLASSIFIED
Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.	UNLIKELY
Report suggesting an adverse reaction. Cannot be judged because information is insufficient or contradictory. Data cannot be supplemented or verified.	UNASSESSABLE/ UNCLASSIFIABLE

and treatment duration do not seem to be associated with the disease.¹³

In this case, diarrhoea disappeared just 1 month after treatment withdrawal. Therefore, treatment discontinuation is the most effective way to treat symptoms and the definitive method to confirm the diagnosis.⁵

Based on the clinical data available, the literature and the results of causality analyses, a relationship of causality between diarrhoea and telmisartan is possible.

The increasing number of cases of SLE secondary to ARB-based therapies other than olmesartan suggests that this adverse event is associated with the sartan class rather than a single drug. Cooperation between physicians and pharmacists is useful in detecting and reporting adverse events, and promotes the safe use of medicines.

Learning points

- The association between telmisartan and the patient's diarrhoea was classified as *possible* by Naranjo adverse drug reaction probability scale and as *probable* by Karch Lasagna and WHO–UMC.
- This case of sprue-like enteropathy suggests that this adverse event might be associated with the sartan class rather than a single drug.
- Cooperation between physicians and pharmacists is useful in detecting and reporting adverse events, and promotes the safe use of medicines.

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