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CASE REPORT

Red-Brown Urine Discolouration in Two Patients Taking Mesalamine

Tim Smeets[1] · **Florence van Hunsel**[1]

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Abstract A 38-year-old male and a 36-year-old female experienced red-brown urine discolouration after 2 and 3 days, respectively, during the use of mesalamine for inflammatory bowel disease. Both patients mentioned that the urine discoloured after contact with sodium hypochlorite detergent in toilet water. Mesalamine and the inactive metabolite *N*-acetyl-5-aminosalicylic acid are primarily excreted in the urine. We hypothesised a possible reaction with sodium hypochlorite and/or light. Naranjo assessment scores of 9 and 6 were obtained for the reports, indicating a certain and probable relationship, respectively, between the red-brown urine discolouration and the use of the suspect drug mesalamine. Knowledge of this harmless reaction is desirable to avoid unnecessary physical examination and worry.

Key Points

The use of sodium hypochlorite as toilet detergent is related to a red-brown urine discolouration in patients taking mesalamine.

It seems that the red-brown discolouration relates to a harmless reaction.

Polymerisation of mesalamine and/or metabolites could be a theoretical mechanism of this discolouration.

✉ Tim Smeets
t.smeets@lareb.nl

[1] Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's Hertogenbosch, The Netherlands

Introduction

Mesalamine is indicated for the treatment of ulcerative colitis and Crohn's disease [1]. The exact working mechanism of mesalamine is not fully understood, but it appears to have anti-inflammatory properties. The drug blocks interleukin-1 and tumour necrosis factor-α. Mesalamine also inhibits the cyclo-oxygenase pathway, leading to inhibition of prostaglandin E_2 in inflamed intestine. Blocking of the lipoxygenase pathway also inhibits the production of leukotrienes [2]. The most common adverse drug reactions (ADRs), as described in the Summary of Product Characteristics (SmPC), are headache, rash and gastrointestinal symptoms, including diarrhoea, nausea, vomiting and abdominal pain [1]. Mesalamine is also associated with the renal ADRs of renal failure, interstitial nephritis and haematuria [1, 3]. In the period from August 2009 to April 2015, the Netherlands Pharmacovigilance Centre Lareb received two case reports of red-brown urine discolouration in association with mesalamine [4]. Both cases were reported by patients and the urine discoloured after contact with the toilet bowl. This discolouration could worry patients and/or encourage healthcare professionals to undertake further examination. This article describes these two reports and summarises the available literature.

Case Reports

Patient A (Report Date April 2015)

This case concerned a 38-year-old male with a history of Crohn's disease. The patient reported separate several episodes of a red-brown deposit in the toilet bowl after the

start of mesalamine in 1999 (Pentasa® slow-release 500 mg tablet). The latest episode occurred in April 2015, 2 days after the use of mesalamine. The patient had a mild form of Crohn's disease that had been stable for 6–8 years and only used mesalamine during episodes of exacerbations. Due to an exacerbation in September 2014, the daily dose of mesalamine was increased from 2 to 4 g. During this dose escalation, the patient recognised the same red-brown deposit that had occurred during previous use. In January 2015, the mesalamine was tapered over a period of 2 months to 2 g once daily and he remained stable. The patient continued 2 g once daily for his report to Lareb. Concomitant medications being taken were simvastatin and unspecified multivitamins. The patient stated that he experienced no physical complaints. He observed that the urine initially had a normal colour and developed the red-brown colour after contact with the water in the toilet bowl. Most of the time the persistent deposit did not appear directly after contact with the toilet water but developed after a few days, despite flushing the toilet. Of note, the deposit in the toilet bowl was more intense during the use of an increased dose of 4 g a day. The patient is under the care of a gastroenterologist and has normal renal function. The patient wondered whether the use of detergents could have caused this kind of discolouration and therefore he cleaned his toilet in the morning with a chlorine-containing detergent. In the evening a red-brown deposit had developed in the toilet bowl and on the seat and the water was unaffected. As the patient wanted more information on the possibility of the discolouration being the result of a reaction with the sodium hypochlorite detergent, he reported it to Lareb.

After the report had been assessed, the Pharmacovigilance Centre Lareb asked the patient to collect his urine and to add household bleach as a test, to which he agreed (Fig. 1). The urine (40 mL) was mixed with 20 mL of sodium hypochlorite bleach and within a few minutes the discolouration developed. After shaking the mixture, all of the urine showed a red-brown discolouration.

Patient B (Report Date August 2009)

This case concerned a 36-year-old woman with ulcerative colitis, for which she is treated with 2 g of mesalamine (Pentasa® sachet 2 g prolonged-release granules) twice daily. She experienced occasional mild exacerbations with diarrhoea and abdominal pain. Since she started taking mesalamine in June 2009, her urine appeared red-brown in the toilet bowl, but only when she had recently cleaned the toilet with sodium hypochlorite detergent. Interestingly, the discolouration did not appear when detergents without sodium chlorite were used. When the patient added a drop of sodium hypochlorite detergent to her normal-coloured urine in the toilet, the same red-brown discolouration occurred immediately. The patient was taking no other concomitant therapy. The patient regularly sees her gastroenterologist, who recognised this phenomenon from other patients. The patient is still taking mesalamine and the phenomenon is still present when cleaning the toilet.

Discussion

Urine discolouration can be caused by several drugs, food intake and diseases. Haematuria is likely the most common cause of red urine. Likewise, the disordered haem production in patients with porphyria can result in red-brown discolouration [5]. Rhabdomyolysis can also result in red discolouration due to myoglubinuria [6]. A red-brown urine discolouration could be perceived as a sign of possible renal impairment or other diseases; however, neither of the described patients are known to have an impaired renal function or physical abnormalities. Furthermore, various drugs are associated with red and/or brown discolouration, e.g. rifampicin, doxorubicin, metronidazole, methyldopa, levodopa and sulfasalazine. A notable difference from the described mesalamine cases is that the urine of patients taking the above-mentioned drugs, such as sulfasalazine, is already discoloured at micturition.

A PubMed search was conducted and it was found that two cases of red-brown urine associated with mesalamine have been reported previously by Sacks and Davis [7]. Both of the male adolescents in these reports experienced the same red-brown urine discolouration after contact with sodium hypochlorite bleach. A similar experiment was performed to that performed by Patient A, and after adding sodium hypochlorite bleach to the collected urine the discolouration developed spontaneously. To our knowledge, there are no other published reports of this association after a chemical reaction with drugs structurally related to mesalamine (sulfasalazine, olsalazine and 4-aminosalicylic acid). Notably, there has been discussion regarding this phenomenon in several patient forums and blogs [8].

Case reports from Altmann and Mansell [9] do, however, describe urine discolouration in patients using methyldopa or levodopa after contact with lavatory bleach and exposure to light. Normal biotransformation of methyldopa produces a variety of metabolites [10]; presumably, these metabolites have properties that form melanin by spontaneous polymerisation, which results in darkening of the urine. Melanins are polymers of phenolic compounds (e.g. dopaquinone, benzothiazole) that are formed by an extensive bio pathway. Melanin is an aggregate of smaller component molecules such as pheomelanin and eumelanin; both of these are initially formed by oxidation of tyrosine and then undergo

Fig. 1 *Red–brown* discolouration after adding sodium hypochlorite bleach to normal-appearing urine (*left*, *right*). Agitation discoloured the urine completely (*right*)

cysteinylation and cyclisation, respectively. The end product is ultimately formed by polymerisation of several different derivatives [11]. The formation of melanin by polymerisation requires a urine pH of 7 or more [9]. Altmann and Mansell [9] found that urine samples that were made alkaline in patients treated with methyldopa or levodopa turned black on exposure to sunlight.

Mesalamine is acetylated by the enzyme *N*-acetyltransferase 1 (NAT1) in the liver and gut mucosal wall into the metabolite *N*-acetyl-5-aminosalicylic acid (*N*-Ac-5ASA). Evidence from the literature indicates that NAT1 is polymorphic, but that these polymorphisms are associated with relatively minor effects on acetylation function [12]. It is unknown whether the patients in our reports have a NAT1 polymorphism, but if so we would expect no significant effect on the propensity of discolouring. Furthermore, this acetylation is minimal when mesalamine and *N*-Ac-5ASA are both secreted back into the lumen by the drug efflux pump P-glycoprotein, excreted in the faeces, absorbed via the colon into the blood and, lastly, eliminated in the urine [13]. The theory is that *N*-Ac-5ASA and/or mesalamine react with the sodium hypochlorite-containing bleach. Sodium hypochlorite usually has a pH of 11–13 and could therefore initiate the reaction as described by Altmann and Mansell [9]. According to the cases reported by Altmann and Mansell [9], it is also possible that a similar polymerisation of mesalamine and/or *N*-Ac-5ASA could cause the discolouration of the urine. Perhaps due to the alkaline environment, partial deprotonation of *N*-Ac-5ASA and mesalamine could also contribute to this reaction.

The two reports received by Lareb emphasise the value of consumer reporting. Since the introduction of the national spontaneous reporting system in 2003 to the general public, consumers have now become the largest group of reporters in the Netherlands [14]. The quality of consumer reports are generally good and these reports highlight via first-hand information the real-life experience of an ADR. Consumers also report different ADRs than healthcare professionals [14, 15]. Being unconstrained with regards to the probability of causality, consumers may report relevant ADRs that healthcare professionals may not recognise initially or consider to be unlikely. Patient B's gastroenterologist recognised the phenomenon, but it is conceivable that not every gastroenterologist will establish a direct relationship between urine discolouration, mesalamine therapy and the use of a specific detergent. The two reports received provide important information about a harmless reaction as this phenomenon probably concerns a lot of other patients using mesalamine.

Conclusion

Based on the described reports and the case reports in the literature, we suggest a causal relationship between red–brown discolouration of urine after contact with sodium hypochlorite detergent and the use of mesalamine. The Naranjo assessment scores for cases A and B were 9 and 6, indicating a certain and probable relationship, respectively. This seems to be a harmless reaction as the patients experienced no physical complaints and in both the Lareb cases and those described by Sacks and Davis [7], the patients were under the care of a gastroenterologist. In the differential diagnosis it is important to be aware that the use of sodium hypochlorite as a toilet detergent could be the cause of coloured deposits in and on the toilet bowl. The presence of sodium hypochlorite does not exclude the possibility of renal impairment; therefore, it is important to distinguish already discoloured urine from normal-coloured urine that only discoloured after contacting the toilet bowl. Knowledge of this harmless reaction is desirable to avoid unnecessary physical examination and worry. Thus, to inform and reassure patients, it might be helpful to mention red-brown discolouration in the patient leaflet for mesalamine.

Compliance with Ethical Standards

Written informed consent was obtained from both patients for the publication of these case reports. Copies of the consents may be requested for review from the corresponding author.

Competing interests/funding Tim Smeets and Florence van Hunsel declare that they have no conflicts of interest. No financial support was received for the conduct of this study or preparation of this manuscript.

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