Mesalamine and dark, red-brown urine

Introduction

Mesalamine, also known as mesalazine or 5-aminosalicylic acid (5-ASA), is indicated for *ulcerative colitis* and *Crohn's disease*. The exact mechanism of mesalamine is unknown, but it is thought to locally suppress inflammation in the gut wall in inflammatory bowel disease. In vitro studies have showed that inhibition of lipoxygenase could play a role, prostaglandin concentrations in the bowel mucosa were observed and mesalamine could serve as binder of reactive oxygen compounds [1]. Mesalamine was granted marketing authorization in the Netherlands in 1984 as Salofalk® [2] and is nowadays also available as various (generic) brands.

Reports

In the period from August 6, 2009 until April 4, 2022 Lareb received 21 reports on mesalamine and a dark, red-brown urine discolouration [3]. Reporters were both health care professionals (8) and consumers (13). Reporters mentioned that the urine discoloured after contact with sodium hypochlorite detergent in toilet water. According to 10 reporters, the dark, red-brown urine left stains in the toilet and on the toilet seat which were hard to clean. Eight reporters mentioned that the urine discolouration was worrisome and was believed to be blood in urine at first glance. In four reports urine tests and/or other physical examinations were performed to exclude other causes.

In 2016, a case series of two of these reports (NL-LRB-90253 and NL-LRB-196150) was published to create awareness for this phenomenon [4]. It included pictures of red brown discoloured urine after sodium hypochlorite bleach was added to the urine of one of the reporting patients. Three additional cases are highlighted below.

Case A (NL-LRB-00370876)

This spontaneous report from a pharmacist concerns a 50-60-year-old female, with black stains in toilet following administration of mesalamine for Crohn's disease. At work black stains where visible in the toilet after urination, which were difficult to remove. The toilet at work was cleaned using bleach, while the patient used a different cleaning product at home. The patient suspected an interaction between her urine and bleach and bought bleach to test it at home. This resulted in the same black stains. The reporting pharmacist tested all medication the patient had been using for the last 1.5 years. Only mesalamine turned black immediately after contact with bleach (figure 1). Mesalamine did not turn black upon contact with cleaning vinegar.

Figure 1. Mesalamine granulate turned black after addition of bleach, while other tablets stay white

Case B (NL-LRB-00696125)

This spontaneous report from a consumer concerns a 30-40-year-old female with red-brown urine following administration of mesalamine for ulcerative colitis. After urinating in a toilet cleaned with bleach, her urine turned red-brown directly. Afraid that her urine contained blood, she also urinated in a separate glass where her urine was a normal yellow. At home, she has already changed several toilet seats because of the stains due to the discoloured urine. Cleaning the toilet without bleach solved the problem.

Case C (NL-LRB-00698174)

This spontaneous report from a physician concerns an 10-20-year-old male, with urine discolouration following administration of mesalamine for ulcerative colitis. At first it was suspected that the urine

contained blood. After urine tests haematuria was excluded as cause for the urine discolouration and the reporter found out that the urine discolouration only occurred if the patient urinated in a toilet cleaned with bleach. The reporter mentioned that the urine discolouration led to worry and uncertainty.

Other sources of information

Summary of Product Characteristics (SmPC) & Patient Information Leaflet (PIL)

Urine discolouration (in Dutch 'verkleuring van urine') is mentioned as a side effect in the Dutch SmPCs of all forms of mesalamine from the brand Pentasa® [5]. However in the PIL this is translated as urine decolouration (in Dutch 'ontkleuring van urine') [6]. Both the SmPC nor the PIL do not state that this only concerns a chemical reaction when urine comes in contact with bleach. In Dutch SmPCs of other brands urine discolouration or chromaturia is not mentioned as an adverse drug reaction [1, 7-12].

Mechanism

Mesalamine and its inactive metabolite N-acetyl-5-aminosalicylic acid are primarily excreted in urine. Cleaning the toilet with sodium hypochlorite creates an alkaline environment. It has been hypothesised that in this alkaline environment polymerisation of mesalamine and/or metabolites in urine could lead to urine discolouration [4].

Prescription data

Table 1. Number of patients using mesalamine in the Netherlands between 2016 and 2020 [13]

Drug	2016	2017	2018	2019	2020
Mesalamine	50,009	50,682	51,633	52,519	51,991

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 21 reports that mentioned a dark, red-brown urine discolouration associated with the use of mesalamine. Most of these reports mention specifically that this reaction occurred when the urine came in contact with sodium hypochlorite bleach. This is supported by two reports in which experiments where performed to confirm that the urine turned dark when it came in contact with bleach and was a normal yellow without contact with bleach. In another report mesalamine granulates turned black when they came in contact with bleach and other medicines from the patient did not have that effect.

Even though the chemical reaction between mesalamine and bleach is harmless, it can lead to unnecessary physical examination and worry as mentioned in the reports received by Lareb. Reporters mentioned that they found information about urine discolouration on the website of the patient organisation Crohn & Colitis NL [14], but not in the PIL. Information in SmPCs and PILs is currently not uniform. Creating more awareness is warranted.

References

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3. Netherlands Pharmacovigilance Centre Lareb Database [Internet]. [cited 04-04-2022].
4. Smeets T, van Hunsel F. Red-Brown Urine Discolouration in Two Patients Taking Mesalamine. Drug Saf Case Rep. 2016;3(1):6.
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14. NL CC. Mesalazine kan zorgen voor een rood-bruine urine bij contact met bleek [updated November 2020. Available from: https://www.crohn-colitis.nl/wp-content/uploads/2020/11/Verkleurde-urine-bij-mesalazine-gebruik-na-contact-met-bleek_def.pdf.

This signal has been raised on June 16, 2022. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl