

## 1.1. Mesalazine and photosensitivity

### Introduction

Mesalazine (Salofalk®) is an aminosalicylate anti-inflammatory agent and is indicated *for the maintenance of remission and for the treatment of patients with mildly to moderately active ulcerative colitis and Crohn's disease*. The mechanism of action of mesalazine is unknown, but appears to be local (in the intestine) rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, ie, prostanoids, and through the lipoxygenase pathways, ie, leukotrienes and hydroxyecosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalazine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon [1].

Mesalazine has been approved for the Dutch market since 1987 [1].

Photosensitivity induced by exogenous agents is a process in which chemicals or drugs that are ingested or applied to the skin promote a photosensitivity reaction when the individual is exposed to sunlight. It can be divided into phototoxic and photoallergic reactions. Phototoxic and photoallergic reactions differ in their clinical features and causative agents. Phototoxicity results from direct tissue or cellular damage following ultraviolet irradiation of a phototoxic agent that has been ingested or applied to the skin. Phototoxicity can occur in any individual in whom the threshold concentration of the chemical or drug has been reached. By contrast, photoallergy is a cell-mediated immune response elicited by small amounts of compound in previously sensitized individuals [2].

The majority of drug-induced photosensitivity reactions are phototoxic. Phototoxic reactions appear as an exaggerated sunburn. The reaction usually evolves within minutes to hours of sun exposure and is restricted to exposed skin.

Photoallergic reactions are typically pruritic, eczematous eruptions in sun-exposed areas of skin that develop 24 to 48 hours after sun exposure [2].

### Reports

Between April 2002 and July 2014 Lareb received five reports of photosensitivity associated with the use of mesalazine.

| Patient, Sex, Age                           | Drug Indication for use                                     | Concomitant medication   | Suspected adverse drug reaction | Time to onset, Action with drug outcome  |
|---|---|--|---------------------------------|--|
| A 123640<br>M, 51-60<br>year,<br>Pharmacist | mesalazine granules, 1<br>dd 3000 mg,<br>colitis ulcerative | macrogol/electroly<br>tes  | photosensitivity<br>reaction    | 4 years, unknown,<br>recovered   |
| B 137841<br>F, 51-60<br>year,<br>Pharmacist | mesalazine granules, 1<br>dd 2000 mg,<br>Crohn's disease    | omeprazol,<br>amlodipine,<br>doxazosine,<br>valsartan,<br>temazepam,<br>metoprolol,<br>ethinylestradiol/le<br>vonorgestrel | photosensitivity<br>reaction    | 2 months, drug<br>withdrawn,<br>recovering   |
| C 35159<br>M, 31-40<br>year,<br>Pharmacist  | mesalazine tablet<br>500mg, 3 dd 1                          |  | photosensitivity<br>reaction    | approximately 1<br>hour after being in<br>the sunshine,<br>dose not<br>changed, not<br>recovered |

| Patient, Sex, Age                         | Drug Indication for use   | Concomitant medication | Suspected adverse drug reaction                     | Time to onset, Action with drug outcome  |
|---|---|------------------------|---|--|
| D 90877<br>M, 41-50<br>year,<br>Consumer  | mesalazine,<br>colitis ulcerative,<br>azathioprine,<br>colitis ulcerative                                     |                        | photosensitivity<br>reaction,<br>scleritis,         | mesalazine, 5<br>years, dose not<br>changed,<br>recovered with<br>sequel<br>azathioprine, 5<br>years, dose not<br>changed,<br>recovered with<br>sequel |
| E 179366<br>F, 31-40<br>year,<br>Consumer | mesalazine tablet 2 dd<br>1000 mg,<br>Crohn's disease<br>azathioprine tablet 1 dd<br>25mg,<br>Crohn's disease | cyanocobalamine        | photosensitivity<br>reaction, cervical<br>dysplasia | mesalazine, 1<br>year, dose not<br>changed, not<br>recovered<br>azathioprine, 1<br>year, dose not<br>changed, not<br>recovered                         |

### Case A

This patient had used mesalazine in the past and experienced sunburns and sun allergy also at that time.

### Case C

This patient has had symptoms of photosensitivity for five years, starting each time approximately one hour after being in the sunshine. The reaction occurred on the hands, underarms, knees and feet. It worsened every year and impaired his quality of life on sunny days.

### Case D

The patient experienced skin burn of the face and chest and subsequent peeling skin with itching. He was treated with hydrocortisone. In the winter he feels better and does not have symptoms of photosensitivity.

### Other sources of information

#### SmPC

The Dutch SmPC of mesalazine does not mention photosensitivity [1]. However, the Dutch SmPC of sulfasalazine (which is metabolised to mesalazine and sulfapyridine) does mention photosensitivity as an adverse reaction with unknown frequency [3]. The US SmPC [4] mentions photosensitivity as an adverse reaction that is reported infrequently (ie, less than 1%).

#### Literature

Several case reports in the literature describe the occurrence of photosensitivity while using mesalazine.

Cozzani et al [5] describe a case report of a 46-year-old man who had been taking mesalazine for 6 months when he suddenly developed severe eczematous dermatitis that was localized on sun-exposed body areas. Based on the clinical presentation and photo-test results a mesalazine-induced photosensitivity reaction was suspected and the drug was stopped leading to slow progressive clinical improvement and resolution within 6 months.

Another case report [6] describes a 56-year-old man who presented with severe photo-aggravation of his eczema and immediate photosensitivity within months after starting mesalazine. He did not take any other medication. Within ten days after withdrawal of mesalazine his photosensitivity completely disappeared.

Horiuchi and Shimakura [7] describe a 48-year-old man who was exposed to the sun and one day later developed several small bullae on the bilateral back of his hands. A skin biopsy showed exudative erythemas with subepidermal blister formation. The bullous eruptions were considered to have resulted from photosensitivity reactions triggered by mesalazine.

## Databases

Table 2. Reports of photosensitivity associated with the use of mesalazine in the Lareb, WHO and Eudravigilance database [8,9].

| Database       | Drug       | Number of reports | ROR (95% CI)   |
|----------------|------------|-------------------|----------------|
| Lareb          | mesalazine | 5                 | 4.5 [1.9-11.0] |
| WHO            | mesalazine | 57                | 2.3 [1.8-3.0]  |
| Eudravigilance | mesalazine | 24                | 3.1 [2.1-4.6]  |

WHO database: 47 reports have mesalazine as single suspect drug and 6 reports have mesalazine co-reported with azathioprine as suspect drugs. There are 11 positive dechallenges and 4 positive rechallenges reported.

Eudravigilance database: 16 reports have mesalazine as single suspect drug and 8 reports have mesalazine co-reported with azathioprine as suspect drugs. There are 6 positive dechallenges and 0 positive rechallenges reported.

### Prescription data [10]

| Drug       | 2010   | 2011   | 2012   | 2013   | 2014   |
|------------|--------|--------|--------|--------|--------|
| mesalazine | 49,688 | 50,121 | 50,004 | 49,586 | 49,655 |

### Mechanism

The pathomechanism of mesalazine-induced photosensitivity is uncertain. Mesalazine is an aminosalicilate. Salicylates have been associated with photosensitivity, particularly phototoxicity. Therefore, it is speculated that it may be an idiosyncratic phototoxic reaction, although a photo-allergic reaction cannot be excluded [6].

### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received five reports of photosensitivity associated with the use of mesalazine. Two patients specifically mention that the reaction occurred on sun-exposed parts of their body. One patient reported having the same symptoms when using mesalazine in the past. Another patient withdrew mesalazine and is recovering.

The reported latency of months/years represents the lag time between the start of mesalazine and the occurrence of symptoms and can thus be prolonged when the patient is not exposed to sunlight for a longer period of time. In reports D and E a role of azathioprine cannot be excluded. In 2008 Lareb wrote a signal about azathioprine and photosensitivity [11] and in 2015 an update of this signal was given [12].

The association of mesalazine and photosensitivity is supported by a statistically significant disproportionality in the database of Lareb, WHO and Eudravigilance and in the literature several case reports are described. Although the Dutch SmPC does not mention this association, the US SmPC does.

The available data suggest an association between mesalazine and photosensitivity.

### References

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4. US SmPC Pentasa®. (version date: 8-5-2015, access date: 2-11-2016) [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/020049s0271bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020049s0271bl.pdf).
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6. Al-Niaimi F, Lyon C. Mesalazine-induced photosensitivity. Eur J Dermatol 2011;21(1):105-6.
7. Horiuchi Y, Shimakura S. Mesalazine and photosensitivity. Am J Gastroenterol 1999;94(11):3386-7.
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9. Eudravigilance database. (version date: 2016, access date: 2-11-2016) <http://bi.eudra.org> (access restricted).

10. GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board. (version date: 4-1-2016, access date: 2-11-2016) <http://www.gipdatabank.nl>.
11. Azathioprine and photosensitivity reactions. (version date: 1-6-2008, access date: 2-11-2016) [http://www.lareb.nl/Signalen/kwb\\_2008\\_1\\_azath](http://www.lareb.nl/Signalen/kwb_2008_1_azath).
12. Azathioprine and photosensitivity reactions-an update. (version date: 3-7-2015, access date: 2-11-2016) [http://www.lareb.nl/Signalen/KWB\\_2015\\_2\\_azathi](http://www.lareb.nl/Signalen/KWB_2015_2_azathi).

*This signal has been raised on February 2017. 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.cbq-meb.nl](http://www.cbq-meb.nl)*