Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Azathioprine and chromaturia

Introduction

Azathioprine is an anti-metabolite (purine antagonist), which was registered in the Netherlands in 1968. Its indications include *immunosuppression in patients undergoing organ transplantation, and moderate to severe inflammatory bowel diseases, such as M. Crohn and ulcerative colitis*. In addition, azathioprine has been used off label with clinical results (sometimes in combination with corticosteroids) in the following indications: *Severe rheumatoid arthritis, pemphigus vulgaris, chronic refractory idiopathic thrombocytopenic purpura, systemic lupus erythematosus, dermatomyositis, polymyositis, polyarteritis nodosa, autoimmune chronic active hepatitis and autoimmune haemolytic anemia* [1-8].
Chromaturia is defined as an abnormal coloration of urine and can have several causes, including dehydration, liver and kidney disorders, and intoxication with lead or mercury. In addition, chromaturia is a well known side effect of certain drugs or their metabolites, such as anthracyclines, levodopa and metronidazole [9].

Reports

On November 30, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained 4 reports concerning chromaturia with the use of azathioprine.

Table 1. Reports of chromaturia associated with the use of azathioprine

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 40781 F, 51-60 years	azathioprine 50mg daily Crohn's disease	prednisone	chromaturia	1 day no change not recovered
B 53591 M, 31-40 years	azathioprine 150mg daily Crohn's disease		chromaturia, sweat discolouration	unknown dose reduction not yet recovered
C 77459 F, 51-60 years	azathioprine 200mg daily		chromaturia	1 day no change unknown
D 110104 M, 41-50 years	azathioprine 150mg daily ulcerative colitis	mesalazine prednisolon	chromaturia, headache, fever, poor sleep, pain in knee, nausea	14 days unknown unknown with respect to chromaturia

Patient A, a female between 51 and 60 years experienced chromaturia (color was lemon yellow) following administration of azathioprine 50mg daily for M. Crohn with a latency of 1 day. Azathioprine was continued and the patient did not recover. Concomitant medication was prednisone (daily dose unknown).

Patient B, a male between 31 and 40 years experienced chromaturia and sweat discoloration (color was dark yellow) following administration of azathioprine 150mg daily for M. Crohn with an unknown latency. The reactions were most profound when the dose of azathioprine was 150mg daily. After dose reduction to 75mg daily, the patient started recovering and the reactions were hardly noticeable. No concomitant medication was reported.

Patient C, a female between 51 and 60 years experienced chromaturia (color was not reported) following administration of azathioprine 200mg daily for an unknown indication with a latency of 1 day. The dose of azathioprine was not changed and the outcome was unknown. No concomitant medication was reported.

Patient D, a male between 41 and 50 years experienced chromaturia (color was green) following administration of azathioprine 150mg daily for ulcerative colitis with a latency of 14 days. The patient also experienced headache, fever, poor sleep, pain in his knees and nausea. The action taken for azathioprine was unknown and the patient recovered with sequelae. Concomitant medication was mesalazine 3000mg daily and prednisolone (decreasing from 10mg daily to 0mg).

Other sources of information

SmPC

Chromaturia is not mentioned in the SmPC of azathioprine containing products [1-8]

Literature

A Medline search revealed no publications on the possible association between azathioprine or its metabolites and chromaturia.

Databases

On November 30, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained four cases of chromaturia in association with azathioprine, which was reported disproportionally (ROR = 20.4, 95% CI: 7.4 – 56.4).
The WHO database of the Uppsala Monitoring Centre contained 17 reports of chromaturia, and this was also reported disproportionally (ROR = 3.0, 95% CI: 1.9 – 4.8).
On January 18, 2011 the Eudravigilance database contained 18 reports (ten males and eight females) of chromaturia associated with the use of azathioprine, which was reported disproportionally (ROR = 1.8, 95% CI: 1.1 – 2.8). The median age of the patients was 50 years (range 18 – 77). Of these reports, 16 were classified as serious, one case was classified as non-serious and in one case seriousness was not reported. Although 16 out of 18 cases were classified as serious, this classification was most likely not due to the chromaturia, but to other ADRs reported in the same case. For example, several cases also mention hepatotoxicity as an ADR, which is most likely the reason these events were qualified as serious. In these cases it is not evident if hepatotoxicity was causing chromaturia or not.

Prescription data

The number of patients using azathioprine in the Netherlands is shown in table 2.

Table 2. Number of patients using azathioprine or methotrexate in the Netherlands between 2005 and 2009 [10]

Drug	2005	2006	2007	2008	2009
Azathioprine	20,123	22,363	22,796	23,427	25,014

Mechanism

The mechanism through which azathioprine may induce chromaturia is unknown. Although it is known that the color of azathioprine as an active substance is yellow [11], it is uncertain whether this could have caused the chromaturia, especially since there was a marked variation in urine color described in the Lareb cases (light yellow, dark yellow and green).

Discussion

Lareb received 4 reports concerning chromaturia with the use of azathioprine. In one case, the patient was recovering at the time of reporting. A mechanism that could explain this association could not be found, which is partly due to the difference in urine color reported. The association between chromaturia and azathioprine is supported by a statistically significant disproportionality in the database of the Netherlands Pharmacovigilance Centre Lareb, the WHO database and the Eudravigilance database.

Conclusion

These cases suggest a signal of chromaturia associated with the use of azathioprine.

- Possible new signal of azathioprine associated with chromaturia

References
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