1.1. Azathioprine and chromaturia - update

Introduction

Azathioprine (Azafalk®, Imuran®) is a prodrug of 6- mercaptopurine, which is a purine antagonist with immunosuppressive activity. It is registered in the Netherlands since 1968. In combination with corticosteroids and/or other immunosuppressants, azathioprine is indicated for *the prevention of rejection in transplantation*. As monotherapy, but also in combination with corticosteroids and/or other immunosuppressants, azathioprine is indicated for the treatment of *moderate to severe inflammatory bowel diseases as Crohn's disease and ulcerative colitis, severe rheumatoid arthritis, pemphigus vulgaris, chronic refractory idiopathic thrombocytopenic purpura, systemic lupus erythematosus, dermatomyositis, polymyositis, polyarteritis nodosa, autoimmune chronic active hepatitis and autoimmune hemolytic anemia [1-3]*.

Chromaturia is defined as an abnormal coloration of urine [4]. There are various circumstances that might cause or influence the urine color, such as liver and kidney disorders, hydration status, consumption of pigment containing foods or supplements, intoxication with lead or mercury and usage of certain medications [5].

In the quarterly report of 2011-2, the Netherlands Pharmacovigilance Centre Lareb described chromaturia in association with azathioprine [6]. Due to a large number of new reports, this signal gives an update of the reports received so far and available literature about this association.

Reports

Between July 8th 2003 and April 14th 2016 the Netherlands Pharmacovigilance Centre Lareb received 31 reports of chromaturia associated with the use of azathioprine. Most reports (n=24) were received in 2016. This is probably due to a publication about this relation on the website of the Dutch association for Crohn's disease and ulcerative colitis in February 2016. None of the reports were serious according to the CIOMS criteria. Consumers reported the most (n=27), followed by physicians (n=2) and pharmacists (n=2). Of all reports, 22 patients were female and nine were male with a median age of 33 years (range 14 – 57 years). The reported indications for azathioprine were Crohn's disease (n=14), ulcerative colitis (n=13), autoimmune hepatitis (n=1), rheumatoid arthritis (n=1) and unknown (n=2). In 26 reports chromaturia was the only reported reaction.
The time to onset varied from minutes to 10 years (median several days). Two patients recovered after withdrawal of azathioprine and one patient recovered after dose reduction. In 19 patients, the dose of azathioprine was not changed, including 15 patients that were not recovered at time of reporting and four patients of which the outcome is unknown. In eight reports it is unknown if any dose adjustments were made. Of them, one patient recovered with sequel and seven patients were not recovered at time of reporting.
In 18 reports the patients used concomitant medication. Six patients used mesalazine as concomitant medication, a drug with orange-red coloration of the urine as adverse event [7]. In two of these reports, an association with mesalazine can not be excluded, because the start date of mesalazine was unknown. In one report the patient recovered after withdrawal of azathioprine. Based on the time to onset, an association with mesalazine was less likely in two reports and more likely in one report. Of the other concomitant medication reported chromaturia is not a known side effect. In one report, the reporter mentioned that the general practitioner thought the coloration was due to a cystitis. However, examination of the urine showed no abnormalities.
In the 31 reports, the urine coloration was described as bright yellow (n=10), marker pen yellow (n=5), urine coloration (n=2), yellow (n=2), green-yellow (n=2), fluorescent (n=2), fluorescent yellow (n=1), neon yellow-green (n=1), green morning urine (n=1), almost green (n=1), dark yellow (n=1), lemon yellow (n=1), excessive yellow (n=1) and striking yellow (n=1). For an overview of the reports see table 3 in the appendix.

Other sources of information

SmPC
Chromaturia or similar events are not mentioned in the Dutch and US SmPC of azathioprine [1-3,8].

Literature

No further information was available in medical reference books about azathioprine or its metabolites in relation to chromaturia. Also, on June 26th 2016 a Medline search revealed no publications on this possible association. However, on several forums patients discussed the occurrence of bright yellow urine while using azathioprine [9-12].

Databases

Table 1. Reports of chromaturia in association with azathioprine in the Lareb, WHO and Eudravigilance database on June 27th 2016 [13-15].

Database	Drug	Number of reports	ROR [95%CI]
Lareb	azathioprine	31	65.7 [44.1-97.8]
WHO	azathioprine	70	4.7 [3.7-5.9]
Eudravigilance	azathioprine	63	3.7 [2.9-4.7]

Prescription data

Table 2. Number of patients using azathioprine in the Netherlands between 2010 and 2014 [16].

Drug	2010	2011	2012	2013	2014
azathioprine	24,989	26,042	26,959	27,374	27,890

Mechanism

Although both azathioprine and 6-mercaptopurine are yellow substances, less than two percent of the drug is eliminated as azathioprine or 6-mercaptopurine [3,17,18]. Another possible theory is that thiopurines are also significant UVA chromophores. Both 6-mercaptopurine and 6-thioguanine nucleotides are UVA photosensitizers which means they can produce a chemical reaction by light absorption [19]. Possibly, this photochemical reaction can cause a rapid discoloration of urine when it is excreted.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 31 reports of chromaturia in association with the use of azathioprine, mostly reported by consumers. In six reports the patients also used mesalazine. However, this drug is known to cause an orange-red coloration of the urine, while in these reports the discoloration of the urine varied from green to bright yellow. Furthermore, in most reports azathioprine was reported as the only suspect drug. Remarkably, many reporters described the urine coloration as bright or marker pen yellow with a plausible median time to onset of days. The chromaturia recovered in the two patients in which azathioprine was withdrawn. Though, for most patients no dose adjustments were made, presumably because the discoloration gave no further complaints. Subsequently, most of them were not recovered at time of reporting. One reporter mentioned that the general practitioner thought the coloration was due to a cystitis. However, this was not confirmed by further examination of the urine. In addition, the association between azathioprine and chromaturia is statistically supported by a significant disproportionality in the databases of the Netherlands Pharmacovigilance Centre Lareb, the Uppsala Monitoring Centre (WHO-collaborating centre) and Eudravigilance. Although in literature no pharmacological information is available about azathioprine or its metabolites in relation to the coloration of urine, these cases suggest an association between the use of azathioprine and chromaturia.

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Addendum

Table 3. Reports of chromaturia associated with the use of azathioprine.

Number, Sex, Age, Reporter	Suspect/ Interacting drug, Dose, Indication	Concomitant medication	Reaction	Time to onset, Action with drug, Outcome
A: 40781, F, 51-70, physician	Imuran® tablet, 50mg 1dd1, Crohn's disease	prednisone tablet 5mg	urine discolouration	1 day, dose not changed, not recovered
B: 53591, M, 31-40, consumer	azathioprine tablet, 50mg 3dd1, Crohn's disease	-	urine discolouration, sweat discolouration	days, dose reduced, recovered
C: 77459, F, 51-60, pharmacist	azathioprine tablet, 50mg 1dd4, unknown	-	urine discoloration	1 day, dose not changed, unknown
D: 110104, M, 41-50, consumer	Imuran® tablet, 50mg 1dd3, ulcerative colitis	mesalazine tablet 250mg, prednisolone tablet 5mg	urine discolouration, nausea, pain in knee, poor sleep, headache, fever	14 days, unknown, recovered with sequel
E: 159662, M, 31-40, physician	azathioprine tablet, 50mg 2dd1, ulcerative colitis	atenolol tablet 100mg, prednisolone tablet 5mg	urine color abnormal, nausea, arthralgia, fever, painful respiration, pancreatitis, stiffness joints	9 days, drug withdrawn, recovered
F: 187401, F, 21-30, consumer	azathioprine tablet, 50mg 1dd1, autoimmune hepatitis	prednisone tablet 5mg	urine discolouration	1 month, dose not changed, not recovered
G: 207641, F, 21-30, consumer	azathioprine tablet, 50mg 1dd1t, rheumatoid arthritis	-	urine color abnormal	3 hours, dose not changed, unknown
H: 214052, F, 21-30, consumer	azathioprine tablet, 25mg 1dd3, ulcerative colitis	-	urine discolouration	7 days, dose increased, unknown
I: 214054, F, 21-30, consumer	azathioprine tablet, 50mg 1d2.5, Crohn's disease	-	urine discolouration	1 hour, dose not changed, not recovered
J: 214058, F, 31-40, consumer	azathioprine tablet, 50mg 1dd3, Crohn's disease	pantoprazole tablet 20mg	urine discolouration	unknown, dose not changed, not recovered
K: 214097, F, 41-50, consumer	azathioprine tablet, 50mg 1dd3, ulcerative colitis, mesalazine tablet, 500mg 1dd4, ulcerative colitis	-	urine discolouration	8 years after start of azathioprine/ hours after start of mesalazine, action azathioprine unknown/ dose mesalazine not changed, not recovered
L: 214119, F, 31-40, consumer	azathioprine, unknown 1dd2, Crohn's disease	mometasone nose spray 50mcg, salmeterol/fluticasone inhaler 50/250mcg, montelukast tablet 4mg, allopurinol capsule 10mg	urine discolouration	24 hours, dose not changed, not recovered
M: 214120, F, 21-30, consumer	azathioprine tablet, 25mg & 50mg 1dd75mg, Crohn's disease	-	urine discolouration	hours, unknown, not recovered

Number, Sex, Age, Reporter	Suspect/ Interacting drug, Dose, Indication	Concomitant medication	Reaction	Time to onset, Action with drug, Outcome
N: 214205, M, 21-30, consumer	azathioprine tablet, 50mg 1dd3, Crohn's disease	omeprazole	urine discolouration	2 hours, dose not changed, not recovered
O: 214554, F, 41-50, consumer	azathioprine tablet, 50mg 1dd3, ulcerative colitis	-	urine discoloration	unknown, dose not changed, not recovered
P: 214555, M, 11-21, consumer	azathioprine, unknown, unknown	-	urine discoloration, fatigue, alopecia	2 months, dose not changed, unknown
Q: 214561, F, 51-60, consumer	Imuran® tablet, 50mg 1dd3, Crohn's disease	tolterodine capsule 4mg, glucosamine 1500mg	urine discolouration	14 days, dose not changed, not recovered
R: 214564, F, 21-30, consumer	Azafalk® tablet, 75mg 1dd2, ulcerative colitis, mesalazine granulate, 1g 3dd1, ulcerative colitis	-	urine discolouration	2 days after start azathioprine/ 3 years after start of mesalazine, action azathioprine unknown/ action mesalazine unknown, not recovered
S: 214565, F, 31-40, consumer	azathioprine, unknown, Crohn's disease	adalimumab injection 50mg/ml	urine discolouration	days, dose not changed, not recovered
T: 214566, F, 21-30, consumer	azathioprine tablet, 50mg 1dd4, Crohn's disease	mebeverine retard capsule 200mg	urine discolouration	2 hours, unknown, not recovered
U: 214567, M, 31-40, consumer	azathioprine tablet, 25mg 1dd2, ulcerative colitis	mesalazine granulate 2g	urine discolouration	2 week, drug withdrawn, recovered
V: 214568, F, 31-40, consumer	azathioprine tablet, 50mg 1dd3,5, ulcerative colitis	mesalazine tablet 1g	urine discolouration	direct after start azathioprine/ 10.5 years after start of mesalazine, unknown, not recovered
W: 214569, F, 11-21, consumer	azathioprine tablet, 100mg 1dd175mg, ulcerative colitis	infliximab infusion	urine discolouration	days, unknown, not recovered
X: 214571, M, 41-50, consumer	azathioprine tablet, 50mg 1dd4, ulcerative colitis	-	urine discolouration	1 hour, dose not changed, not recovered
Y: 214596, F, 31-40, consumer	azathioprine tablet, 50mg 1dd4, Crohn's disease	-	urine discolouration, urine odour abnormal	months, dose not changed, not recovered
Z: 214757, F, 31-40, pharmacist	azathioprine tablet, 50mg 2dd3, Crohn's disease	beclomethasone/ mesalazine clyster 3mg/2g	urine discolouration	1 day, action azathioprine dose not changed/ action beclometason/ mesalazine unknown, not recovered
AA: 215299, F, 21-30, consumer	azathioprine tablet, 50mg 1dd3, ulcerative colitis	-	urine discoloration	unknown, dose not changed, unknown
BB: 215563, M, 21-30, consumer	azathioprine tablet, 50mg 1dd1.5, ulcerative colitis	allopurinol tablet 100mg	urine discolouration	minutes, unknown, not recovered
CC: 215565, F, 11-21, consumer	azathioprine, unknown 1dd2, ulcerative colitis	-	urine discolouration	direct after start, dose not changed, not recovered

Number, Sex, Age, Reporter	Suspect/ Interacting drug, Dose, Indication	Concomitant medication	Reaction	Time to onset, Action with drug, Outcome
DD: 216530, M, 31-30, consumer	azathioprine tablet, 50mg 1dd3, Crohn's disease	-	urine discolouration	1 week, dose not changed, not recovered
EE: 217293, F, 41-50, consumer	azathioprine tablet, 50mg 1dd3, Crohn's disease	bisoprolol	urine discolouration	10 years, dose not changed, not recovered