Mercaptopurine and photosensitivity

Introduction

Mercaptopurine (Puri-Nethol®) has been registered since August 1967. It is indicated for *the treatment of acute lymphatic leukaemia (ALL) and for lymphoid blast crisis in patients with chronic myeloid leukaemia (CML)* [1]. The mechanism of action of mercaptopurine is based on its cytotoxic antimetabolite activity. The drug is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to tioguanine nucleotides for cytotoxicity. The mercaptopurine metabolites inhibit *de novo* purine synthesis and purine nucleotide interconversions

In the first quarter of 2008, Lareb wrote a quarterly report on photosensitivity reactions in patients using azathioprine [2]. The conclusion of that report was that photosensitivity reactions could be related to the use of this drug. Since mercaptopurine is the active metabolite of azathioprine, it is plausible to assume that similar reactions may occur in patients using mercaptopurine.

The current observation describes the possible association between mercaptopurine and photosensitivity reactions.

Reports

On March 21st 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports of photosensitivity reactions associated with the use of mercaptopurine.

Case A (report number 48298)
This non-serious spontaneous report from a pharmacist concerned a male aged between 21 and 30 years, who experienced severe itching after exposure to a solarium during the use of mercaptopurine for Crohn's disease. At the time of exposure, mercaptopurine had been used for approximately four months. The patient recovered from the symptoms two days after exposure to the UV light. Liver function tests showed no abnormalities. The patient experienced a similar reaction previously when he used mercaptopurine and was exposed to a solarium.

Case B (report number 139939)
This non-serious spontaneous report from a pharmacist concerns a male aged between 61 and 70 years, who experienced a facial eczematous rash following administration of mercaptopurine with a latency of 5 months after start. The patient had been exposed to sunlight for several hours and had been using sun tan lotion factor 15. His face was the only part of his body that had been exposed to the sun light. Mercaptopurine was continued and the patient was recovering at the time of reporting (approximately 2 weeks after start of the complaints). Concomitant medication was acenocoumarol.

Other sources of information

SPC

Photosensitivity reactions are not mentioned in the SmPC of mercaptopurine [1].

Literature

Since Lareb published the quarterly report on azathioprine and photosensitivity reactions, two additional papers on this association were published [3,4].

Databases

Since a minimum of three reports is required for a reliable ROR calculation, and the Lareb database only contains 2 cases, no ROR was estimated for the Lareb database.
On March 25st 2013, the WHO database of the Uppsala Monitoring Centre contained nine reports of photosensitivity reactions associated with the use of mercaptopurine, which was not reported disproportionally (ROR = 1.1, 95% CI 0.6 – 2.1).
On March 25st 2013, the Eudravigilance database contained three reports of photosensitivity reactions associated with the use of mercaptopurine, which was not reported disproportionally (ROR = 1.8, 95% CI: 0.6 – 5.6).
Data for azathioprine are present in table 1 for comparative purposes.

Table 1. Reports of photosensitivity reactions associated with mercaptopurine and azathioprine in the databases of the Netherlands Pharmacovigilance Centre Lareb, WHO and EMA.

Drug	Number of reports	ROR (95% CI)
Mercaptopurine	Lareb: 2 WHO: 9 EMA: 3	N.A.* 1.1 (0.6 – 2.1) 1.8 (0.6 – 5.6)
Azathioprine	Lareb: 13 WHO: 75 EMA: 22	7.2 (4.1 – 12.6) 2.2 (1.7 – 2.7) 2.0 (1.3 – 3.0)

* Not applicable since the number of cases is lower than 3

Prescription data

The number of patients using mercaptopurine in the Netherlands is shown in table 2 [5]. It should be noted however, that the data in the GIP database apply to the extramural use of drugs. Since mercaptopurine is mainly used in the hospital, these data probably underestimate the actual number of patients using the drug.

Table 2. Number of patients using mercaptopurine in the Netherlands between 2007 and 2011 [5].

Drug	2007	2008	2009	2010	2011
Mercaptopurine	1,834	2,194	2,603	3,234	3,862

Mechanism

The mechanism is most likely identical to the mechanism of azathioprine as described in the quarterly report of 2008.
"*The active metabolite 6-TG has an absorbance maximum of 342 nm wavelength which is within the UVA spectrum, giving this substance a potential for formation of free radicals or reactive oxygen species. In an in-vitro study, photosensitivity effects of cellular damage, notably at DNA level, was demonstrated in cellular cultures that were exposed to low intensity UVA [6].*"

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received two reports of photosensitivity reactions associated with the use of mercaptopurine. The cases are similar to those reported in the previously published quarterly report (2008) concerning photosensitivity reactions in patients using azathioprine. Since mercaptopurine is an active metabolite of azathioprine, it is plausible to assume that the signal that existed for azathioprine also applies to mercaptopurine.

- Signal of photosensitivity reactions with the use of mercaptopurine

References

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6. O'Donovan P, Perrett CM, Zhang X, Montaner B, Xu YZ, Harwood CA, McGregor JM, Walker SL, Hanaoka F, Karran P. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science 2005;309(5742):1871-4.

This signal has been raised on July 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).

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