Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Azathioprine and photosensitivity reactions

Introduction

Azathioprine (Imuran®) is registered in the Netherlands since 1968 for use *as immunosuppressant both after transplantation as in autoimmune or chronic inflammatory diseases. It is used as monotherapy but often in combination with other medication (usually corticosteroids) and methods influencing immune response for rheumatoid arthritis, pemphigus vulgaris, chronic refractory idiopathic thrombocytopenic purpura, systemic lupus erythematodes, M. Crohn and colitis ulcerosa. Its use usually in combination with corticosteroids and/or other interventions is indicated for dermatomyositis, polymyositis, polyarteritis nodaso, chronic active hepatitis and haemolytic anaemia (auto-immune basis).*
Commonly occurring ADRs with azathioprine are gastrointestinal symptoms, hypersensitivity reactions and immunosuppression related infection [1].
Azathioprine's mechanism of action remains to be elucidated, but suggested mechanisms for it's immunosuppressive properties include:
- the release of 6-mercaptopurine (6-MP) which act as a purine antimetabolite
- the possible blockade of –SH groups by alkylation
- the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response
- damage to deoxyribonucleic acid(DNA) through incorporation of purine thio-analogues.

Azathioprine and long-wave ultraviolet light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine for a range of disorders. As is usual for patients with an increased risk of skin cancer exposure to sunlight and UV light should be limited and patients should wear protective clothing and use sunscreen with a high protection factor.

Photosensitivity reactions are not mentioned in the SmPC of azathioprine.

Reports

On November 26th, 2007, the database of the Netherlands Pharmacovigilance Centre Lareb contained nine reports of photosensitivity (patients A-I) and one photosensitivity allergic reaction (patient I) following use of azathioprine. Report characteristics are presented in table 1.

Table 1. reports of photosensitivity reactions or photosensitivity allergic reactions related to the use of azathioprine.

patient, sex, age number	dose indication for use	concomitant medication	ADR	time to onset, action taken with drug, outcome	remarks
A F, 62	2x50 mg rheumatoid arthritis	naproxen	photosensitivity reaction	3 weeks withdrawn not specified	reported as itch, dermatitis and oedema after exposition

patient, sex, age number	dose indication for use	concomitant medication	ADR	time to onset, action taken with drug, outcome	remarks
					to the sun during a stay in Spain
B F, 44	1x 100 mg ulcerative colitis	omeprazole, misoprostol, oxazepam, triamcinolon cream	photosensitivity reaction, skin infection	unknown, unknown unknown	-
C F,21	1x150mg Crohn's disease	desogestrel, diclofenac, calcium carbonate, colecalciferol	photosensitivity reaction	unknown, dose not changed, recovered	reaction was treated with fexofenadine
D F,28	1x 75/1x 25 mg Crohn's disease	calciumcarbo-nate, colecalciferol, ferro gradumet	photosensitivity reaction	unknown, dose not changed, recovered	two episodes of dermatitis related to the use of a sun bed
E F, 23	1x100mg ulcerative colitis	-	photosensitivity reaction	4 months dose not changed not recovered	symptoms were treated with a sun block
F F, 22	1x150 mg Crohn's disease	esomeprazole, metoprolol, ferrofumarate, psyllium	photosensitivity reaction	7 months, withdrawn, recovering	-
G M, 37	1x75mg ulcerative colitis	-	photosensitivity reaction	1 year temporarily withdrawn recovered	symptoms treated with cetirizine, prior episode of dermal reaction. reaction occurred after using a sunbed.
H F,62	1x150mg Crohn's disease	mesalazine, calcium carbonate, hydrocobalamin	photosensitivity reaction alopecia	3 weeks withdrawn unknown	urticarial rash on hands, arms and neck
I F, 36	3x50 mg rheumatoid arthritis	enalapril, ethinylestradiol/levonorgestrel	photosensitivity reaction	16 months	use of a sun bed and exposition to sun light
J F, 24	1x50 mg Crohn's disease	-	photosensitivity allergic reaction, naevus	1 year dose reduced not recovered	treated with sun block

Other sources of information

SmPC

Photosensitivity reactions are not described in the SmPC for the azathioprine preparations. Yet its mutagenic effects when the patient is exposed to sunlight are mentioned. In this perspective it is advised in section 4.4 of the SmPC to avoid sunlight when using azathioprine [1]. In at least three of the above mentioned

cases exposition to UVA in a sun bed was a contributing factor in occurrence of dermal symptoms. Apparently the advise to avoid UVA exposure is difficult to follow.

Literature

Photo-absorbing properties of azathioprine are described in literature [2-4]. However, no publications are presented in a Pubmed search using MESH terms azathioprine and phototoxic dermatitis. Nor were cases of immunologically mediated photosensitivity reactions published.

Databases

The nine reports of a photosensitivity reaction occurring in relation to the use of azathioprine in the Lareb database are disproportionally represented in the Lareb database (ROR 11 95%CI 5.5 - 21).

In the WHO Uppsala Monitoring Centre database a total 36 cases of photosensitivity reactions related to azathioprine exist (ROR 1.4, 95%CI 1.0 - 1.9).

Mechanism

First, the active substance 6-TG has an absorbance maximum of 342 nm wavelength which is whithin the UVA spectrum, giving this substance a potential for formation of free radicals or reactive oxygen species. In an in-vitrostudy photosensitivity effects of cellular damage, notably at DNA level, was demonstrated in cellular cultures that were exposed to low intensity UVA [3].

Furthermore dermal lesions related to sunlight exposure have been described both in relation to use of azathioprine for inflammatory bowel disease and in relation to the disease itself [4,5]. Symptoms resemble dermal lesions in pellagra, a disorder characterized by a deficiency in niacin (vitamin B3), due to dietary unbalances, or to malabsorption or to ingestion of substances blocking Niacin metabolism [5]. 6-MP is implicated in blocking this pathway, and thus increases the chance for dermal lesions during sunlight exposure in inflammatory bowel disease [4].

Discussion

Azathioprine can be involved in oxidative stress both by increasing absorption of ultraviolet radiation and by diminishing reductive reactions by inhibiting niacin metabolism. A potential confounder can be inflammatory bowel disease activity since this can lead to reduction in intestinal niacin absorption.
Yet two of nine patients with photosensitivity used azathioprine for rheumatoid arthritis and in the remaining patients no signs of increased disease activity, like extensive diarrhoea or intestinal surgery were mentioned.

In six reports, a dermal disorder led to discontinuation of azathioprine therapy, leading to recovery in two cases. Causality rating is complicated by the necessity of two factors being involved in the occurrence of an increased dermal sensitivity to

exposure of sunlight or UVA radiation. Reported latencies only take into account the lag time between start of use of azathioprine and evolvement of symptoms and can thus be prolonged when the patient is not exposed to UVA for a longer period. Furthermore, symptoms can resolve when this exposure is reduced while the use of azathioprine is continued.

Conclusion

The use of azathioprine is related to the occurrence of photosensitivity reactions.

References
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