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Azathioprine in Dermatology

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SUMMARY Azathioprine is a synthetic purine analog derived from 6-mercaptopurine. It is a purine antagonist and its active metabolites act by disrupting the function of endogenous purines. It has a cytotoxic and immunosuppressive mechanism of action. It is used in dermatology for treatment of immunobullous diseases, generalized eczematous disorders and photodermatoses. There is an enzyme in the metabolism of azathioprine called thiopurine s-methyltransferase (TPMT). It is very important to measure the TPMT activity before initiating therapy so that proper dosing of azathioprine can be achieved.

KEY WORDS: azathioprine, azathioprine use in dermatology, adverse effects of azathioprine

INTRODUCTION

Dermatologists have been at the forefront of the application of azathioprine. It has been utilized in dermatology for several decades. Azathioprine is a synthetic purine analog derived from 6-mercaptopurine (6-MP). It is thought to act by disrupting nucleic acid synthesis and has recently been found to interfere with T-cell activation. The most recognized uses of azathioprine in dermatology are for immunobullous diseases, generalized eczematous disorders and photodermatoses.

In hopes of protecting 6-MP from metabolic degradation, an imidazole ring was attached to the molecule and as a result, azathioprine (trade name, Imuran; GlaxoSmithKline) was created (1). Because of the favorable therapeutic index of azathioprine over other traditional immunosuppressants like 6-MP, methotrexate, 5-fluorouracil and actinomycin C (2), it has been utilized as a corticosteroid sparing agent and as monotherapy. The official US Food and Drug Administration indications are for prevention of rejection in renal homotransplantation and for refractory, severe rheumatoid arthritis, yet physicians have successfully employed azathioprine to treat many conditions, including inflammatory bowel disease (Crohn's disease and ulcerative colitis), multiple sclerosis, myasthenia gravis, malignancies and autoimmune conditions (3).

Azathioprine pharmacology

All cells require nucleic acids for their growth. Knowing that, Hitchings and Elion postulated that synthetic purine analogs might halt growth of rapidly dividing cells (4). They wanted to increase the

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efficiency of 6-MP by protecting it from rapid metabolic catabolism. So, azathioprine was produced with the addition of an imidazole ring to the basic structure of 6-MP. Their intention was for azathioprine to be resistant to immediate catabolism and to be more selective in activation in target cells. In short period of time, the researches demonstrated that azathioprine was more active and had better therapeutic index than 6-MP did (1).

Pharmacokinetics and metabolism

Azathioprine is quickly and almost completely absorbed from the digestive tract and does not cross the blood-brain barrier (5). It reaches the peak serum levels 2 hours after ingestion, and the half-life, including all active metabolites, is approximately 5 hours. Azathioprine is extensively metabolized, and only about 2% is excreted, unchanged, in the urine (6). There are two important enzymes in the metabolism of azathioprine. They are thiopurine s-methyltransferase (TPMT) and xanthine oxidase (XO). They are important because as the result of their activity, the inactive metabolites are produced, and as the result of their decreased activity the toxic metabolites are produced. Decreased TPMT activity is a consequence of genetic polymorphisms, while decreased XO activity is frequently mediated by medications such as allopurinol. The main active metabolites of azathioprine are 6-thioguanine nucleotides.

Mechanism of action

Azathioprine is a purine antagonist. The 6-thioguanine active metabolites of azathioprine disrupt the function of endogenous purines (7). So the generally accepted mechanism of azathioprine's cytotoxic and immunosuppressive activities is disruption of nucleic acids and the interference with the activation of T cells. Because the nucleic acids are the building blocks of DNA, RNA and certain coenzymes, the synthesis of DNA, RNA and proteins is disrupted (8).

Thiopurine methyltransferase

Application of azathioprine to a patient with TPMT deficiency results in significant accumulation of toxic metabolites, and it is clinically manifested by increased hematopoietic toxicity, with potentially grave consequences (9).

Testing for TPMT levels is helpful in the care of dermatologic patients in order to achieving proper dosing (10).

AZATHIOPRINE USE IN DERMATOLOGY

Azathioprine has been used successfully to treat immunobullous diseases, precisely in pemphigus vulgaris for nearly 35 years, and has been accepted despite the lack of multiple perspective randomized, double-blinded controlled trials to support its use. It is used for treating eczema, actinic dermatitis and immunobullous diseases. Patients reported to have an excellent response are those who were able to eventually discontinue or reduce their corticosteroids to a very low dose (10 mg or less of prednisone equivalent) daily or a low dose (20 mg or less of prednisone equivalent) every day. Many patients were able to discontinue completely their corticosteroids after several months of azathioprine treatment.

Immunobullous diseases

Since1969, it has been successfully used for treating pemphigus vulgaris (11). Some clinicians also prefer it over other immunosuppressant medications in the treatment of pemphigoid. It has also been used in treating cicatricial pemphigoid.

Psoriasis and eczematous diseases

It has been used in the treatment of psoriasis (12), eczema (atopic dermatitis, hand eczema, adult eczema) (12) and contact dermatitis. Interest in azathioprine for treatment of psoriasis appears to have waned, but several recent publications have documented its successful use in adult and childhood eczema. Of all evidence supporting the use of azathioprine in dermatology, its use in eczematous diseases appears to be strongest. It also works extremely well to control generalized eczematous and pruritic conditions.

Photodermatoses

Chronic actinic dermatitis is a group of disorders aggravated by ultraviolet and visible light. It includes numerous photodermatoses such as photosensitive eczema, photosensitivity dermatitis, persistent light reaction, and actinic reticuloid. Strong evidence supports the use of azathioprine in the treatment of chronic actinic dermatitis (12). Some consider it the first choice for long-term immunosuppression of these conditions. It has also been reported to be helpful in severe polymorphous light eruption.

Other uses

Azathioprine has also been used to treat Behçet syndrome, pityriasis rubra pilaris, erythema

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multiforme, lichen planus, vasculitis, cutaneous lupus, Reiter syndrome, graft-versus-host disease, prurigo nodularis, Sulzberger and Garbe, and acne fulminans. It continues to be actively used in fields outside dermatology. Rheumatologists have employed it to treat systemic lupus erythematosus (SLE), scleroderma and dermatomyositis. It has also been utilized by gastroenterologists, neurologists and surgeons.

Dosing

Dermatologists have only recently begun checking TPMT activity before initiating therapy. Since TPMT was not measured in most prior studies, the lack of benefit may be accounted for by inadequate dosing-underdosing in patients with high TPMT activity (13).

PREGNANCY AND PEDIATRIC USE

Pregnancy considerations

Azathioprine and 6-MP have been shown to cross human placenta in low concentrations and appear in fetal plasma after 24 hours. Although both drugs have been found in the placenta and amniotic fluid of patients taking azathioprine, the inactive metabolite thiouric acid has the greatest concentration (14). The immature liver lacks the enzyme necessary for conversion of 6-MP to the active metabolites, so the developing fetus likely has some protection from azathioprine toxicity early in pregnancy (14). Azathioprine's teratogenicity has not been conclusively established. It is tolerated fairly well in pregnancy, but the most commonly accepted concerns include infants born prematurely and infants small for gestational age. The rate of congenital malformations is dose-dependent and varies from 3% to 9%. The malformations reported with azathioprine include microcephaly, myelomeningocele, preaxial polydactyly, thymic atrophy, adrenal hypoplasia and hypospadias. Hematologic abnormalities have also been reported, but it appears that maintaining the maternal leukocyte count within the normal limits may avert neonatal leukopenia and thrombocytopenia. Reports of infection have been minimal, but cytomegalovirus and gram-negative infections have been reported. Azathioprine may in fact be unrelated to some of the reported anomalies, and alternatively, such defects may be due to the underlying disease state instead. The general consensus is to reserve azathioprine for those pregnant patients with severe or life-threatening disease. Azathioprine does not appear to affect fertility. Minimal concentrations of azathioprine and its metabolites have been found in breast milk. The hemoglobin, leukocyte count, platelet count and growth rate were normal in a breast-fed infant of a patient on azathioprine. However, the potential risk of immune suppression and the theoretical risk of carcinogenesis outweigh the potential benefits of nursing according to the World Health Organization (15).

Use in pediatric patients

Azathioprine has been used successfully in pediatric patients with immunobullous diseases, SLE and dermatomyositis. However, because of immunosuppression concerns regarding the risk of infection and potential development of malignancy, azathioprine should be reserved for those pediatric patients in whom safer therapies have failed.

Drug interactions

The most obvious interaction is with allopurinol, an XO inhibitor used most often to treat gout. Since azathioprine is catabolized in part by XO, concomitant use may result in severe azathioprine toxicity and hematologic complications. Hematologic complications appear to rise 4 to 6 weeks after combination therapy and reverse with its cessation. However, if both medications are absolutely essential, one-quarter to one-third of the original azathioprine dose is recommended with close laboratory monitoring.

Azathioprine has also been reported to induce warfarin resistance. There have been reports of patients on warfarin that bled severely after azathioprine was discontinued. Recurrent thrombosis with initiation of azathioprine therapy has also been reported. This interaction appears to be dose-dependent, so the warfarin dose may have to be increased 3 to 4 times to compensate for azathioprine's interaction.

ADVERSE EFFECTS

Common side effects

Azathioprine is generally well tolerated and has a favorable therapeutic index compared with many other traditional immunosuppressants. Patients overdosed on massive amounts of azathioprine were not left with any permanent impairment. The most common symptomatic side effects of azathioprine are gastrointestinal, ranging from nausea, vomiting to diarrhea. These symptoms may respond to dose adjustment (16), or taking the medication with food. However, azathioprine should be

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immediately discontinued in those patients with severe gastrointestinal symptoms, as they may be developing an intolerant or hypersensitivity reaction. Well-accepted concern with azathioprine is bone marrow depression, so laboratory monitoring of complete blood count is important during the initial weeks of therapy.

Dermatologic problems are more frequent in transplantation patients than in non-transplantation patients on azathioprine (17). Pale skin types, excess sun exposure and duration of allograft seem to be important risk factors in the development of skin lesions. Common skin problems include alopecia, verrucae, zoster, increased skin color and malignant neoplasms.

Uncommon side effects

Allergic contact dermatitis has been reported in persons who come into physical contact with azathioprine tablets. More severe systemic hypersensitivity reactions have been reported in patients taking azathioprine. This azathioprine intolerance or hypersensitivity reaction commonly occurs within the first 4 weeks of therapy. The findings of hypersensitivity greatly vary and can range from fever, nausea, vomiting, diarrhea, arthralgia and malaise to hypotension, shock and possibly even death (18). Most of the cases are reported in patients with neurologic diseases, rheumatologic disorders and in transplantation patients. Hypersensitivity symptoms typically resolve in a few days (between 12 hours and 20 days) after discontinuation of azathioprine.

Malignancy potential

Skin type, sun exposure, dose and length of azathioprine treatment are important factors in determining the risk of the development of skin cancer. Patients on higher doses and longer durations of azathioprine have been shown to be at an increased risk of skin cancer, particularly squamous cell carcinoma. Aggressive squamous cell carcinoma has been reported in dermatology patients with type 1 skin and greater than 4 years of azathioprine therapy. Those with more immune suppression, such as heart transplantation patients, appear to be at a greater risk than those with lesser suppression, like kidney transplantation patients. Patients with psoriasis and dermatomyositis who have been undergoing azathioprine treatment for more than 5 years have been reported to develop non-Hodgkin lymphoma. Like skin cancer, internal malignancies such as lymphoma are increased in patients with higher doses and longer duration of immune suppression.

DOSING AND MONITORING

A TPMT value should be obtained before starting treatment, so the proper dose of azathioprine could be determined. Patients generally have responses after 150 mg/day in a few months of therapy, and a trial should not be considered a failure unless the patient has been on an adequate dose for at least 3 months. The dose can be reduced on 50 mg/kg. It is recommended to perform TPMT, pregnancy test, complete blood count and complete metabolic panel at baseline. After initiation of therapy, complete blood cell count bimonthly and complete metabolic panel monthly for the first 2 months of therapy, then monthly for a few months, and then every 3 months is suggested. Complete skin examination should be performed regularly if the patient has been on azathioprine for more than 2 years.

CONCLUSION

Azathioprine has been utilized for several decades, yet only in a few studies TPMT levels were measured. It is possible that many patients found to be unresponsive to azathioprine were underdosed, and those determined to have significant hematologic toxicity had no or low TPMT activity.

Azathioprine is an effective immunosuppressant that is extremely valuable in treating pemphigus vulgaris, pemphigoid, generalized eczematous disorders and actinic dermatitis, and will probably remain in dermatology for years to come.

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