Lesson of the Week

Asymptomatic hyperuricaemia and allopurinol induced toxic epidermal necrolysis

J AUBÖCK, P FRITSCH

Allopurinol, a potent inhibitor of the synthesis of uric acid, is the drug most commonly prescribed for the treatment of primary and secondary hyperuricaemia; worldwide sales are estimated at about 240 million single doses (71 tonnes) each year.¹ Generally the drug is well tolerated, although 2% of patients treated develop a mildly pruritic rash.² If allopurinol is administered together with ampicillin or in renal insufficiency this incidence may increase to 20%. Less common but more severe cutaneous intolerance reactions to allopurinol may occur (see below),^{3,5} which are often associated with multisystemic disease such as immune complex vasculitis, eosinophilia, hepatitis, and progressive renal failure (allopurinol hypersensitivity syndrome)^{1,6}; impaired renal function and concomitant intake of diuretics (especially thiazides) may be predisposing factors. Reports of such reactions seem not to have affected the number of prescriptions for allopurinol, which is increasing (two million in America in 1975⁷ and four million in the Federal Republic of Germany in 1983⁸). In this report we think that allopurinol may be administered unnecessarily in many cases, which is an important hazard in view of its extensive use.

Severe cutaneous intolerance reactions to allopurinol include exfoliative erythroderma, the Stevens-Johnson syndrome, and, as the most severe reaction, toxic epidermal necrolysis, which is an excessive mucocutaneous reaction pattern in which internal organs (respiratory and urinary tracts) are often affected and which carries a high mortality (25-50%). Cutaneous signs include a rapidly spreading erythematous eruption leading to widespread necrosis and bullous detachment of the epidermis. At the peak stage large parts of the skin and mucous membranes (oronasal, conjunctival, urogenital, and anal) are denuded and skin appendages (hair and nails) lost.^{9,10}

Details of cases

In the past five years we observed six cases of drug induced toxic epidermal necrolysis that were clearly (five patients) or possibly (one, case 2) due to treatment with allopurinol (table). Toxic epidermal necrolysis developed one to five weeks after the start of allopurinol treatment (300 mg daily) and followed a typical course in all the patients. Despite appropriate treatment (correction of loss of fluids, electrolytes, and proteins; high dose corticosteroids, and antibiotics) one patient (case 5) died from cardiac failure. Severe sequelae of scarring occurred in two patients: one became blind after massive bilateral conjunctival damage leading to synechiae and pannus (case 2) and the other developed strictures of the urethra necessitating surgical revision (case 6). Permanent partial anonychia and scarring alopecia occurred in these and two other patients (cases 1 and 4).

These reactions to allopurinol prompted us to examine retrospectively

Prophylaxis with allopurinol is of doubtful value and may cause severe side effects; thus allopurinol should be given in hyperuricaemia only when the serum uric acid concentration persistently exceeds 0.6 mmol/l (10 mg/100 ml)

why this drug had been prescribed for our patients. Surprisingly, allopurinol had been prescribed for no particular therapeutic reason and on the basis of insufficient diagnostic procedures in all six patients: none had ever experienced clinical symptoms of gouty arthritis (though two had had episodes of mild uncharacteristic arthralgias). In four patients only one single blood test had shown slightly raised uric acid concentrations; no control measurements had been performed to exclude transient hyperuricaemia, which often occurs under physiological conditions—for example, stress and dietary factors. Only one patient had persistent asymptomatic hyperuricaemia on multiple control examinations after stopping treatment (case 5).

Discussion

Undoubtedly, allopurinol is useful for treating symptomatic hyperuricaemia (serum uric acid concentrations exceeding 0.4 mmol/l (7 mg/100 ml))—that is, if hyperuricaemia is associated with clinical symptoms of gout. This is not so, however, in asymptomatic hyperuricaemia, when allopurinol is often prescribed in an attempt to prevent gouty arthritis, nephrolithiasis, and uric nephropathy (interstitial nephritis). Although large studies suggest that asymptomatic hyperuricaemia does indeed predispose to these conditions, allopurinol should still not be administered indiscriminately for the following reasons^{7,11,12}: (1) Asymptomatic hyperuricaemia often precedes the first attack of gouty arthritis by many years. (2) If acute attacks occur they can be easily and effectively treated. (3) Recurrent attacks are unlikely to follow the first attack for several years, if at all. (4) Uric acid nephrolithiasis is only weakly correlated with asymptomatic hyperuricaemia. In a large study the incidence of stones in patients with asymptomatic hyperuricaemia was only one out of 295 patients each year, which is about twice that in a population with normal uric acid concentrations; thus 294 out of 295 patients would receive prophylactic treatment unnecessarily.¹¹ (5) Hyperuricaemia rarely leads to renal insufficiency. No appreciable loss of renal function was noted in 112 patients with gout as compared with subjects with normal uric acid concentrations followed up for 12 years.¹² Another prospective study showed that allopurinol did not prevent renal insufficiency in subjects with asymptomatic hyperuricaemia.¹² (6) Costs of long term treatment with allopurinol are considerable, and compliance of asymptomatic patients is poor.

The benefits of treatment with allopurinol appear questionable in patients with asymptomatic hyperuricaemia and do not justify the risks associated with long term administration. Use of allopurinol

Department of Dermatology, University of Innsbruck, A-6020 Innsbruck, Austria

J AUBÖCK, MD, resident

P FRITSCH, MD, professor of dermatology

Correspondence to: Dr Josef Auböck.

Details of six cases of drug induced toxic epidermal necrolysis

Case No	Sex, Age	Pre-existing disorders	Treatment*	Uric acid before allopurinol (mmol/l)	Duration of allopurinol treatment before toxic epidermal necrolysis (weeks)	Uric acid (range) after withdrawal of allopurinol (mmol/l)	Disorders due to toxic epidermal necrolysis	Outcome
1	F 52	Cardiac insufficiency Emphysema Secondary polycythaemia	Spironolactone† Buthiazide‡ Medigoxin†	0.55 (single value)	2	0.35 (0.25-0.46)	Hepatic dysfunction (serum glutamic pyruvic transaminase 36 IU/l, γ -glutamyl transferase 59 IU/l) Leucocytosis ($10.2 \times 10^9/l$)	Recovery, partial anonychia
2	F 72	Hypertension Cardiac insufficiency Sigmoidal colostomy Urinary tract infection	Dihydralazine Hydrochlorothiazide† Medigoxin† Co-trimoxazole	Unknown	5	0.22 (0.16-0.38)	Leucocytosis ($12.7 \times 10^9/l$) Pneumonia Organic psychosyndrome	Recovery, blindness, scarring alopecia partial anonychia
3	M 73	None	None	Not done arthralgia	1	0.24 (0.2-0.28)	Hepatic dysfunction (serum glutamic pyruvic transaminase 27 IU/l, γ -glutamyl transferase 42 IU/l)	Recovery, no sequelae
4	F 77	Cardiac insufficiency	Spironolactone† Hydrochlorothiazide† Medigoxin†	0.49 (single value)	4	0.35 (0.26-0.51)	Hepatic dysfunction (serum glutamic oxaloacetic acid transaminase 43 IU/l, serum glutamic pyruvic transaminase 35 IU/l, γ -glutamyl transferase 35 IU/l) Severe tracheobronchitis	Recovery, partial anonychia
5	F 62	Cardiac insufficiency Hepatic dysfunction (serum glutamic oxaloacetic acid transaminase 36 IU/l, serum glutamic pyruvic transaminase 32 IU/l, bilirubin 67 μ mol/l) Renal insufficiency (blood urea nitrogen 75.7 mmol/l, creatinine 180 μ mol/l)	Ethacrynic acid† Digitoxin†	0.62 (single value)	3	0.6 (0.55-0.65)		Death from cardiac failure
6	M 32	None	None	0.51 (single value) arthralgia	2	0.29 (0.23-0.37)	Severe hepatic dysfunction (serum glutamic oxaloacetic acid transaminase 148 IU/l, serum glutamic pyruvic transaminase 190 IU/l, γ -glutamyl transferase 157 IU/l) Leucocytosis ($37.3 \times 10^9/l$) Severe urethritis Urinary tract infection	Recovery, urethral stricture, partial anonychia, scarring alopecia

* Treatment started several months before onset of toxic epidermal necrolysis except for co-trimoxazole in case 2 (one week before onset).

† Continued through toxic epidermal necrolysis.

‡ Restarted after toxic epidermal necrolysis without toxicity.

Conversion: SI to traditional units: Uric acid: 1 mmol/l $\approx$ 16.8 mg/100 ml. Bilirubin: 1 μ mol/l $\approx$ 0.06 mg/100 ml. Creatinine: 1 μ mol/l $\approx$ 0.01 ml/100 ml. Blood urea nitrogen: 1 mmol/l $\approx$ 2.8 mg/100 ml.

should be limited to patients with persistent hyperuricaemia (serum uric acid concentrations exceeding 0.6 mmol/l (10 mg/100 ml) who do not respond to alternative and less aggressive measures—for example, dietary reduction of intake of purines, reduction in weight, abstinence from alcohol, and elimination of drugs such as thiazides or aspirin.¹³

Allopurinol is a popular drug; in many Western countries it is used extensively for treatment, mainly as a cosmetic procedure beyond clinical justification and perhaps against medical common sense. In view of the severe intolerance reactions that may result the attitude towards prescription of allopurinol ought to be reconsidered.

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Why is it necessary when taking the progestogen only pill to use additional contraception for a full 14 days if a dose is taken late, as advised with the combined pill?

The mode of action of the progestogen only pill is poorly understood. In some women it prevents ovulation, particularly with increased duration of use.¹ Corpus luteum function is suppressed in about 50% of women, and progesterone levels become too low to support early pregnancy.¹ Cervical mucus remains impenetrable to sperm throughout the cycle, and progestogens may affect sperm directly.² Tubal motility is affected. The normal cycle of the endometrium is altered and it becomes unsuitable for implantation: indeed, the endometrium may be the primary site of contraceptive action of these pills because the ectopic pregnancy rate is hardly affected.³ Women must take the pill at the same time each day for maximum effectiveness.

Pregnancy may occur if a woman misses only one or two pills,³ and the risk seems greatest if a pill is forgotten at midcycle.³ Additional precautions are therefore needed if a pill is missed, but their duration will remain uncertain until the relative importance of the pill's effects—particularly on cervical mucus and the endometrium—are fully understood. Some manufacturers recommend additional precautions until the next menses, others say 14 days, but seven days may be the most logical recommendation.⁴—JAMES OWEN DRIFE, senior lecturer in obstetrics and gynaecology, Leicester.

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