Allopurinol and Bone Marrow Aplasia

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Dear Sir,

Allopurinol is a drug used in the treatment of hyperuricemia, some types of kidney stone disease and for the prophylactic treatment of uric gout due to its strong inhibition of the xanthine oxidase enzyme.

It is mainly converted to oxypurinol, a metabolite which is also active and which has a long plasma half-life, of 18-30 h. Both substances are eliminated by the kidneys. In chronic renal failure (CRF with $\text{GFR} < 50\text{-}10\text{ ml/min}$), the adjusted dose is 75-50% of the normal [1].

On rare occasions, the use of allopurinol can give rise to adverse side effects of which gastrointestinal disturbances, skin rash, epidermic necrolysis and drowsiness are the most frequent. Very occasionally, hepato-toxicity and hematopoietic disturbances can be found, mainly in leukocytes [2-5].

We report a fatal **medullar aplasia** which has some singular features in comparison to previously reported cases.

A 40-year-old man with CRF due to **IgA nephropathy** was diagnosed in 1987 as having uric gout with acute podagra and serum urate of 11 mg/dl ($654\text{ }\mu\text{mol/l}$). At the moment of diagnosis, his serum creatinine was 2.3 mg/dl ($203\text{ }\mu\text{mol/l}$) with a GFR of 41 ml/min (0.68 ml/s). Treatment with indo-methacin was initiated during the acute phase, followed by allopurinol at 100 mg/day . Three months later, a hematopoietic disorder was detected, with decline of **hemato-crit** (from 36 to 32%), leukocytes (from 7.6 to $3.1 \times 10^9\text{ cells/l}$ without eosinophilia) and platelets (from 213 to $73 \times 10^9\text{ cells/l}$). Liver function tests were normal (AST, ALT, LDH and LAP). Bone marrow study showed moderate hypoplasia.

Hematological parameters were completely restored after treatment with allopurinol was ended.

Two and a half years later, the patient resumed allopurinol treatment at a low dosage (50 mg/day) following another acute attack of arthritis. Two months later, he was treated for a purpuric eruption. Laboratory tests gave the following results: hematocrit 19%, hemoglobin 62 g/l (6.2 g/dl), platelets $5,000\text{ cells/mm}^3$ ($5 \times 10^9\text{ cells/l}$), leukocytes 900 cells/mm^3 ($0.9 \times 10^9\text{ cells/l}$). A differential count of leukocytes in peripheral blood showed 38% neutrophils, 52% lymphocytes, 8% monocytes, 1% eosinophils and 1% basophils and a partial thromboplastin time of 72 s (control 35 s). Prothrombin content was 35%. AST was 18 U/l ($0.30\text{ }\mu\text{kat/l}$); GPT 13 U/l

(0.21 μ kat/l); LDH 383 U/ml (Wroblewski, maximum 450); LAP 110 U/ml (Goldbarg-Rutenburg, maximum 230) and total bilirubin of 1 mg/dl (17.1 μ mol/l). Bone marrow showed severe medullar aplasia of all hematopoietic cells with edema and interstitial hemorrhage.

Allopurinol medication was terminated, and the patient was treated using broad-spectrum antibiotics, blood compound transfusions, corticosteroids, androgens and, later, antithymocytic globulin. Nevertheless, the aplasia did not rescind and the patient died from a massive digestive hemorrhage during sepsis caused by *Pseudomonas aeruginosa*.

Although this widely used medicine rarely gives rise to side effects (3-5%) [2], the possibility of serious reactions in the form of hepatic and hematological dysfunctions cannot be ruled out, especially when there is associated CRF [6].

This case differs from others which have been reported previously, in that here, the dosage of allopurinol was much lower than those described first (300-1000 mg/day) [4, 5]. Nevertheless, some similarities with Conrad's [7] report do exist, in that severe aplasia took place during the second exposure to the drug, although the author did not specify the dose used.

We believe that the mechanisms governing the majority of the adverse effects of this drug are hypersensitivity reactions, as other authors have considered proposing desensitisation protocols [8-10]. However, we cannot exclude the possibility of another mechanism, such as direct toxicity, being responsible for medullar aplasia.

To conclude, allopurinol is potentially dangerous in cases of CRF, even at low doses which have been adjusted to renal function, and once a side effect has been observed, its use should be discontinued.

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