Letter to the Editors

Oxypurinol, allopurinol and allopurinol-1-riboside in plasma following an acute overdose of allopurinol in a patient with advanced chronic kidney disease

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Allopurinol is used to prevent gout. It is metabolized by xanthine oxidoreductase to oxypurinol, itself a xanthine oxidoreductase inhibitor, thereby reducing urate formation. It may also be metabolized by aldehyde oxidase to oxypurinol [1]. Another metabolite of allopurinol is allopurinol-1-riboside, formed directly by the enzyme purine nucleoside phosphorylase or indirectly through the dephosphorylation of allopurinol-1-ribotide [2]. An acute overdose of allopurinol can have contrasting outcomes. Severe reactions were reported in two cases [3,4], while no reaction was reported in one case [5]. Allopurinol and oxypurinol are renally excreted, so renal impairment would reduce its clearance and possibly potentiate acute toxicity. However, the effect of renal impairment on clinical outcomes following an acute overdose has not been described.

We report a case of allopurinol overdose in a patient with advanced chronic kidney disease. The case is of interest because accumulation of oxypurinol during routine dosing in renal failure has been considered a risk factor for severe allopurinol toxicity, including Stevens–Johnson syndrome and toxic epidermal necrolysis [6], which have mortalities of 30–50%.

A 36-year-old transgender woman presented to hospital 30 min after ingesting 10 g allopurinol. The patient selected allopurinol because Internet information indicated low toxicity in overdose. There were no abnormal clinical signs on presentation and no adverse sequelae. She was discharged within 24 h. The medical history included an overdose of allopurinol 2 years earlier (oxypurinol concentration 44 mg l⁻¹; time after allopurinol ingestion unknown), from which she also suffered no adverse effects. Her medical history also included gout (20 years), hypertension, hypercholesterolaemia and advanced chronic kidney disease [creatinine 493 µm; estimated glomerular

filtration rate of 10–12 ml min⁻¹ (1.73 m⁻²)] due to focal segmental glomerulosclerosis. The patient was reportedly taking allopurinol 100 mg day⁻¹ prior to the overdose. Other medications included perindopril and rosuvastatin, as well as synthetic oestrogens. Urine screening was positive for opiates, benzodiazepines and amphetamines. She consented to return over the next week for additional blood tests.

Allopurinol, oxypurinol and allopurinol-1-riboside concentrations were determined by high-performance liquid chromatography. The assay is validated for oxypurinol [7], and standard curves for all analytes were linear ($r^2 > 0.999$). The identity and purity of each analyte was confirmed by comparison of retention times against standards and by scanning UV spectrophotometry of the peaks. Apparent elimination half-lives ($t_{1/2}$) were estimated by nonlinear regression, assuming a one-compartment model.

The $t_{1/2}$ of oxypurinol was 65 h, considerably longer than found in healthy subjects (approximately 24 h) [1]. The longer $t_{1/2}$ is attributed to the impaired renal function of this patient, as oxypurinol is renally excreted [1]. The peak plasma concentration ($C_{\max}$) of oxypurinol in this patient was 106 mg l⁻¹.

The apparent elimination $t_{1/2}$ of allopurinol was 4.4 h. Again, this is longer than the $t_{1/2}$ (1.2 ± 0.3 h) in healthy subjects [1], possibly due to saturation of xanthine oxidoreductase. The patient's poor renal function may also have contributed to slower elimination, although renal clearance usually accounts for only approximately 10% of an oral dose of allopurinol [1]. The $C_{\max}$ of allopurinol following a therapeutic dose of allopurinol (300 mg) is about 3 mg l⁻¹ [1]. By contrast, the $C_{\max}$ in this patient was much higher, at 29 mg l⁻¹ (Figure 1).

Approximately 10% of allopurinol is excreted as allopurinol-1-riboside [1]. The $t_{1/2}$ of the allopurinol-1-

Figure 1

Time courses of allopurinol, oxypurinol and allopurinol-1-riboside after an overdose of allopurinol (10 g). Oxypurinol (—●—); Allopurinol (---■---); Allopurinol-1-riboside (---△---)

riboside is approximately 3 h following dosage of the riboside itself [8]. We found substantial concentrations of the riboside (up to 19 mg l⁻¹). Given its high aqueous solubility, its renal excretion may be delayed in chronic kidney disease.

One of the three previously reported cases of acute allopurinol overdose died from hepatic centrilobular necrosis. The dose of allopurinol was unknown, but the plasma concentration was recorded as 231 mg l⁻¹, which is much greater than the value for our patient (29 mg l⁻¹). The assay details were, however, not presented, and it is unclear whether oxypurinol or allopurinol was measured. Other causes of the hepatotoxicity may have been concurrent use of indomethacin and captopril [3]. Another patient who ingested 20 g allopurinol developed a variety of toxic effects, including hepatitis, leukopaenia, fever and diarrhoea but recovered with supportive care [4]. By contrast, in a third case, no adverse effects following the ingestion of approximately 20 g allopurinol were reported. The oxypurinol concentration for this latter subject was approximately 43 mg l⁻¹ at approximately 12 h and the elimination half-life was 26 h [5]. By comparison, in our patient who purportedly took 10 g allopurinol, the estimated plasma concentration of oxypurinol at 12 h was approximately 100 mg l⁻¹ (Figure 1). It is not known why there was no clinical toxicity. In the two cases where toxicity was reported, involvement of other drugs may have been contributory. The relationship between plasma concentrations of oxypurinol and adverse reactions is still unclear. Further investigation is required to clarify these observations.

In summary, it is unclear whether or not adverse effects from acute overdoses of allopurinol are expected. Despite

high concentrations of allopurinol and metabolites, our patient was largely unaffected by the overdose. Renal impairment appears to have contributed to the delayed elimination of allopurinol and its metabolites.

Competing Interests

There are no competing interests to declare.

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