VARIATIONS IN ALLOPURINOL METABOLISM
BY XANTHINURIC SUBJECTS

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(Received 27 March 1974)

SUMMARY

1. The metabolism of allopurinol was studied in a newly discovered patient with xanthinuria.
2. No oxipurinol was detectable in the urine during allopurinol administration, in direct contrast to the results in a patient previously studied by one of us.
3. Other equally discrepant effects of allopurinol on urinary purine and pyrimidine excretion in these two cases are compared with those in the three other recorded cases.

Key words: xanthine, hypoxanthine, allopurinol, orotidine, purine, pyrimidine, pyrazolopyrimidine.

Since the original report by Dent & Philpot (1954), a total of eighteen cases of xanthinuria have now been recorded (Wyngaarden, 1972; Castro-Mendoza, Cifuentes Delatte & Rapado Errazti, 1972; Sørensen, Tesar, Ellman & Colwell, 1972; Auscher, Pasquier, Mercier & Delbarre, 1973; Holmes, Mason & Kelley, 1973). Xanthinuria results from a congenital deficiency of the enzyme xanthine oxidase (xanthine oxygen oxidoreductase, EC 1.2.3.2) (Watts, Engleman, Klinenberg, Seegmiller & Sjoerdsma, 1964) normally responsible for the oxidation of hypoxanthine and xanthine to uric acid.

In all normal subjects and gouty patients studied, allopurinol [4-hydroxypyrazolo-(3,4-d)-pyrimidine] is rapidly oxidized in vivo to oxipurinol [4,6-dihydroxypyrazolo-(3,4-d)-pyrimidine] (Elion, Kovensky, Hitchings, Metz & Rundles, 1966; Simmonds, 1969b; Simmonds & Bowyer, 1974), an oxidation also attributed to xanthine oxidase activity. Patients with xanthinuria would not therefore be expected to oxidize allopurinol to oxipurinol. This paper gives detailed results of the effect of allopurinol on purine metabolism in a new patient with xanthinuria (B. Levin, unpublished work) (Table 1) and compares these results with four similar studies recorded in the literature (Auscher et al., 1973; Holmes et al., 1973; Elion et al., 1966; Chalmers, Parker, Simmonds, Snedden & Watts, 1969).

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### Table 1. Effects of allopurinol on some aspects of purine and pyrimidine metabolism in xanthinuria

<table>
<thead>
<tr>
<th>Allopurinol dosage (mg/24 h)</th>
<th>Engleman et al. (1964)</th>
<th>Simmonds (1969)</th>
<th>Auscher et al. (1973)</th>
<th>Holmes et al. (1973)</th>
<th>Present report</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mmol/24 h)</td>
<td>400-800</td>
<td>400</td>
<td>800</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Duration of allopurinol treatment (days)</td>
<td>1*-8+</td>
<td>30</td>
<td>7</td>
<td>Not stated</td>
<td>6</td>
</tr>
<tr>
<td>Total purine excretion</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Xanthine/hypoxanthine ratio</td>
<td>Reversed*</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Reversed</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Allopurinol: excreted form</td>
<td>Allopurinol*</td>
<td>63% as oxipurinol</td>
<td>65% as oxipurinol</td>
<td>Allopurinol</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Orotic acid + orotidine excretion</td>
<td>—</td>
<td>Increased</td>
<td>—</td>
<td>Unchanged</td>
<td>Increased</td>
</tr>
</tbody>
</table>

* This patient’s xanthine/hypoxanthine ratio was reversed after 6 days on allopurinol, but the urine was examined for allopurinol metabolites after only 1 day on the drug (Elion et al., 1966).

### Table 2. Urinary purine, pyrimidine and pyrazolopyrimidine excretion in a patient with xanthinuria treated with allopurinol

Results given are mean values with the range for the periods indicated.

<table>
<thead>
<tr>
<th>Excretion (mmol/24 h)</th>
<th>No treatment</th>
<th>Allopurinol 4·42 mmol (600 mg)/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of study (days)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Xanthine</td>
<td>1·25 (1·06-1·58)</td>
<td>1·31 (1·05-1·54)</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>0·26 (0·16-0·37)</td>
<td>0·24 (0·18-0·32)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0·046 (0·032-0·061)</td>
<td>0·044 (0·025-0·071)</td>
</tr>
<tr>
<td>Allantoin</td>
<td>0·15 (0·086-0·21)</td>
<td>0·18 (0·12-0·21)</td>
</tr>
<tr>
<td>Mean total purine excretion</td>
<td>1·71</td>
<td>1·77</td>
</tr>
<tr>
<td>Mean xanthine/hypoxanthine ratio</td>
<td>5·01</td>
<td>5·35</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>1·15 (0·63-1·45)</td>
<td></td>
</tr>
<tr>
<td>Allopurinol riboside</td>
<td>2·13 (1·64-2·76)</td>
<td>Not detected</td>
</tr>
<tr>
<td>Oxpurinol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orotidine + orotic acid*</td>
<td>0·013 (0·008-0·019)</td>
<td>0·063 (0·053-0·074)</td>
</tr>
</tbody>
</table>

* Expressed as orotic acid.
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**METHODS AND RESULTS**

The patient, a European male aged 50 years, was an orphan with no traceable descendants. During the study he was given a low purine diet (90 mg/day). Clinical data on this patient, in whom the enzyme defect was demonstrated both in jejunal and liver biopsy specimens by a modification of the method of Sperling, Liberman, Frank & de Vries (1971), will be the subject of a separate report.

Details of treatment are given in Table 1. Specimens were collected and purines, pyrimidines and pyrazolopyrimidines estimated by methods which have been described in previous publications (Simmonds, 1969a, b).

Allopurinol administration (Table 2) did not alter either total urinary purine excretion or the ratio of the principal purine end products, xanthine and hypoxanthine, in this xanthinuric subject during 6 days of therapy. The drug itself was excreted as unchanged allopurinol or its riboside and no oxipurinol could be detected in any specimen during the period of study. Urinary pyrimidine excretion did show a fivefold increase during allopurinol administration, albeit from extremely low concentrations, so that levels during therapy were still within the upper limits of normal.

**DISCUSSION**

The effect of allopurinol ingestion on urinary purine excretion and the metabolism of the drug itself has now been investigated in five of the eighteen xanthinuric patients so far recorded in the literature with conflicting results. In the first study (Engleman, Watts, Klinenberg, Sjoerdsm & Seegmiller, 1964) allopurinol was, as expected, excreted unchanged (Elion et al., 1966), and the ratio of xanthine to hypoxanthine in the urine was reversed after 7 days of treatment. The second patient, of Chalmers et al. (1969), also investigated by one of us (Simmonds, 1969b), showed no alteration in urinary xanthine/hypoxanthine ratios over a 4-week period, but constantly excreted 65% of the administered allopurinol as oxipurinol—an unexpected result in view of the demonstrated absence of xanthine oxidase (Chalmers et al., 1969). The patient recently studied by Auscher et al. (1973) also excreted 65% of the allopurinol as oxipurinol, and likewise the urinary xanthine/hypoxanthine ratio was unaltered and total purine excretion unchanged. By contrast, the patient investigated by Holmes et al. (1973) produced results comparable with those in the first case. Although the patient studied by Elion et al. (1966) had taken allopurinol for only 1 day, which might explain the lack of observed conversion of allopurinol into oxipurinol, the fact that the patient studied by Auscher et al. (1973) excreted 65% of the allopurinol dose as oxipurinol after only 1 day makes this possibility unlikely.

The data in the present patient accord with none of these, except that in all cases total purine excretion was unaltered by allopurinol administration. No oxipurinol was detected in the urine in this study, even after 6 days, the only metabolite, apart from unchanged allopurinol, being allopurinol riboside. However, unlike the patients of Engleman et al. (1964) and Holmes et al. (1973), the urinary ratio of xanthine to hypoxanthine of 5.01 before treatment was relatively unchanged at 5.35 during allopurinol administration at 4.42 mmol (600 mg)/day. It is possible that the 6-day period of investigation was too short to demonstrate a change in the ratio since, in the patient studied by Engleman et al. (1964), on 2.94 mmol (400 mg) of allopurinol per day, no change was noted until the sixth day. However, our data do not support
the possibility that a change was beginning to appear in the later part of the study since the ratio was highest on the sixth day.

It seems surprising that, in the two patients who were able to convert allopurinol into oxipurinol, as much as two-thirds of the allopurinol administered, a fraction comparable with that excreted by normal subjects, should be so converted. This observation seems inconsistent with the presence of only residual xanthine oxidase activity. On the other hand, the oxipurinol produced by these patients could not have arisen by the alternative route originally suggested at the nucleotide level (Chalmers et al., 1969) since allopurinol ribotide has recently been shown not to be a substrate for inosinic acid dehydrogenase (EC 1.2.1.14) (Nelson, Bugge, Kransky & Elion, 1973).

Reports of the effect of allopurinol on pyrimidine metabolism in xanthinuric patients have likewise been conflicting. In this study allopurinol produced a fivefold increase in orotidine plus orotic acid excretion, although from somewhat low initial levels. In the second patient of Chalmers et al. (1969), urinary excretion showed a much greater absolute increase, from 0·035 mmol (5·5 mg) on a purine-free diet to a mean of 0·158 (24·7 mg)/24 h during allopurinol therapy. This effect of allopurinol on pyrimidine metabolism has been attributed to inhibition of orotidine 5'-phosphate decarboxylase (EC 4.1.1.23) by nucleotide derivatives of allopurinol or oxipurinol, both inhibitors in vitro of this enzyme (Fox, Wood & O'Sullivan, 1971). Although the formation in vivo of these nucleotides occurs only at normally undetectable levels (10^{-9}–10^{-6} mol/l in whole tissue; Elion & Nelson, 1973) this is apparently sufficient to account for the observed effect on pyrimidine production de novo (Nelson et al., 1973). Since patients with a deficiency of hypoxanthine–guanine phosphoribosyltransferase (EC 2.4.2.8) (Kelley & Wyngaarden, 1972), unable to form allopurinol or oxipurinol-1-ribotides (Nelson et al., 1973), also show orotidinuria during allopurinol therapy the purine ribotide analogue oxipurinol-7-ribotide alone has been implicated in this effect (Fox et al., 1971). The present study suggests that allopurinol-1-ribotide may also have a similar, if smaller, effect. However, allopurinol did not produce orotic acid and orotidinuria in the patient reported by Holmes et al. (1973), which is inconsistent with this suggestion. The one constant finding appears to be that untreated xanthinuric patients do not exhibit increased urinary levels of orotic acid and orotidine (Sørensen et al., 1972; Holmes et al., 1973; Simmonds, 1969a), indicating that inhibition of xanthine oxidase per se is not directly involved in the increased excretion of these compounds during therapy.

There seems at present no simple explanation for the findings presented here. One possibility may lie in the similarities reported for the species and organ distribution of xanthine oxidase and aldehyde oxidase (aldehyde–oxygen oxidoreductase EC 1.2.3.1) (Krenitsky, 1973). Both enzymes possess the ability to catalyse the oxidation of a wide variety of substrates (Johns, 1967; Rajagopalan, Fridovich & Handler, 1962), but although both contain iron, molybdenum and flavinadenine dinucleotide in the proportion 4:1:1, aldehyde oxidase alone contains an additional component, coenzyme Q 10, which xanthine oxidase does not. Krenitsky, Neil, Elion & Hitchings (1972) have shown that both allopurinol and its riboside are oxidized by aldehyde oxidase, an oxidation which they suggest might be relevant to the excretion of oxipurinol in the patient previously studied by one of us (Simmonds, 1969b). T. A. Krenitsky (personal communication) has proposed therefore that investigation of aldehyde oxidase activity, which has not yet been measured in xanthinuria, might throw some light on these anomalous findings.
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Clearly this variation in allopurinol metabolism, which has not previously been noted in a wide variety of gouty and psoriatic patients or healthy controls (Simmonds, 1969b; Simmonds & Bowyer, 1974), and which produces differing effects on both purine and pyrimidine metabolism in xanthinuria, could be genetically determined. However, such an hypothesis could only be tested by appropriate studies in first-degree relatives, which unfortunately are not possible in this case.

REFERENCES

AUSCHER, C., PASQUIER, C., MERCIER, N. & DELBARRE, F. (1973) Oxidation of pyrazole (3,4-d) pyrimidine in a xanthinuric man. Israel Journal of Medical Sciences, 9, 3.


