Thiopurinol and purine metabolism

Metabolic and radioisotope studies

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Thiopurinol (4-mercaptopyrazolo (3,4-d) pyrimidine) is the 4-thio analogue of allopurinol (4-hydroxypyrazolo (3,4-d) pyrimidine) (Elion, Ben Ezra, Canellas, Carrington, and Hitchings, 1968a). Like its analogue, thiopurinol has been shown to be an effective agent for the reduction of hyperuricaemia in man (Delbarre, Auscher, de Gery, Brouilhet, and Olivier, 1968; Serre, Simon, and Claustre, 1970; Grahame, Simmonds, Cadenhead, and Dean, 1973). It is, however, not widely used and has been the subject of only two large clinical studies (Delbarre and others, 1968; Serre and others, 1970).

Thiopurinol apparently differs from allopurinol in two respects. First, although it lowers the uric acid concentrations in both plasma and urine in gouty hyperexcretors of uric acid, only plasma levels are effected in the case of normoexcretors, and neither are reduced in HGPRT-deficient patients (Delbarre and others, 1968; Serre and others, 1970; Grahame and others, 1973). Secondly, a corresponding increase in the urinary excretion of the precursor oxypurines xanthine and hypoxanthine is not produced in any of these situations, suggesting the mode of action of thiopurinol is not through xanthine oxidase inhibition. As xanthine is even more insoluble than uric acid, there is a risk of xanthine nephropathy during allopurinol therapy. Though this has never been noted in classical gout, xanthine nephropathy during allopurinol therapy has been cited in 4 cases, all gross hyperexcretors of uric acid. Two of these were cases of HGPRTase deficiency, while the other 2 were cases of lymphosarcoma and Burkitt's lymphoma treated with cytotoxic drugs (Greene, Fujimoto, and Seegmiller, 1969; Sorensen and Seegmiller, 1968; Band, Silverberg, Henderson, Ulan, Wensel, Banerjee, and Little, 1970; Ablin, Stephens, Hirata, Wilson, and Williams, 1972). It follows that in some circumstances thiopurinol could have certain therapeutic advantages over its analogue allopurinol. However, the postulated mode of action

—conversion to the nucleotide to act as a feedback inhibitor of *de novo* purine production (Delbarre and others, 1968; Serre and others, 1970; Auscher, Mercier, Pasquier, and Delbarre, 1973a), in much the same way as its analogue 6-mercaptopurine (Brockman, 1963), might negate these advantages if subsequent tissue incorporation were to occur. Drugs with sulphur groups have in addition a potential toxicity through forming disulphide bonds with naturally occurring sulphur-containing compounds, as does penicillamine for example (Fellers and Shahidi, 1959).

In view of the possible involvement of thiopurinol in any of these pathways we have studied the pharmacokinetics of orally administered [6-¹⁴C]thiopurinol during the long-term administration of the unlabelled drug in an animal model, the pig. We have previously shown (Cameron, Simmonds, Hatfield, Jones, and Cadenhead, 1973) that this species is superior to other nonprimates for such studies because of its similarity to man in the distribution of enzymes of purine metabolism, renal structure and function, and the excretion of a comparable purine load in relation to urine volume. Purine and pyrimidine excretion during administration of the unlabelled drug has also been documented.

Methods and materials

[6-¹⁴C]Thiopurinol (specific activity 4.53 mCi/mmol) was synthesized at the Wellcome Research Laboratories, Kent, from [6-¹⁴C]allopurinol (purchased from New England Nuclear and generously given by Dr. D. Munro-Faure of the Wellcome Foundation).

TREATMENT

Male castrate pigs weighing 30–35 kg, from a minimal disease breed of large white/landrace cross, were housed in metabolic cages. They were maintained on a purine-free diet of barley and skim milk and given thiopurinol (600 mg/day) twice daily with the food. After a stabilization period of 6 days on the unlabelled drug, [6-¹⁴C]thiopurinol (1 mCi) was administered to one animal in capsule

form half-way through the morning feed. The metabolic fate of the radioactivity was followed for one week during which the animal continued to receive the unlabelled drug. At the end of this time the animal was slaughtered and the tissues were examined for residual radioactivity. An identical animal was given the unlabelled drug for a similar period of time, while the control litter mates were fed the barley and skim milk diet only.

COLLECTION OF SAMPLES AND BIOCHEMICAL METHODS

Procedures for the collection and preservation of specimens, the isolation and identification of urinary metabolites, and radioactive counting of urine, plasma, faecal, and tissue samples have been reported in a previous publication (Simmonds, Rising, Cadenhead, Hatfield, Jones, and Cameron, 1973b). Radioactivity was determined in a Packard Tri-Carb scintillation spectrometer followed either by internal or external standardization using the method of Johnson, Rising, and Rising (1972).

Results

I METABOLIC STUDIES

The concentrations of purines and pyrimidines excreted in the urine are given in Table I. These are documented for weeks one and two of thiopurinol therapy and compared with the control for the corresponding period.

Purine excretion

Total purine excretion was reduced only slightly during the 2-week period of study (5–6% reduction) and allantoin excretion (the principal urinary purine end-product) was also relatively unchanged. Mean uric acid excretion did show a reduction during thiopurinol administration, but this represents only a very small fraction of total purine excretion in the pig and is consequently of little significance. As in our human studies (Grahame and others, 1973), the urinary levels of the precursor oxypurines

Table I Urinary purine and pyrimidine excretion in the pig during thiopurinol therapy (mmol/24 hrs)

	Control		Thiopurinol-treated	
	Week 1	Week 2	Week 1	Week 2
Allantoin	4.00	4.30	3.79	4.07
Xanthine	0.15	0.17	0.13	0.18
Hypoxanthine	0.07	0.09	0.07	0.07
Uric acid	0.41	0.43	0.30	0.29
Total	4.63	4.99	4.46	4.61
Orotic acid + orotidine*	5.9	6.2	5.1	6.1

Results are the mean of 3 consecutive midweek specimens for two animals in each group. Purine excretion is given in mmol/24 hrs. *Since the method does not distinguish between orotidine and orotic acid excretion, pyrimidine excretion is given only in mg/24 hrs.

xanthine and hypoxanthine were relatively unaltered during the period of thiopurinol administration.

Pyrimidine excretion

No difference in the urinary excretion of the pyrimidines orotidine and orotic acid was noted between the control period and the period of thiopurinol therapy the excretion levels being less than 10 mg/24 hrs in both cases.

II RADIOISOTOPE STUDIES

Plasma levels

Plasma levels after the ingestion of [6-¹⁴C]thiopurinol are shown in Fig. 1. Peak plasma levels were obtained between 14 and 24 hrs after ingestion of the labelled drug. The rate of absorption was not rapid, especially when compared with the previous allopurinol study where peak levels were reached in 1–2 hrs (Simmonds and others, 1973b) and were of much greater magnitude. This could possibly be due to binding of thiopurinol to cellular proteins and serum albumin as recently shown (Dean, Perrett, Simmonds, and Grahame, 1974). Alternatively, the two peaks could represent uptake by the liver, biotransformation, and subsequent release of a metabolite which was fairly rapidly excreted.

Urinary excretion

Urinary levels are also given in Figs 1 and 2 which show that the pattern follows the corresponding plasma curve. A total of 65.9% of the radioactive dose was excreted in the urine principally over the first 48-hour period of dosage.

Faecal excretion

Table II gives the radioactivity in freeze-dried samples of faeces. This shows that a total of 36.5%

FIG. 1 The clearance of radioactivity from plasma and rate of urinary [¹⁴C] excretion after oral administration of [¹⁴C]thiopurinol. Experimental procedures were as given in Methods

FIG. 2 Cumulative excretion of radioactivity expressed as per cent. of the dose in urine and faeces after a single oral dose of [¹⁴C]thiopurinol. Results are plotted over the 7-day period of study

Table II Excretion of radioactivity after oral administration of [¹⁴C]thiopurinol

Hours after administration	Urine	Faeces	Cumulative total excretion
0-24	41.21	0.8	42.01
24-48	21.76	15.1	78.87
48-72	2.06	17.9	98.83
72-96	0.58	2.2	101.61
96-120	0.09	0.5	102.20
120-168	0.14	0.1	102.34
Total	65.84	36.5	

Experimental conditions were as described in Methods. Results are expressed as a percentage of the total radioactive dose.

of the radioactivity was recovered in the faeces, principally in the second and third days, which is in accordance with the normal transit time for the pig gut (Castle and Castle, 1957) and suggests that this amount of radioactivity represents unabsorbed drug. Total recovery of radioactivity was thus obtained in urine and faeces alone and elimination from the body was rapid, being essentially complete in 3 days, as shown in Fig. 2.

Tissue incorporation

Data in Table III indicate that the only tissues to show any measurable degree of radioactivity were the liver and kidney, none of which was further shown to be in the form of tissue nucleotides. The slower clearance of thiopurinol or its metabolite, which as mentioned previously may be related to its protein binding (Dean and others, 1974), could explain the small amount of residual radioactivity (less than 0.02% of the dose) in liver and kidney.

URINARY METABOLITES OF THIOPURINOL

Elimination of radioactivity in serial urine samples is shown in Fig. 3 which indicates that the appearance

Table III Incorporation of radioactivity from [¹⁴C]thiopurinol into various freeze-dried pig tissues

Tissue	Total dpm/tissue (x 10 ⁻⁵)	% of dose
Kidney	3.445	0.02
Liver	3.116	0.02
Spleen	0.109	0.01
Lungs	1.001	0.01
Heart	0.561	0.01
Muscle	—	—
Duodenum and pancreas	—	—
Brain	—	—

Experimental conditions were as given in Methods. The incorporation of radioactivity where applicable is expressed as a percentage of the dose for the whole organ.

of radioactivity in urinary metabolites occurred within 60 minutes. In the electrophoretic system used it had previously been established that thiopurinol remained at the origin. Thus, even at 60 minutes no unchanged thiopurinol was excreted in the urine, indicating the metabolism of thiopurinol to be extremely rapid indeed. Although radioactivity appeared in several minor urinary metabolites, one of which was identified as oxipurinol (less than 1% of the dose), this represented only a small fraction of the total urinary radioactivity which was therefore present in one principal metabolite. This metabolite has the same chromatographic and electrophoretic mobilities as the single metabolite isolated in separate studies from human urine after thiopurinol administration (Grahame and others, 1973). In the electrophoretic and chromatographic systems employed (Simmonds, 1969), both human and pig metabolites were identical with an authentic sample of 6-hydroxy-4-mercaptopyrazolo (3,4-d) pyrimidine (a gift from Wellcome Research Laboratories). The ultraviolet absorption spectra of both metabolites ($\lambda_{\max}$ pH 2.0: 257 and 324 nm) were also identical with that of the 6-OH, 4-SH compound. Identification by mass spectrometry has not yet been completed.

Discussion

These studies using [6-¹⁴C]thiopurinol have shown that at least 66% of the administered dose is absorbed from the gastrointestinal tract of the pig and excreted in the urine. This result compares favourably with the finding in comparable studies in man reported by Auscher, Pasquier, Mercier, and Delbarre (1973b) that 70% of orally administered thiopurinol was excreted daily in the urine. The excretion of 36% of the radioactivity in the faeces suggests relatively poorer absorption of thiopurinol when compared with a previous study of allopurinol absorption in the pig (Simmonds and others, 1973b) where 92% of the radioactivity was recovered in the urine and

FIG. 3 Urinary metabolites of $[^{14}\text{C}]$ thiopurinol detected by autoradiography after direct high voltage electrophoresis of comparable aliquots of urine on thin layer plates. The urine specimens were collected at the time intervals indicated after the oral administration of 1 mCi $[^{14}\text{C}]$ labelled thiopurinol. Details of the methods used are given in Methods and are described in a previous publication (Simmonds and others, 1973b)

only 7.5% in the faeces. Absorption must also have been slower in the case of thiopurinol, as peak levels of radioactivity in blood and urine occurred 24 hours after administration; whereas in the previous study using $[^{14}\text{C}]$ allopurinol, peak levels were attained within 2 hours of administration. These results could relate to two factors; first we have previously shown that thiopurinol is potentially considerably bound to plasma proteins and cellular membranes which could to a large extent slow its transport and therefore clearance (Dean and others, 1974). Secondly, the two drugs were given at very different levels for specific reasons. In the case of allopurinol, this was at 30 times normal human dosage in order to achieve maximal inhibition of xanthine oxidase (Simmonds and others, 1973b), while in this study thiopurinol was administered at maximal human dosage levels only. In the former study, therefore, at the high dose, 75% of the drug would have remained as unchanged allopurinol or its riboside (Simmonds, Hatfield, Cameron, Jones, and Cadenhead, 1973a), both of which appear to be cleared rapidly by glomerular filtration alone, unlike oxipurinol which is cleared much more slowly in a manner comparable with uric acid because of tubular reabsorption (Eliou, Yü, Gutman, and Hitchings, 1968b). The clearance of thiopurinol is not known and difficult to assess for reasons given above. Moreover,

since it appears to be rapidly and almost totally converted to a metabolite, none of the parent compound appearing in the urine even at 60 minutes, the clearance of this metabolite is obviously the critical factor and requires investigation.

The *in vivo* oxidation of thiopurinol has been shown to be extremely rapid in these experiments, no unchanged drug being present in the urine even at 60 minutes, with all the radioactivity localized principally in one metabolite. Auscher and others (1973b), in studies in man, have also found no unchanged thiopurinol in the urine, the drug being excreted almost totally as one metabolite, the 6-hydroxy oxidation product of thiopurinol, i.e. oxithiopurinol (4-thio, 6-hydroxypyrazolo (3,4-d) pyrimidine). The metabolism of thiopurinol appears to be the same in man and the pig, for in separate studies in man (Grahame and others, 1973) we have also found a single urinary metabolite and no unchanged drug in the urine. Although we await confirmation by mass spectrometry of the structure of the metabolite, the identity in different systems between the pig and human metabolite and an authentic sample of 6-hydroxy-4-mercaptopyrazolo (3,4-d) pyrimidine suggests clearly that they correspond with the compound identified by Auscher and others, 1973b.

The finding of one principal metabolite in these experiments with a minimal amount of radioactivity

in oxipurinol (identifiable only by autoradiography) shows that oxidative removal of the sulphur with subsequent formation of the apparently more active *in vivo* metabolite of allopurinol, oxipurinol, has not occurred to account for the effect of thiopurinol on uric acid levels in man. Elion and others (1968a) have also reported only 0.2% of the dose of thiopurinol to be excreted as oxipurinol in the mouse.

Although thiopurinol has been shown by these workers in both *in vitro* and *in vivo* experiments (in mice) to be a relatively inactive inhibitor of xanthine oxidase, *in vitro* its metabolite oxithiopurinol is equal in potency to allopurinol. However, thiopurinol administration in the pig, as in man, had little effect in increasing the excretion of the precursor oxypurines, xanthine and hypoxanthine, which based on current methods of evaluation suggests that neither thiopurinol nor its metabolite are active *in vivo* inhibitors of xanthine oxidase. The fact that thiopurinol is apparently a poor substrate for xanthine oxidase *in vitro* (Elion and others, 1968a) plus the excretion of the drug totally as oxithiopurinol in a xanthinuric patient has led Auscher and others (1973b) to speculate that this rapid *in vivo* oxidation is not mediated by xanthine oxidase. The alternative route of oxidation utilizing aldehyde oxidase has been suggested by Krenitsky, Neil, Elion, and Hitchings (1972), to explain the oxidation of allopurinol to oxipurinol in Auscher's patient. However, from the *in vitro* data of Krenitsky and others (1972) this pathway appears not to operate in the case of thiopurinol to any degree.

The mode of action of thiopurinol is still unclear. If it is converted to its nucleotide *in vivo* to act as a feedback inhibitor of *de novo* purine production it must be subsequently degraded without measurable incorporation into body tissues. Although nucleotides of both allopurinol and thiopurinol are readily synthesized by haemolysates under appropriate conditions *in vitro* (Dean and others, 1974; Auscher and others, 1973a), we have been unable to detect *in vivo* formation or incorporation of radioactivity into either nucleotides or nucleic acids under our experimental conditions in the pig. Nucleotides of allopurinol and oxipurinol have been detected by Nelson, Buggé, Kransy, and Elion (1973) in rats slaughtered soon after injection using intravenously administered allopurinol of extremely high specific activity. Since our animals were slaughtered one week after the radioactivity such transitory incorporation would not be detectable. In *in vitro* studies thiopurinol has been found to be 25% bound to plasma proteins and moreover to reduce urate binding to plasma albumin (Dean and others, 1974). The relevance of these findings, which suggests a potential uricosuric effect (Schlosstein, Kippen, Whitehouse, Bluestone, Paulus, and Klinenberg, 1973), has yet to be determined but must be borne in mind when evaluating the mode of action of the drug.

The minimal effect of thiopurinol on total urinary purine excretion in the pig is comparable with the lack of effect reported for this drug on total urinary purine excretion in normoexcretors of uric acid (Serre and others, 1970). Again, in contrast to allopurinol (Simmonds and others, 1973a), thiopurinol in the pig as in man does not appear to increase the urinary excretion of either xanthine or hypoxanthine, or the pyrimidines orotic acid and orotidine in either man (Fox, Wood, and O'Sullivan, 1971) or pig (Simmonds and others, 1973a). This latter finding suggests that if extremely low levels of nucleotides of thiopurinol are formed *in vivo* they are not inhibitors of orotidylic decarboxylase as are the nucleotides of allopurinol and oxipurinol (Nelson and others, 1973).

From these studies in the pig it appears that thiopurinol could have certain advantages over allopurinol in some situations (*e.g.* impaired renal function), in that it does not increase the excretion of the relatively insoluble xanthine nor does it increase the urinary excretion of the pyrimidines orotidine and orotic acid. The latter effect is normally of little significance compared with total pyrimidine turnover. However, it has been shown to be of greater magnitude in renal failure, and this effect is aggravated by the thiazide diuretics frequently used in this condition (Wood, Sebel, and O'Sullivan, 1972). No single theory to explain the different effects in hyperexcretors, normoexcretors, and HGPRT-deficient patients (Delbarre and others, 1968; Serre and others, 1970; Grahame and others, 1973) completely fits the mode of action of thiopurinol, be it uricosuric or inhibitor of *de novo* purine production. Since thiopurinol appears from these studies to be very rapidly oxidized *in vivo*, future studies should be directed towards this metabolite.

Summary

A single dose of [6-¹⁴C]thiopurinol was given orally to pigs during long-term administration of the drug. 65.9% of the administered radioactivity was recovered in the urine within 7 days, the greater part during the first 48 hrs, with the balance being recovered in the faeces. Less than 0.02% of the radioactivity was found in any tissue and none of this was in the form of nucleotides. Peak plasma and urinary levels of radioactivity occurred between 14 and 24 hrs after administration, after which the disappearance of radioactivity from both plasma and urine was rapid. The majority of the urinary radioactivity was detected in one metabolite (6-hydroxy-4-mercaptopyrazolo (3,4-d) pyrimidine) and no unchanged thiopurinol was detected, even in specimens passed 60 minutes after administration of the labelled drug.

The drug had little effect on total purine excretion in the pig, nor did it alter the urinary excretion levels

of the purines hypoxanthine and xanthine, or of the pyrimidines orotidine and orotic acid.

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