EFFECTS OF DRUGS ON URIC ACID IN MAN

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INTRODUCTION

A large number of drugs affect the serum urate concentration. In virtually every case, whether the serum urate concentration is raised or lowered due to administration of the agent, the effect is of potential clinical significance. Hyperuricemic agents may contribute to the ultimate development of gouty arthritis or uric acid nephropathy. In addition, several of these agents have been used to help define the mechanism by which uric acid is synthesized and excreted in normal and gouty man. Hypouricemic agents may contribute to the precipitation of acute gouty arthritis or uric acid stone formation. More important, they may be useful in the control of hyperuricemia. Drugs exhibiting either effect may complicate interpretation of the serum urate value in the patient with arthritis.

In the last review of drugs and uric acid appearing in this series (1), major emphasis was placed on the hypouricemic agent, allopurinol. At that time allopurinol was a relatively new agent which had been studied extensively but had just been introduced for regular clinical use. Over the ensuing years the major developments have been in the metabolism, mechanism of action, and side effects of a wide number of different agents affecting the serum urate concentration. Accordingly, in this review, an attempt is made to consider the effect of drugs on uric acid in a somewhat broader sense.

DRUGS ELEVATING THE SERUM URATE CONCENTRATION

Drugs play an important role in the pathogenesis of hyperuricemia in man. Paulus et al noted that drugs were a major factor in the development of an elevated serum urate concentration in 20% of the hyperuricemic subjects in one hospital study (2). Of the new cases of gout in Framingham, Massachusetts, approximately 50% have developed in subjects taking drugs that may elevate the serum urate concentration (3). The most important group of drugs capable of producing hyperuricemia are the diuretic agents. Additional agents in common clinical use, which are capable of producing sustained hyperuricemia, include salicylates in low dosage, pyrazina-

mide, nicotinic acid, ethambutol, and ethanol. Finally, a number of other drugs are capable of producing rather striking, though usually transient, hyperuricemia. These include fructose, 2-ethylamino-1,3,4-thiadiazole, and the cytotoxic agents.

Diuretics

The more potent diuretic agents frequently lead to an increased serum urate concentration. The administration of thiazide and chlorothiazide for 3 days to 10 months led to a mean increase in the serum urate concentration of 1.8 mg/100 ml in a total of 28 patients (4–6). The administration of chlorthalidone over a 19 week period produced an increase in the serum urate of greater than 1 mg/100 ml in 50% of 62 patients with a mean increase 1.3 mg/100 ml in all patients (7). Similar results were reported with acetazolamide (8), furosemide (9), and ethacrynic acid (10).

The data are contradictory with some of the less potent diuretics. Triamterene was shown with chronic use to lead to the development of hyperuricemia in several studies (11,12), whereas no effect was noted in another (13). Amiloride has been shown to be associated with a mild elevation of the serum urate (14) whereas spironolactone has not. The incidence of hyperuricemia after repeated administration of the mercurial diuretics has not been established. However, the organomercurials are listed as capable of producing hyperuricemia by Beyer & Baer (15).

There are several mechanisms by which potent diuretic agents may produce hyperuricemia. Replacement studies led Suki et al (16) to postulate that thiazide-induced hyperuricemia is a byproduct of extracellular fluid volume contraction. The work of Steele & Oppenheimer (17,18) with furosemide and ethacrynic acid supported this hypothesis and led them to suggest that tubular reabsorption of filtered urate was increased with volume contraction. However, factors other than volume contraction may also contribute to the hyperuricemic effect of the diuretic agents. Furosemide induces hyperlacticacidemia sufficient to suppress tubular excretion of urate (19). This is also true for diazoxide, a nondiuretic thiazide which promotes muscle glycolysis and leads to hyperlacticacidemia (20). Thiazide-induced hyperuricemia is corrected by KCl or NH_4Cl suggesting that a redistribution of urate among body compartments may be a contributing factor (21). Ayvazian & Ayvazian suggested that hydrochlorothiazide may also stimulate an increased production of uric acid (8); however, as they pointed out, alternative explanations existed to account for their observations. Finally it has been proposed that the thiazides may decrease the fractional excretion rate of uric acid by interfering directly, in a competitive manner, with urate secretion (7).

Most of the diuretic agents, when given intravenously in high dose, have a transient uricosuric effect. Although this could be related to a direct effect on uric acid transport it seems equally plausible that this effect of the diuretic agents is related to the striking increase in sodium excretion.

Diuretic-induced hyperuricemia can be readily controlled with hypouricemic agents when indicated (22,23) without apparently altering the natruretic effect of the diuretic agent. Beyer & Baer noted that the secretion of chlorothiazides by renal tissue from mongrel dogs was inhibited by probenecid (24,25). Because the natru-

retic effect of this class of diuretic agents depends on drug concentration within the tubular lumen, these observations suggested that uricosuric agents, like probenecid, might block the natriuretic effect of the diuretics. Indeed, the natriuretic effect of mercurials in chickens (26) and of furosemide in mongrel dogs (27) is markedly reduced by the administration of probenecid. Although this possibility has not been examined extensively in man, zoxazolamine (28) and probenecid (29) are said to have no effect on the natriuretic effect of the chlorothiazides in man.

Salicylates

Salicylates have a dual effect on uric acid excretion; small doses produce uric acid retention whereas large doses produce uricosuria. Retention of uric acid in response to low doses of salicylic acid was first reported by Salome (30) in 1885, which was eight years after See (31) had produced uricosuria and resolution of tophi in a gouty subject by the administration of large doses of salicylates. The hyperuricemic effect of acetylsalicylic acid in doses of less than 2.0 g per day was subsequently demonstrated by many investigators (32–39). For example, treatment with acetylsalicylate at a dose of 1.2 g for 4 days led to an increase in the serum urate from 1.0 to 1.8 mg/100 ml in males and from 0 to 1.0 mg/100 ml in females whereas a dose of 2.4 g per day produced uricosuria in most subjects including three of seven male subjects and eight of eight females (40). Gouty patients are said to be especially sensitive to the urate-retaining properties of salicylates.

Yu & Gutman (41) found that the maximal antiuricosuric effect of salicylates occurred at a plasma concentration of 5 mg/100 ml, and uricosuria began to occur at a concentration in excess of 10 mg/100 ml. However, this paradoxical effect of salicylates on uric acid clearance was found to be more dependent on the concentration of free salicylate in the tubular urine than either the dose administered or the plasma concentration. Uric acid retention was observed at an excretion rate of free salicylate below 0.5 mg/min whereas uricosuria was observed at salicylate excretion rates in excess of this value. Thus, alkalinization of the urine, which increases the excretion of ionized salicylate at any plasma salicylate level, would enhance the excretion of uric acid. Although the effects of salicylate on the serum urate concentration appear to be related to an alteration in the renal handling of uric acid, the exact mechanisms involved remain to be established.

Interference with the colorimetric procedure for uric acid by salicylate metabolites, predominately gentisic acid, may lead to confusion in the interpretation of uric acid values (40). At serum salicylate concentrations from 25 to 35 mg/100 ml, the colorimetric urate determination ranged from 13% (1.3 mg/100 ml) to 75% (7.0 mg/100 ml) higher than the true serum urate concentration (40).

Salicylate at any dose inhibits the uricosuric effect of many uricosuric agents including sulfinpyrazone, probenecid, and iopanoic acid (42,43). Concomitant administration of acetylsalicylate is a common factor when uricosuric therapy fails to control hyperuricemia. The nature of the interactions between salicylates and other drugs as related to their effect on uric acid clearance are complex and incompletely understood.

Pyrazinamide

The antituberculous agent, pyrazinamide, is the most powerful agent causing urate retention in man. It was first noted to produce hyperuricemia in 1956. In reporting 3 cases of clinical gout occurring while patients were on pyrazinamide therapy, Cullen et al (44) noted hyperuricemia in all patients receiving the drug. Subsequently, Shapiro & Hyde noted the development of hyperuricemia in 46 patients receiving pyrazinamide. In five patients also receiving *p*-aminosalicylic acid (PAS) the development of hyperuricemia was delayed, whereas in three patients receiving sodium salicylate or acetylsalicylate in addition to pyrazinamide (45) hyperuricemia did not occur. Cullen et al (46), suggested that the hyperuricemic effect of pyrazinamide was due to a reduction in the renal excretion of uric acid.

The metabolism of pyrazinamide is summarized in Figure 1. The parent compound is slowly deamidated to pyrazinoic acid by one of the hepatic microsomal drug-metabolizing enzymes, pyrazinamide deamidase (47–49), which appears to be different from the enzyme which deamidates nicotinamide. Pyrazinoic acid is then oxidized to 5-hydroxypyrazinoic acid by xanthine oxidase (47). Although pyrazinamide is also metabolized to another compound, whose structure is not defined, and

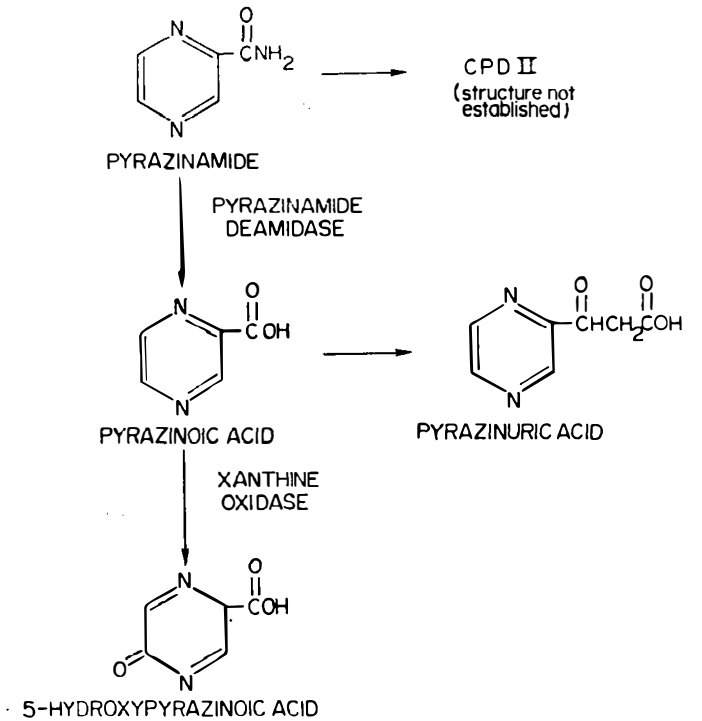

Figure 1 Metabolism of pyrazinamide.

pyrazinoic acid may be converted to pyrazinuric acid, these are metabolic pathways of minor importance.

The administration of pyrazinamide consistently leads to an 80 to 90% reduction in the renal clearance of uric acid (50–52). Several lines of evidence suggest that this effect of pyrazinamide is due to the major metabolite, pyrazinoic acid. 1. Pyrazinoic acid is more potent in producing a decreased renal clearance of uric acid than pyrazinamide (51). 2. The effect of pyrazinamide on uric acid transport begins at the time that pyrazinoic acid appears in the plasma (47). 3. The effect of pyrazinoic acid on uric acid transport occurs even if further metabolism of the drug is inhibited by the administration of allopurinol (47).

Pyrazinoic acid appears, like most other drugs affecting uric acid excretion, to have a dual effect on uric acid transport. A decreased excretion of uric acid is the usual response observed following the administration of pyrazinoic acid in humans (47), chimpanzee (53), Cebus monkey (54), mongrel dog (47), Dalmation coach hound (50), and guinea pig (55), whereas an increased excretion of uric acid is usually observed in the rabbit (56) and rat (57). However, following massive doses of the drug, the opposite effect, a uricosuric response, can be demonstrated in the mongrel dog and chimpanzee (47). Neither pyrazinamide nor pyrazinoic acid has been shown in humans, to date, to produce an increased clearance of uric acid. It seems likely, however, that such would occur if high enough plasma levels of pyrazinoic acid could be achieved. Although the hyperuricemic effect of pyrazinoic acid (and hence pyrazinamide) has been attributed to selective inhibition of renal urate secretion, it seems quite likely, from a consideration of the data cited above, that uric acid reabsorption may also be altered. The importance of this in the interpretation of the "pyrazinamide suppression test" has been considered elsewhere (58).

Pyrazinamide hyperuricemia does not respond to uricosuric therapy (59,60). However, both acetylsalicylic acid (61) and PAS (59) may prevent or delay the development of hyperuricemia during pyrazinamide therapy for tuberculosis. Petty & Dalrymple (62) observed that a dose of acetylsalicylic acid (2.4 g per day), which may produce uric acid retention, was capable of completely reversing the hyperuricemic effect of pyrazinamide in 11 patients. The nature of this paradoxical effect of acetylsalicylic acid remains unclear.

Nicotinic Acid

Hyperuricemia occurred in 41 to 78% of subjects receiving 3 to 6 g of nicotinic acid daily in the treatment of hypercholesterolemia (63–65). A mean increase of 1.3 mg/100 ml was observed in one study of 25 patients (65).

The structural similarity of pyrazinoic acid (Figure 1) and nicotinic acid (Figure 2) suggests that the mechanism responsible for the antiuricosuric effect of each compound might be similar. Gaut et al noted a 75% decrease in the clearance of uric acid over a 3 week period following the administration of nicotinic acid at a dose of 4.5 g day to five subjects (66). Gershon & Fox (67) recorded a 62% decrease in the fractional excretion rate of uric acid 1 hr after the administration of 1 g of nicotinic acid orally to nine subjects. Thus the hyperuricemic effect of nicotinic acid

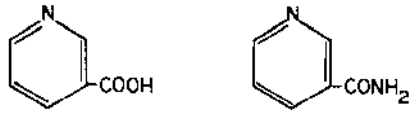

Figure 2 Structure of nicotinic acid (*left*) and nicotinamide (*right*).

like pyrazinoic acid appears to be due, at least partly, to a reduced renal excretion of uric acid. Nicotinic acid differs from pyrazinoic acid, however, in that its hyperuricemic effect is not reversed by acetylsalicylic acid (67). Nicotinamide, the amide derivative of nicotinic acid (Figure 2), at a dose of 4.5 g per day had little, if any, effect on uric acid excretion (67).

The importance of changes in uric acid synthesis during nicotinic acid administration is unclear. Becker et al noted an increase in the rate of purine biosynthesis de novo following the administration of nicotinic acid in man (68). In addition, nicotinamide stimulates purine biosynthesis de novo in rat liver and kidney by activation of the hexosemonophosphate shunt (69,70). However, nicotinic acid reduces the rate of purine biosynthesis de novo in cultured human fibroblasts (71). The significance of the reduction of intracellular phosphoribosyl pyrophosphate (PP-ribose-P) following exposure to nicotinic acid in cell culture (71) and in vivo (67) is also difficult to interpret at the present time.

The uricosuric effect of agents such as sulfinpyrazone and iopanoic acid is inhibited by nicotinic acid (67). This suggests that control of nicotinic acid-induced hyperuricemia, when indicated, will require the use of a xanthine oxidase inhibitor.

Ethambutol

Ethambutol is used clinically in the treatment of mycobacterium tuberculosis infections in man (Figure 3). Postlethwaite et al (72) noted an increase in the serum urate concentration of 2.4 mg/100 ml or greater in 15 of 24 patients with active tuberculosis who were treated with ethambutol at doses ranging from 12 to 19 mg/kg per day. An increase in the serum urate concentration was noted as early as 24 hr after the administration of a single dose of ethambutol or as late as 90 days after initiation of continuous therapy with the drug.

The hyperuricemic effect of ethambutol is due to a decreased renal clearance of uric acid (72,73). Ethambutol differs from pyrazinamide in that its hyperuricemic effect is not reversed by acetylsalicylic acid. Unlike acetylsalicylic acid and nicotinic acid, ethambutol does not block the effect of probenecid or sulfinpyrazone. The hyperuricemic effect of ethambutol also cannot be attributed to lactic acid accumu-

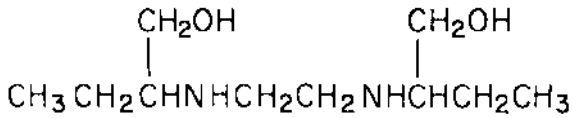

Figure 3 Structure of ethambutol.

lation or extracellular fluid (ECF) volume depletion. Thus, although the exact mechanism responsible for the hyperuricemic effect of ethambutol remains undefined, several characteristics distinguish its effect from that of other agents that produce hyperuricemia by altering the renal handling of uric acid.

The hyperuricemia observed during ethambutol therapy responds equally well to probenecid, sulfinpyrazone, and allopurinol (73).

Ethanol

In his classic review on gout published in 1863, A. B. Garrod (74) wrote: "There is no truth in medicine better established than the fact that the use of fermented liquors is the most powerful of all the predisposing causes of gout; nay, so powerful, that it may be a question whether gout would ever have been known to mankind had such beverages not been indulged in."

The centuries-old belief that the acute gouty paroxysm may be associated with overindulgence in drink has at long last acquired a physiologic explanation. Hyperuricemia is common in inebriated subjects (75), and infusions of ethanol result in hyperuricemia (76). As ethanol is metabolized by alcohol dehydrogenase, NAD is reduced, and this may account in part for the excessive conversion of pyruvate to lactate. The levels of hyperlacticacidemia achieved (76) are adequate to suppress the renal excretion of uric acid and to induce hyperuricemia (77).

The changes occurring in the serum urate concentration may be quite large and rapid. In five acutely intoxicated subjects who were hyperuricemic on admission to the hospital, Lieber et al (76) noted a subsequent decrease in the serum urate ranging from 4.0 to 6.8 mg/100 ml over an ensuing 11 day period. The administration of alcohol, orally or intravenously, to seven normal subjects led to an increase in the serum urate in six of the subjects which ranged from 1.0 to 3.0 mg/100 ml. This occurred in most cases in less than 12 hr.

More recently, Maclachlan & Rodnan (78) have observed that the combination of ethanol ingestion and fasting may be additive or synergistic with respect to the effects of each of these factors on uric acid metabolism. Presumably, the ketonemia associated with both fasting (79) and ethanol-induced glycogen depletion (80) leads to a further reduction in uric acid excretion.

Several epidemiologic studies have reported a correlation between serum urate levels and habitual alcohol intake (81,82). The daily ingestion of alcohol in significant but tolerated amounts, eg. 100 ml per 24 hr, may be associated with hyperuricemia and an increased urinary excretion of uric acid, both of which may return toward or to normal during protracted periods (days) of abstinence and normal diet. These cycles are not explained by reduced urinary clearance of uric acid. An effect upon purine synthesis has, therefore, also been postulated (83). It seems likely that several additional factors such as muscle hyperactivity and ECF volume depletion may contribute to the development or maintenance of hyperuricemia particularly during the phase of alcohol withdrawal.

The relationship of ethanol to uric acid metabolism has been reviewed recently by Newcombe (84).

L-Dopa

Several reports suggest that L-dopa may lead to the development of hyperuricemia (85–87). However, it is possible that in some patients this effect is due to interference by L-dopa with the phosphotungstic acid method for determining uric acid (88,89). A similar effect may be observed with α-methyldopa. Clearly, the mechanism and significance of this effect of L-dopa remains to be further clarified.

Fructose

The phenomenon of fructose-induced hyperuricemia was initially described in man by Perheentupa & Raivio (90). Although this effect of fructose has not been consistently confirmed by other investigators (91), there appears to be a relationship between the rate of fructose administration and the degree of hyperuricemia produced (92). The effects of the acute intravenous administration of large doses of fructose may be summarized as follows: (*a*) increased serum urate; (*b*) increased urinary inosine, hypoxanthine, and xanthine excretion (93); (*c*) increased urinary uric acid excretion (90, 93, 94); (*d*) increased fractional excretion rate of uric acid (94); (*e*) decreased hepatic ATP and ADP with no change in AMP (95, 96); (*f*) increased incorporation of glycine-^{14}C into adenine nucleotides (97) and uric acid (98); (*g*) decreased PP-ribose-P and ribose-5-P content in erythrocytes; and (*h*) increased plasma lactate (90–92).

These findings are most consistent with a model in which fructose leads to a rapid degradation of purine nucleotides with the consequent formation of inosine, hypoxanthine, xanthine, and uric acid. Because ATP normally inhibits 5'-nucleotidase and inorganic phosphate inhibits AMP deaminase, the reduced intracellular content of both compounds associated with the phosphorylation of fructose stimulates the catabolism of AMP to inosine and subsequently uric acid. Although the hyperlacticacidemia may contribute to the development of hyperuricemia, it appears to be a relatively unimportant factor (93). Approximately equimolar infusions of glucose and galactose do not produce a similar effect on purine metabolism (94).

The possibility that fructose may cause hyperuricemia by increasing the rate of purine biosynthesis de novo must also be considered. Fructose is both a precursor and stimulator of PP-ribose-P synthesis in human cells in vitro (93). Because PP-ribose-P is a limiting substrate for the initial step of purine biosynthesis de novo, an increased concentration of PP-ribose-P would be expected to increase the rate of purine synthesis de novo. However, several findings indicate that the rapid increase in plasma urate concentration, which occurs 30 to 45 min after the infusion of fructose, is not due to this mechanism. 1. The infusion of fructose does not increase PP-ribose-P levels in erythrocytes in vivo; in fact, the intracellular concentration of PP-ribose-P, as well as its immediate precursor, ribose-5-phosphate, appears to decrease. 2. Hyperuricemia occurs following the infusion of fructose to patients with hereditary fructose intolerance in whom there is a genetically determined block in the further metabolism of fructose-1-phosphate (90). This finding also suggests that increased uric acid production can occur without stimulating PP-ribose-P synthesis. 3. It seems unlikely that an increase in purine biosynthesis de novo would lead to so rapid an increase in the serum urate concentration. As

discussed later, the most potent stimulator of purine biosynthesis de novo known in man, 2-ethylamino-1,3,4-thiadiazole, increases the serum urate concentration in 24 to 48 hr, not in 30 to 45 min.

The chronic ingestion of fructose leads to little if any detectable change in the serum or urinary uric acid (94). Although an increase in the incorporation of glycine-^{14}C into uric acid suggests that the chronic as well as the acute administration of fructose is associated with an enhanced rate of purine biosynthesis de novo (98), it is not possible to discern in either case if this is a primary or secondary effect.

2-Ethylamino-1,3,4-thiadiazole

The compound, 2-ethylamino-1,3,4-thiadiazole (EA-TDA) (Figure 4), was found to arrest the growth of experimental tumors in mice (99). When administered to human subjects, however, it produced a several fold increase in both the serum urate level and the excretion of uric acid in the urine (100). Subsequent studies demonstrated a striking increase in the rate of purine biosynthesis de novo in man following administration of the drug (101–103) as reflected in (*a*) an increased incorporation of glycine-^{14}C into urinary uric acid, hypoxanthine, xanthine, adenine, guanine, and methylguanine and (*b*) an increased excretion rate of those compounds.

The mechanism responsible for this effect of EA-TDA still remains unclear. The effect of the drug on purine metabolism in man can be prevented by the simultaneous administration of nicotinamide at a dose 4 times greater than that of EA-TDA (102, 103), and by nicotinic acid (102). In the chick embryo the effect of EA-TDA is reversed by allopurinol (104) as well as by a number of nicotinamide antagonists (105). Whatever the mechanism, it does not require the presence of hypoxanthine-guanine phosphoribosyltransferase in man (106).

Cytotoxic Drugs

Hyperuricemia may occur following the administration of any agent that leads to a breakdown of cells. In this setting there is a rapid release of preformed purine nucleotides and cellular nucleic acids leading to an increased synthesis of uric acid. This effect of the cytotoxic agents usually occurs in association with the treatment of neoplastic disease.

DRUGS REDUCING THE SERUM URATE CONCENTRATION

Drugs may reduce the serum urate concentration by increasing the rate of elimination of the compound or decreasing its rate of synthesis. An increased rate of elimination could theoretically be achieved by increasing urate destruction (e.g.

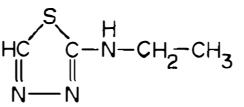

Figure 4 Structure of 2-ethylamino-1,3-4-thiadiazole.

uricase), by increasing its disposal through the gastrointestinal tract, or by increasing renal excretion of the compound. For practical purposes, the latter mechanism is the only one of importance at this time. A decreased synthesis of uric acid could also potentially be achieved at a number of different sites in the pathway. However, inhibition of the final step leading to the synthesis of uric acid has proven to be most important. In this review, therefore, the hypouricemic agents are considered in two sections, uricosuric agents and xanthine oxidase inhibitors.

Uricosuric Drugs

A large number of drugs with diverse chemical and pharmacologic properties decrease the serum urate concentration in man by enhancing the renal excretion of uric acid. These compounds are listed in Table 1. At the present time, probenecid (Benemid ®) (Figure 5) and sulfinpyrazone (Anturan) (Figure 6) are most widely employed for this purpose in the United States; in Europe benzbromarone and zoxazolamine are used as well.

MECHANISM OF ACTION The renal handling of uric acid has been reviewed elsewhere (107, 108). Briefly, uric acid is filtered at the glomerulus, and reabsorbed and secreted within the nephron. The exact location and quantitative significance of the latter two processes, however, remains to be established. The uricosuric effect of a drug could be due to an increase in the quantity of urate filtered, an inhibition of the tubular reabsorption of urate, or an enhancement of its secretion.

Drugs could increase the quantity of urate filtered by increasing either the glomerular filtration rate or the plasma concentration of free urate. Although the former mechanism has not been demonstrated, the latter has received some support (109, 110). A number of agents with a uricosuric effect in man such as sulfinpyra-

Table 1 Drugs shown to be uricosuric in man

Acetohexamide	Iodopyracet
Azauridine	Iopanoic acid
Benzbromarone	Meglumine iodipamide
Benziodarone	*p*-Nitrophenylbutazone
Calcium ipodate	Orotic acid
Chlorprothixene	Outdated tetracyclines
Cinchophen	Phenolsulfonphthalein
Citrate	Phenylbutazone
Dicumarol	Phenylindandione
Diflumidone	Probenecid
Estrogens	Salicylates
Ethyl biscoumacetate	Sodium diatrizoate
Ethyl *p*-chlorophenoxyisobutyric acid	Sulfaethylthiadiazole
Glyceryl guaiacolate	Sulfinpyrazone
Glycine	W 2354
Glycopyrrolate	Zoxazolamine
Halofenate	

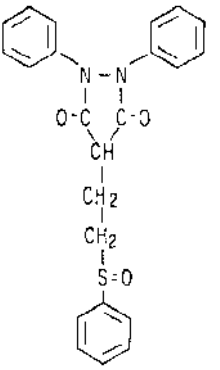

Figure 5 Structure of probenecid.

zone, probenecid, salicylates, phenylbutazone, sulfaethylthiadiazole, diflumidone, W2354, and halofenate, have been shown to reduce the binding of uric acid to albumin in vitro (108, 110, 111). In addition, there is recent evidence that salicylates may reduce urate binding to protein in vivo (112). If urate is displaced from plasma proteins in vivo this would increase the filtered load of free urate and could account for at least part of the uricosuric effect of these drugs. With the exception of salicylates, however, there is no evidence that these agents actually displace uric acid binding in vivo.

The uricosuric effect of most agents studied including probenecid, salicylates, and sulfinpyrazone has been attributed to inhibition of the tubular reabsorption of filtered urate. With several exceptions, drugs with a significant uricosuric effect in man (113) are, like uric acid itself, weak organic acids. Since tubular reabsorption of uric acid is thought to occur by a process common to many organic acids, it has been assumed that these drugs inhibit this process in a competitive manner.

Four drugs that are not organic acids have a uricosuric effect in man. Studies with two of these agents, outdated tetracycline (114) and chlorprothixene (115), suggest that they may inhibit the reabsorption of uric acid in the proximal tubule in a nonspecific manner that also affects the reabsorption of other compounds in this segment of the nephron. Glycopyrrolate may exert its uricosuric effect by virtue of its anticholinergic properties (116). The precise mechanism of action of the final agent in this group, zoxazolamine, has not been established.

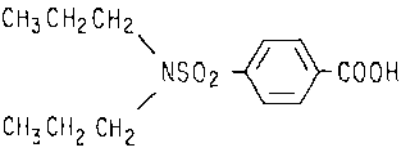

Figure 6 Structure of sulfinpyrazone.

It has been suggested recently that several drugs including glycine (117), benziodarone (118), and the X-ray contrast agents (119) may enhance the tubular secretion of urate. This hypothesis is based on the observation that the effect of these drugs is completely or partially blocked by the prior administration of pyrazinamide (PZA). A more recent interpretation of this response to pyrazinamide would suggest that these drugs do not enhance uric acid secretion but inhibit the reabsorption of uric acid distal to the secretory site (107). The difficulty in interpretation of the "PZA suppression test" has been discussed elsewhere (108) and is not reviewed here.

METABOLISM AND DOSE Because probenecid and sulfinpyrazone are the two most commonly used uricosuric agents, their metabolism is reviewed in some detail.

Probenecid, *p*-(di-*n*-propylsulfamyl)benzoic acid (Figure 5), was developed originally as an inhibitor of renal tubular secretion of penicillin. Shortly afterward, it was found to have a potent uricosuric effect in man, and its value in the control of hyperuricemia was soon demonstrated. The drug is readily absorbed in the gastrointestinal tract. The half-life of probenecid in plasma is dose-dependent (120), but ranges from 6 to 12 hr. It is readily bound to plasma proteins (89–94% of drug) and is largely confined to the extracellular fluid.

The drug is rapidly metabolized in vivo as shown by the recovery in the urine of less than 5% of the administered dose within 24 hr. The major urinary metabolite, probenecid acyl monoglucuronide, accounts for 41% of the administered compound within 48 hr. The remainder of the metabolites result from oxidative attack of the *n*-propyl side chain and are the monohydroxylated derivatives at the secondary (7.2–12.5%) and terminal (1.6–3.7%) positions and the carboxyl (6.3–9.2%) and N-dipropyl (4.6–8.0%) compounds (121, 122). The side-chain metabolites possess uricosuric activity in animals (123).

Probenecid was the first agent found to be consistently effective in lowering the serum urate concentration in gout. The maintenance dose ranges from 500 mg to 3 g per day given in 3 or 4 divided doses (124). The initial dose should be low (e.g. 250 mg 2 to 3 times per day) in order to avoid sudden mobilization of large quantities of urate.

Sulfinpyrazone was specifically developed for use as a uricosuric agent and is one of the most potent known (Figure 6). It is rapidly and completely absorbed, with a peak concentration in the serum 1 hr after its oral administration. The half-life in serum is 1 to 3 hr (125, 126). At a serum concentration of 10 mg/100 ml, 98% of the drug is bound to plasma proteins. As a result, sulfinpyrazone, like probenecid, is largely confined to the extracellular fluid (126, 127). Some 20 to 45% of the drug is excreted unchanged in 24 hr, predominately during the first 6 hr (125, 127). Most of the drug is excreted in the urine as the parahydroxyl metabolite, which is also uricosuric in man.

A dose of sulfinpyrazone of 35 mg has a uricosuric effect comparable to 100 mg of probenecid (125), and 400 mg per day has an effect similar to that observed with 1.5 to 2.0 g of probenecid per day (128). Hence sulfinpyrazone is 3 to 6 times more potent than probenecid on a weight basis (121). The usual maintenance dose ranges

from 200 to 400 mg/day in 3 or 4 equally divided doses, although a maximal effect is frequently not reached until a dose of 800 mg/day is administered. Sulfinpyrazone has an additional uricosuric effect in subjects receiving the maximal effective dose of probenecid.

SIDE EFFECTS Side effects of probenecid include an 8 to 18% incidence of gastrointestinal complaints, a 5% incidence of hypersensitivity and rash, and a 10 to 20% incidence of gouty arthritis. However, serious side effects of probenecid seem to be extremely rare. Hepatic necrosis has been reported in one patient (129) and the nephrotic syndrome in another (130). One patient, who took a massive overdose of probenecid (42.5 g) in a suicidal attempt, developed seizures but had no apparent long-term sequelae.

The incidence of gastrointestinal symptoms with sulfinpyrazone (10 to 15%) is roughly the same as that observed with probenecid (128, 131–133). However, sulfinpyrazone appears to produce a higher incidence of bone marrow changes as compared with probenecid (128, 134, 135).

A complication of therapy with either probenecid or sulfinpyrazone which is preventable, is uric acid stone formation. Initiation of uricosuric therapy leads to a transient increase in uric acid excretion. After the serum urate level drops, the urinary uric acid excretion will return essentially to pretreatment values. Because uric acid is relatively insoluble, especially in acid urine, this transient increase in uric acid excretion can lead to the development of uric acid stones. This complication was recorded in 9% of the patients treated by Gutman & Yu (124).

Uric acid stone formation can be minimized by initiating uricosuric therapy with a relatively low dose and increasing it over a period of days or weeks, by maintaining an adequate urine flow, and by alkalinizing the urine with the oral administration of sodium bicarbonate or sodium citrate during the early course of drug therapy. After the hyperuricemia has been controlled and the urinary uric acid has returned to normal, these precautions are no longer necessary in most patients.

Probenecid also has a number of effects which could be of physiologic significance. Probenecid blocks the transport of serotonin and dopamine out of the cerebrospinal fluid (CSF). This is reflected in an increase in the concentration of 5-hydroxyindoleacetic acid and homovanillic acid in CSF obtained from patients being treated with probenecid (136–138). In addition, probenecid reduces the renal excretion of pantothenic acid (139, 140), androsterone (141), ACTH (142), and diiodotyrosine (143). Although probenecid may reduce the elevated serum phosphorous concentration in patients with hypoparathyroidism (144–146), it appears to have no effect on serum phosphorous, amino acid excretion (121, 147), or glucose excretion (121) in normal subjects. Finally, this drug seems to inhibit in some manner the conjugation of benzoic derivatives with glycine (148).

It is not known whether sulfinpyrazone has any or all of these effects on the transport, excretion, or metabolism of endogenous substances. However, one action of this agent of potential therapeutic significance is the reduction in platelet function observed following its administration. As a result of this effect sulfinpyrazone decreased thrombosis in arteriovenous shunts (149) and prolonged platelet survival in

patients with prosthetic heart valves, rheumatic heart disease, and recurrent venous thrombosis (150, 151). This effect of sulfinpyrazone on platelet function can be demonstrated in vitro and thus appears to be unrelated to its hypouricemic effect.

INTERACTION WITH OTHER DRUGS Probenecid has a number of effects on the renal excretion, volume of distribution and/or hepatic uptake of a number of drugs. These are summarized in Table 2. As a result of these interactions certain drugs should be used with caution in patients receiving probenecid. Dapsone and indomethacin, for example, should be used at a lower dose in patients receiving probenecid. Aspirin and its closely related compounds should not be given with probenecid. Not only does probenecid delay the renal excretion of salicylic acid and many of its glucuronide derivatives, but acetylsalicylate completely blocks the uricosuric effect of probenecid and most other uricosuric agents.

The effect of probenecid on the metabolism of some drugs has been used to good advantage. Probenecid has been used, for example, to enhance the blood levels of ampicillin and penicillin. In addition, the prolonged half-life of Rifampicin ® observed in the presence of probenecid may be therapeutically useful. Probenecid also appears to reduce the volume of distribution of several antibiotics, including ampicillin, ancilin, nafcillin, and cephalordine (152); should the concentration of these antibiotics be significantly reduced in certain body fluids or spaces in the presence of probenecid the net effect could be detrimental.

It seems quite possible that sulfinpyrazone may inhibit the excretion or metabolism of many of the same compounds altered by probenecid. At the present time there is relatively little data on these potential effects of sulfinpyrazone.

Table 2 Effects of probenecid on metabolism of other drugs

Decreased renal excretion
Paraaminohippuric acid
Phenolsulfonphthalein
Salicylic acid and its acyl and phenolic glucuronides
Phlorizin and its glucuronide
Acetazolamide
Dapsone and its metabolites
Sulfinpyrazone and its parahydroxy metabolite
Indomethacin
Ampicillin
Penicillin
Reduced volume of distribution
Ampicillin
Ancilin
Nafcilin
Cephaloridine
Impairment of hepatic uptake
Bromsulfonphthalein
Indocyanin green
Rifampicin

Decreased Uric Acid Formation

For practical purposes the only therapeutically effective method for decreasing uric acid formation at the present time involves inhibition of xanthine oxidase. The final steps leading to the synthesis of uric acid involve the conversion of hypoxanthine to xanthine and xanthine to uric acid and are catalyzed by a single enzyme, xanthine oxidase. Many inhibitors of xanthine oxidase are known, including 6-pteridylaldehyde and various purine analogs such as adenine, 2,6-diaminopurine, 6-thiopurine, symmetrical triazines, 6-chloropurine, and 4-diazoimidazole-5-carboxamide. Allopurinol, however, has proved to be the most important compound in this group. This compound is a purine analog that differs from hypoxanthine in that the positions of the 7-nitrogen and 8-carbon are reversed.

Both allopurinol and its major metabolic product, oxipurinol, an analog of xanthine, are potent inhibitors of xanthine oxidase (1, 153–155) (Figure 7). The Michaelis constant of allopurinol is some 15 to 200 times lower than that of xanthine, whereas that of oxipurinol is comparable to that of xanthine (153). Allopurinol may show substrate-competitive kinetics. Both allopurinol and oxipurinol produce pseudo-irreversible inactivation of xanthine oxidase. Such inactivation occurs when allopurinol and enzyme are incubated in the absence of substrate, but enzyme activity can be restored by prolonged dialysis. Oxipurinol has no effect on enzyme alone, but inactivates it in the presence of xanthine (1, 153).

Allopurinol was first synthesized for trial as a chemotherapeutic agent, but by itself had little or no effect upon experimental tumors (156, 157). It was found to be an inhibitor of xanthine oxidase (154) and to inhibit the conversion of 6-thiopurine to 6-thiouric acid in mouse and man (158). It was first introduced clinically as adjunct therapy in patients receiving 6-thiopurine for leukemia (159). Patients given allopurinol showed a pronounced reduction in both serum and urinary uric acid values (159, 160). These observations suggested a trial of the agent in gout and it is now established as one of the standard forms of therapy of hyperuricemia and uric acid stones.

The administration of allopurinol in man is followed by a prompt decrease in the serum and urinary uric acid within 24–48 hr, reaching a maximum in 4 days to 2 weeks and remaining relatively constant over prolonged periods of time (157, 161). There is no evidence for irreversible inactivation of xanthine oxidase in man as has been observed in vitro or, for that matter, of enzyme induction. Withdrawal results in a return to pretreatment serum urate levels within a few days, and the exceptional, more prolonged effects are usually associated with delayed excretion of oxipurinol.

METABOLISM AND DOSE Allopurinol has a very short biological half-life of only 2–3 hr (162). Some 3–10% of an administered dose is excreted with a clearance rate approximately equal to the glomerular filtration rate (162). Most of the allopurinol (45–65%) is rapidly oxidized to oxipurinol in vivo, with a smaller portion being converted to allopurinol ribonucleoside (163) and allopurinol ribonucleotide (164). Most of the oxipurinol formed is excreted unchanged by the kidney with a relatively long half-life (28 hr) (162). A portion is metabolized to the 7-N-ribosyloxipurinol (oxipurinol ribonucleoside) and the 1-N-ribosyloxipurinol (165) derivatives as well as the corresponding ribonucleotide derivatives (166). The pathways involved in the

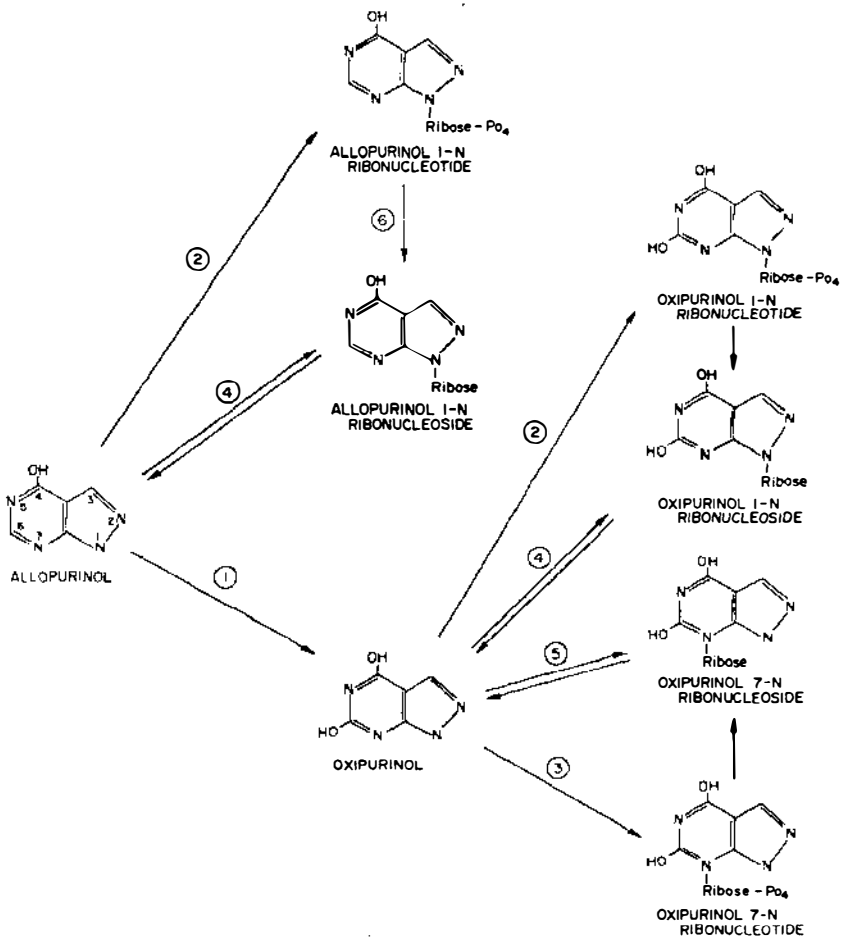

Figure 7 Metabolism of allopurinol. The reactions indicated by the numbers are catalyzed by the following enzymes: 1, xanthine oxidase; 2, hypoxanthine-guanine phosphoribosyltransferase; 3, orotate phosphoribosyltransferase; 4, purine nucleoside phosphorylase; 5, pyrimidine nucleoside phosphorylase; 6,5'nucleotidase.

metabolism of allopurinol are summarized in Figure 7. Factors that affect uric acid excretion generally alter oxipurinol excretion in a similar manner (165).

It has been suggested that oxipurinol rather than allopurinol is primarily responsible for xanthine oxidase inhibition in vivo (153). A direct comparison of the two drugs indicates that allopurinol is probably the more effective but this is due to the relatively poor absorption of oxipurinol in the gastorintestinal tract (167).

With the use of allopurinol a normal serum urate value can be achieved in all but a few patients. The doses required to reduce elevated serum levels to normal average 200–400 mg/day. In contrast to the uricosuric agents, allopurinol therapy can be

initiated at a dose that is expected to provide effective control of the hyperuricemia. Although allopurinol is usually given in 3 or 4 divided doses, a single daily dose may be adequate because of the relatively prolonged half-life of oxipurinol.

SIDE EFFECTS More than half of the increase in urinary oxypurines observed with allopurinol therapy consists of xanthine, a relatively insoluble compound in acid and neutral urine (168). The levels attained with full doses of allopurinol may equal those observed in patients with xanthinuria who lack xanthine oxidase activity as an inborn error of metabolism. These levels of xanthine in the urine have been associated in the xanthinuria patients with the occurrence of urinary calculi composed of xanthine. Thus far, development of xanthine crystalluria or lithiasis as a complication of allopurinol therapy has not been observed in any patient given the drug for treatment of gout or uric acid stones. Three instances of xanthine stone formation, related to allopurinol therapy, have been reported in other circumstances. Two occurred in children with the Lesch-Nyhan syndrome (169, 170) and the third in an adult patient with lymphosarcoma (171). All three patients excreted approximately 1500 mg of uric acid per day. One child, who received 9 mg of allopurinol per kg, excreted as much as 800 mg of xanthine per day while on therapy (172, 173). It appears that allopurinol should be given cautiously and in minimal doses to patients with extraordinarily great uric acid excretion values, particularly those with inability to reutilize hypoxanthine and xanthine because of HGPRT deficiency (174).

When allopurinol is given, serum oxypurine levels rise only slightly, reaching 0.5–1.0 (159, 168) or, rarely, 2.0 mg/100 ml (175) because of the relatively high renal clearance of oxypurines. As Klinenberg et al point out, the oxypurine levels achieved are well below the solubility limits of hypoxanthine or xanthine in serum (168). However, hypoxanthine, xanthine, and oxipurinol crystals have been noted in skeletal muscle from gouty subjects treated with allopurinol (176). In these patients the concentration of hypoxanthine and xanthine in muscle is considerably less than observed in patients congenitally deficient in xanthine oxidase (177), and it is not certain that significant clinical symptoms result from this phenomenon.

Serious complications of allopurinol therapy appear to have been rare during its initial 8 years in general use. Approximately 5% of patients find it necessary to discontinue the drug (178). Allopurinol may lead to the development of gastrointestinal intolerance (175), skin rashes, sometimes with fever (168), leukopenia, thrombocytopenia, hepatitis, or vasculitis (179). It is not clear whether these are related to hypersensitivity or to a toxic effect of the drug. These complications tend to occur more often in the presence of renal insufficiency. Despite earlier reports to the contrary, allopurinol has no significant effect
tion (1).

In addition, allopurinol has several other effects that have been demonstrated in man. Inhibition of both purine and pyrimidine biosynthesis de novo and depletion of intracellular PP-ribose-P are the effects most consistently observed in vivo.

In most patients the replacement of urinary uric acid by the oxypurines, hypoxanthine and xanthine, is less than stoichiometric (159, 174, 180). The deficit ranges

from 10–60% and is roughly proportional to the pretreatment level of uric acid excretion (176). The total deficit may amount to several hundred milligrams of total purines (uric acid plus oxypurines) per day (159, 175). In addition, the reduction in total purine excretion is associated with a decreased incorporation of isotopic glycine into urinary uric acid (181). This effect of allopurinol requires the presence of hypoxanthine-guanine phosphoribosyltransferase (182) and may be due to a combination of factors, including (*a*) an increased conversion of hypoxanthine to inosine 5'-monophosphate (IMP) (161), with the reduction in purine biosynthesis de novo due to the inhibitory action of purine ribonucleotides derived from IMP, (*b*) the conversion of allopurinol to its ribonucleotide, and the reduction of purine biosynthesis de novo by the inhibitory effect of allopurinol ribonucleotide upon glutamine PP-ribose-P amidotransferase (183, 184), and (*c*) depletion of PP-ribose-P, an essential substrate of PP-ribose-P amidotransferase (164, 185), as a result of the conversion of either allopurinol or hypoxanthine to their respective ribonucleotide derivatives.

The administration of allopurinol leads to a substantial reduction of erythrocyte PP-ribose-P content, which occurs 3–5 hr after administration of the drug (164). This effect in the erythrocytes is due to consumption of PP-ribose-P by the conversion of allopurinol to its ribonucleotide. It is not attributable to increased reutilization of hypoxanthine and xanthine, because PP-ribose-P levels do not fall after oxipurinol administration (164). Nevertheless, it has been shown that reutilization of hypoxanthine (186) and xanthine (187) for nucleic acid synthesis is markedly enhanced in the intact rat when their oxidation is inhibited by allopurinol.

The administration of allopurinol and oxipurinol in man is accompanied by a striking increase in the excretion of orotidine and orotic acid (188, 189). Studies in vivo and in cell culture demonstrate that this effect results from inhibition of orotidine 5'-phosphate decarboxylase, which catalyzes a step in the conversion of orotic acid to uridine 5'-monophosphate (UMP). Inhibition of orotidine 5'-phosphate decarboxylase in vivo is not dependent on the presence of hypoxanthine-guanine phosphoribosyltransferase activity and therefore cannot be completely attributed to the formation of 1-N-ribosyloxipurinol 5'-monophosphate, allopurinol ribonucleotide, or xanthosine-5'-monophosphate, each of which is a potent inhibitor of orotidine 5'-phospate decarboxylase in vitro (190). At least in hypoxanthine-guanine phosphoriboxyltransferase-deficient cells, the inhibitory effect of these compounds on pyrimidine biosynthesis appears to involve formation of derivatives that are analogs of the purine 3-N-ribonucleotides (191, 192) whose formation is catalyzed by a different enzyme, orotate phosphoribosyltransferase (166). It seems likely at this time that the inhibition of orotidine 5'-phosphate decarboxylase is largely due to both 1-N-ribosyloxipurinol 5'-phosphate and 7-N-ribosyloxipurinol 5'-phosphate. The administration of allopurinol to rats is associated with a transient decrease in UMP and UDP pools in the liver whereas UTP levels are actually elevated; no change is observed in the level of uridine nucleotides in the kidney (193). These studies suggest that, at least in the rat, any reduction of intracellular pyrimidine nucleotides due to the inhibition of pyrimidine biosynthesis de novo is rapidly corrected presumably by an enhanced conversion of uridine to UMP.

The administration of allopurinol also leads to an eightfold increase in the activity of orotate phosphoribosyltransferase and orotidine 5'-phosphate decarboxylase in circulating erythrocytes (188, 194). The increase can usually be demonstrated within one week of allopurinol therapy and the activity appears to level off after 3 to 6 weeks. The mechanism responsible for this has been somewhat controversial. The ribonucleotide derivatives of both allopurinol and oxipurinol are capable of shifting the configuration of the complex of orotate phosphoribosyltransferase and orotidine 5'-phosphate decarboxylase to a larger, more stable molecular species (195). Most of the data currently available are consistent with the hypothesis that the apparent increase in enzyme activity is due to stabilization of the enzyme complex to the extraction procedure. Other possibilities include stabilization of the enzyme complex to degradation in vivo or "activation" of the enzyme complex. Irrespective of the mechanism, this latter change in enzyme activity during allopurinol therapy appears at the present time to be of little clinical consequence.

Allopurinol also has a number of other metabolic effects, which have been demonstrated in vitro or in lower animals. Through its action upon xanthine oxidase it inhibits tryptophan pyrrolase (196), probably by limiting the availability of H_2O_2 to the latter enzyme (197, 198). Allopurinol also inhibits purine nucleoside phosphorylase (163, 199) and pyrimidine deoxyribosyltransferase (200) in vitro. It activates, and at a higher concentration inhibits, urate oxidase (201).

INTERACTION WITH OTHER DRUGS There are several potentially important drug-drug interactions involving allopurinol which deserve comment. Purine analogs such as 6-mercaptopurine and azathioprine, which are inactivated by xanthine oxidase, are potentiated by the xanthine oxidase inhibition associated with al-

Table 3 Metabolic effects of allopurinol

Clinical Effect	Mechanism	Effector
1. Hypouricemia	Xanthine oxidase inhibition	Allopurinol Oxipurinol
2. Decreased total purine production	Inhibition of PP-ribose-P amidotransferase	Allopurinol-1-N-ribosylphosphate IMP
	PP-ribose-P depletion	Allopurinol
3. Orotidinuria	Inhibition of orotine 5'-phosphate decarboxylase	Oxipurinol-7-N-ribosylphosphate Oxipurinol-1-N-ribosylphosphate Allopurinol-1-N-ribosylphosphate
4. Orotic aciduria	Inhibition of orotate phosphoribosyltransferase	? OMP
	PP-ribose-P depletion	Allopurinol
5. Prolonigation of half-life of drugs metabolized by the microsomal oxidizing system	Inhibition of hepatic microsomal drug-metabolizing enzymes	Unknown
6. Apparent increased activity of orotate phosphoribosyltransferase and orotidylic decarboxylase	? Stabilization of enzymes to extraction	Allopurinol-1-N-ribosylphosphate
	? Activation	Unknown

lopurinol administration. In addition, allopurinol has an inhibitory effect on the hepatic microsomal drug-metabolizing enzymes (202). Thus drugs such as antipyrine and bishydroxycoumarin, which are metabolized by this system, should be used with caution and at a lower dose in patients receiving allopurinol. The half-life of probenecid is prolonged by about 50% in the presence of allopurinol (203), which has been attributed to the inhibitory effect of allopurinol on the microsomal drug-metabolizing system. The administration of allopurinol is associated with a threefold higher incidence of ampicillin-related skin rash (204). However, it is not clear from the latter study whether this potentiation is due to allopurinol, or to the presence of hyperuricemia.

Some of the metabolic effects of allopurinol are summarized in Table 3.

SUMMARY

In this review the drugs capable of increasing or lowering the serum urate concentration are considered with regard to mechanism of action and significance of the effect, where known. Several hypouricemic agents, probenecid, sulfinpyrazone, and allopurinol, are considered in further detail because of their major clinical importance. No effort has been made, however, to summarize the relative clinical indications for each agent. In addition, in those cases where specific details could not be included because of limitations of space, the appropriate reference has been given.

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