Br. J. Pharmac. (1973), **48**, 693–698.

Influence of allopurinol on drug metabolism in man

M. D. RAWLINS* AND S. E. SMITH

Departments of Medicine and Pharmacology, St. Thomas's Hospital Medical School, London S.E.1

Summary

1. Elimination rates of phenylbutazone and warfarin after single oral doses in human volunteers, and steady-state plasma concentrations of these drugs in patients have been measured before, during and after administration of allopurinol.

2. Allopurinol, in usual clinical doses, had no significant influence on the elimination rate of either drug in the group of volunteers as a whole although in a few individuals an apparent inhibitory effect was observed.

3. No significant changes in the steady-state plasma concentrations of either phenylbutazone or warfarin were observed in patients during the administration of allopurinol.

4. It is concluded that although allopurinol may have an apparent inhibitory effect on drug elimination in a few individuals, its administration to most patients on anticoagulant therapy is unlikely to alter dose requirements.

Introduction

Allopurinol, a drug commonly used in the management of hyperuricaemia, has been shown to inhibit the biosynthesis of purines and pyrimidines in man (Fox, Royse-Smith & O'Sullivan, 1970; Kelley & Beardmore, 1970; Fox, Wood & O'Sullivan, 1971). Its administration to healthy volunteers impairs the metabolism of antipyrine and bishydroxycoumarin (Vesell, Passananti & Greene, 1970). Animal studies (Vesell *et al.*, 1970) suggest that this effect is caused by a reduction in hepatic microsomal cytochrome P-450 content rather than by substrate or product inhibition. Such an effect might be the consequence of reduced purine and pyrimidine biosynthesis. This action of allopurinol could lead to the accumulation of concurrently administered drugs undergoing extensive oxidation by the liver. In particular, this might be expected to occur during the chronic administration of either phenylbutazone or warfarin since both these drugs are eliminated to a considerable extent by oxidative hepatic metabolism (Burns, Yü, Dayton, Gutman & Brodie, 1960; Lewis & Trager, 1971). This interaction could result in considerable problems in patient management because inhibition of warfarin metabolism would be expected to increase its hypoprothrombinaemic effect whilst high plasma concentrations of phenylbutazone are associated with increased side-effects (Strandberg, 1964).

The present study was undertaken to see if allopurinol inhibits the metabolism of phenylbutazone and warfarin and if it causes accumulation of these two drugs on chronic administration.

* Present address: Department of Clinical Pharmacology, Karolinska Institute, 141 86 Huddinge, Stockholm, Sweden.

Methods

Volunteer studies

In the first part of the investigation, elimination rate constants (k_{el}) were determined in six male, healthy volunteers (aged 20–30 years) following the fasting oral administration of phenylbutazone tablets (Biorex Ltd.) 200 mg, and warfarin tablets (W. B. Pharmaceuticals Ltd.) 50 mg. Subjects taking warfarin were also given oral vitamin K_1 10 mg daily for the first three days after each dose. Five plasma samples were taken over the 72 h following dosing, together with a sixth sample immediately prior to dosing to act as a 'blank'. After a control study, each subject received oral allopurinol 100 mg thrice daily for 28 days. Estimates of k_{el} following single doses were repeated at 15, 29 and 50 days after the start of allopurinol treatment. Each subject was investigated twice, once with phenylbutazone and once with warfarin with an interval of at least six months, three of the subjects receiving phenylbutazone first.

Patient studies

In the second part of the study five patients were investigated. Informed consent was obtained from each. Clinical details and drug therapy which was administered twice daily in divided doses are given in Table 1. All patients denied taking drugs other than those outlined. Single blood samples were taken for drug assay 7 h after the morning dose at weekly intervals before, during and after administration of allopurinol 100 mg thrice daily for 21 or 28 days.

TABLE 1. *Patients participating in allopurinol study*

Patient	Sex	Age	Diagnosis	Drug therapy (daily dose–mg)	Duration of allopurinol treatment (days)
A.F.	M	18	sacroiliitis	phenylbutazone 200	28
E.S.	M	46	rheumatoid arthritis	phenylbutazone 300	28
S.S.	M	52	ankylosing spondylitis	phenylbutazone 200	21
R.H.	F	60	mitral valve disease	warfarin 3 digoxin 0·5	21
P.M.	M	52	mitral valve disease	warfarin 5	21

Analytical methods

Plasma phenylbutazone concentrations were measured spectrophotometrically (Burns, Rose, Chenkin, Goldman, Schulert & Brodie, 1953) and warfarin concentrations spectrofluorimetrically (Corn & Berberich, 1967). Plasma blank values were used in the first part of the study and reagent blanks in the second, because the patients were already receiving drugs at the start of the investigation. Pilot studies, however, showed that drug-free, blank plasma produced interference of less than 15 μg/ml phenylbutazone and 0·4 μg/ml warfarin and that allopurinol interfered with neither assay.

Prothrombin ratios (ratio of patient plasma to normal plasma prothrombin time) were measured by a standard Quick one-stage method using British Comparative Thromboplastin reagent.

Calculations

For the single oral dose studies, log-concentration time regression lines were fitted by the method of least squares and the slopes of the lines used to calculate (Riggs, 1963) k_{el} (per hour):

$$\text{slope} = -\frac{K_{el}}{2.3} \qquad \text{equation (i)}$$

Back extrapolation of this line enabled the theoretical plasma concentration at zero time (Cp_o) to be determined and the apparent volume of distribution (V_d) to be calculated assuming complete bioavailability (F=1):

$$V_d = \frac{F \,.\, \text{dose}}{Cp_o} \qquad \text{equation (ii)}$$

The plasma clearance (Vp) (Riggs, 1963) was then calculated

$$Vp = V_d \,.\, k_{el} \qquad \text{equation (iii)}$$

and expressed in units of ml/minute.

Results

Volunteer studies

The elimination rate constants (k_{el}) of phenylbutazone and warfarin before, during and after allopurinol administration are shown in Table 2. Following two weeks

TABLE 2. *Elimination rate constants (per hour) of phenylbutazone (PBZ) and warfarin (Warf) in six subjects before, during and after allopurinol administration (±standard error)*

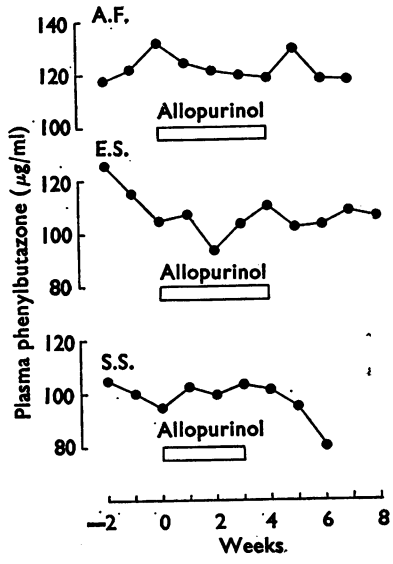
Drug	Subject	Before allopurinol	During allopurinol 2 weeks	During allopurinol 4 weeks	After allopurinol
PBZ	AB	0·0122 ±0·0008	0·0153 ±0·0014	0·0052*** ±0·0004	0·0058*** ±0·0005
	NB	0·0129 ±0·0010	0·0129 ±0·0005	0·0118 ±0·0010	—
	ND	0·0104 ±0·0011	0·0126 ±0·0012	0·0138 ±0·0011	—
	AP	0·0103 ±0·0004	0·0100 ±0·0014	0·0098 ±0·0005	—
	MR	0·0207 ±0·0031	0·0192 ±0·0021	0·0089** ±0·0003	0·0137 ±0·0022
	AY	0·0078 ±0·0008	0·0112 ±0·0009	0·0052* ±0·0006	0·0073 ±0·0006
	Mean S.E.M.	0·0124 ±0·0018	0·0135 ±0·0013	0·0091 ±0·0015	
Warf	AB	0·0161 ±0·0013	0·0128 ±0·0009	0·0181 ±0·0013	0·0168 ±0·0009
	NB	0·0107 ±0·0022	0·0165 ±0·0017	0·0138 ±0·0008	0·0132 ±0·0004
	ND	0·0200 ±0·0035	0·0169 ±0·0008	0·0159 ±0·0009	0·0150 ±0·0015
	AP	0·0087 ±0·0015	0·0117 ±0·0008	0·0140 ±0·0004	—
	MR	0·0179 ±0·0012	0·0148 ±0·0002	0·0115** ±0·0013	—
	AY	0·0125 ±0·0009	0·0157 ±0·0012	0·0121 ±0·0008	0·0144 ±0·0020
	Mean S.E.M.	0·0147 ±0·0015	0·0148 ±0·0008	0·0142 ±0·0010	

* P<0·05 ** P<0·02 *** P<0·01

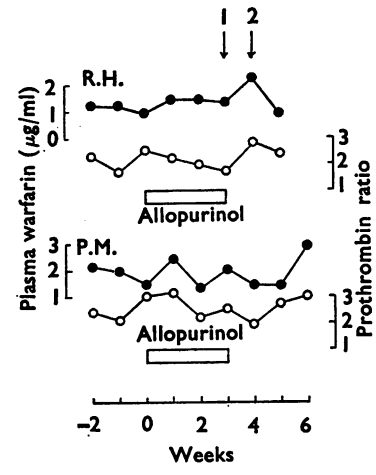
of allopurinol administration, k_{el} was unaltered, but after four weeks phenylbutazone k_{el} was significantly reduced in three individuals (A. B., M. R. and A. Y.) and warfarin in one (M. R.) without change in distribution volumes. In the group as a whole there was no significant (paired data) change in k_{el} at four weeks of either phenylbutazone ($t=1{\cdot}64$, $P>0{\cdot}10$) or warfarin ($t=0{\cdot}27$, $P>0{\cdot}10$). Phenylbutazone k_{el} in one individual who was affected by the allopurinol had not yet returned to the pretreatment value three weeks after stopping treatment. Neither phenylbutazone nor warfarin plasma clearances (Vp) were significantly altered after either two weeks (for phenylbutazone, $\dot{V}p=1{\cdot}32$ S.E.M. $\pm 0{\cdot}03$ ml/min; for warfarin, $\dot{V}p=2{\cdot}44 \pm 0{\cdot}18$ ml/min) or four weeks (for phenylbutazone, $\dot{V}p=1{\cdot}03 \pm 0{\cdot}17$ ml/min; for warfarin, $\dot{V}p=2{\cdot}19 \pm 0{\cdot}18$ ml/min) allopurinol administration compared to pretreatment values (for phenylbutazone, $\dot{V}p=1{\cdot}42 \pm 0{\cdot}12$ ml/min; for warfarin, $\dot{V}p=2{\cdot}49 \pm 0{\cdot}37$ ml/min).

Patient studies

Plasma concentrations of phenylbutazone and warfarin in patients before, during and after allopurinol administration are illustrated in Figures 1 and 2. In no case did allopurinol induce any appreciable change, nor did it alter prothrombin ratios of those patients who were receiving warfarin.



(FIG. 1.)



(FIG. 2.)

FIG. 1. Plasma phenylbutazone concentrations in three patients before, during and after allopurinol administration.

FIG. 2. Plasma warfarin concentrations (closed circles) and prothrombin ratios (open circles) in two patients before, during and after allopurinol administration. At first arrow, warfarin dose for subject R. H. increased from 3 mg to 4 mg daily. At second arrow, dose reduced to 3·5 mg daily.

Discussion

Much interest has been aroused in recent years by the finding that enzyme inducers increase greatly the requirements of drugs in anticoagulant therapy and

antidiabetic therapy due to accelerated metabolism (Breckenridge & Orme, 1972; Kater, Tobon & Iber, 1969). Drug-induced microsomal enzyme inhibition has received less attention, though the implication that drugs may reduce metabolizing capacity might be of even greater importance in therapeutics. Vesell *et al.* (1970) observed that allopurinol consistently reduces the rates of antipyrine and bishydroxycoumarin elimination in man and prompted us to perform the present studies. In the volunteer experiments considered as a whole, treatment with allopurinol for one month did not produce any significant changes in either phenylbutazone or warfarin k_{el}. Moreover, no overall changes in clearance of either drug were observed in the group although complete confidence in the estimate of this parameter is not possible because of the assumption of complete bioavailability ($F=1$ in equation ii) in the calculation of the apparent volume of distribution. However, in three subjects considerable reductions in k_{el} were observed after one month's allopurinol treatment. Since the estimation of phenylbutazone k_{el} is reproducible in man using the technique described in the present study (Vesell & Page, 1968; Whittaker & Evans, 1970) the data suggest that some impairment of metabolism occurred in these subjects as a consequence of allopurinol administration. Similarly, one subject showed a 30% reduction of warfarin k_{el} after receiving allopurinol for one month (see Table 2).

Allopurinol had no influence on steady-state phenylbutazone concentrations in three patients. Presumably, therefore, the drug did not reduce their microsomal oxidizing activity. The situation is complicated, however, by the fact that phenylbutazone itself is an enzyme inducer in man (Chen, Vrindten, Dayton & Burns, 1962). In patients taking phenylbutazone the degree of self-induction may have been such as to override any inhibiting effect of the allopurinol.

The results of the warfarin assay must be accepted with caution since the method used also estimates some of the metabolites which may have biological activity. Furthermore, commercially available warfarin which we used is a racemate and there are known to be differences in both elimination and biological activity of the two component isomers (Lewis & Trager, 1971; Breckenridge & Orme, 1972). However, in both volunteers and patients allopurinol appeared to exert little influence, except in one instance, and it did not alter prothrombin ratios in the patients. In the light of our findings, therefore, allopurinol does not seem to be contra-indicated in patients receiving warfarin. Our volunteer studies suggest, however, that there is wide individual variability in its effect on drug metabolism and that warfarin requirements may be reduced in a few patients. More frequent monitoring of the anticoagulant effect may consequently be advisable when allopurinol is used coincidently.

We thank the volunteers for their co-operation, Mrs. C. Gallen and Mr. F. Goodwin for technical help and Professor W. I. Cranston, Dr. G. I. C. Ingram, Dr. J. A. Matthews and Dr. D. A. H. Yates for allowing us to study patients under their care.

REFERENCES

BRECKENRIDGE, A. & ORME, M. L'E. (1972). The plasma half-lives and the pharmacological effect of the enantiomers of warfarin in rats. *Life Sci.*, **11**, 337–345.

BURNS, J. J., ROSE, R. K., CHENKIN, T., GOLDMAN, A., SCHULERT, A. & BRODIE, B. B. (1953). The physiological disposition of phenylbutazone (Butazolidin) in man and a method for its estimation in biological material. *J. Pharmac. exp. Ther.*, **109**, 346–357.

BURNS, J. J., YÜ, T. F., DAYTON, P. G., GUTMAN, A. B. & BRODIE, B. B. (1960). Biochemical pharmacological considerations of phenylbutazone and its analogues. *Ann. N.Y. Acad. Sci.*, **86**, 253–262.

CHEN, W., VRINDTEN, P. A., DAYTON, P. G. & BURNS, J. J. (1962). Accelerated aminopyrine metabolism in human subjects treated with phenylbutazone. *Life Sci.*, **1**, 35–42.

CORN, M. & BERBERICH, R. (1967). Rapid fluorimetric assay for plasma warfarin. *Clin. Chem.*, **13**, 126–131.

FOX, R. M., ROYSE-SMITH, D. & O'SULLIVAN, W. J. (1970). Orotidinuria induced by allopurinol. *Science, N.Y.* **168**, 861–862.

FOX, R. M., WOOD, M. H. & O'SULLIVAN, W. J. (1971). Studies on the coordinate activity and lability of orotidylate phosphoribosyltransferase and decarboxylase in human erythrocytes, and the effects of allopurinol administration. *J. clin. Invest.*, **50**, 1050–1060.

KATER, R. M. H., TOBON, F. & IBER, F. L. (1969). Increased rate of tolbutamide metabolism in alcoholic patients. *J. Amer. med. Ass.*, **207**, 363–365.

KELLEY, W. N. & BEARDMORE, T. D. (1970). Allopurinol: alteration in pyrimidine metabolism in man. *Science, N.Y.*, **169**, 388–390.

LEWIS, R. J. & TRAGER, W. F. (1971). The metabolic fate of warfarin: studies on the metabolites in plasma. *Ann. N.Y. Acad. Sci.*, **179**, 205–212.

RIGGS, D. S. (1963). *The mathematical approach to physiological problems.* Cambridge, Mass.: M.I.T. Press.

STRANDBERG, B. (1964). Phenylbutazone in the treatment of rheumatic disorders. A survey and clinical report. *Acta rheum. scand.* (Suppl. **10**), 1–50.

VESELL, E. S. & PAGE, J. G. (1968). Genetic control of drug levels in man: phenylbutazone. *Science, N.Y.*, **159**, 1479–1480.

VESELL, E. S., PASSANANTI, T. & GREENE, F. E. (1970). Impairment of drug metabolism in man by allopurinol and nortriptyline. *New. Engl. J. Med.*, **283**, 1484–1488.

WHITTAKER, J. & EVANS, D. A. P. (1970). Genetic control of phenylbutazone metabolism in man. *Brit. med. J.*, **4**, 323–328.

(*Received February* 26, 1973)