The effect of allopurinol on the steady-state pharmacokinetics of indomethacin

T. PULLAR, O. MYALL, J. R. M. HAIGH, J. R. LOWE, J. S. DIXON & H. A. BIRD

Departments of Medicine and Pharmacology, University of Leeds, Leeds LS1 3EX

The effect of 5 days treatment with allopurinol (300mg) on the pharmacokinetics of indomethacin at steady-state was investigated in eight patients. Allopurinol produced no significant effect on the indomethacin serum concentration-time curve. Allopurinol did not alter significantly the amounts of indomethacin excreted in the urine within 8 h. However, the urinary ratio of *N*-deschlorobenzoylindomethacin to indomethacin was reduced significantly by allopurinol administration ($P < 0.05$).

Keywords allopurinol indomethacin pharmacokinetics

Introduction

Indomethacin undergoes Phase I metabolism by the hepatic microsomal mixed function oxidase enzyme system to *O*-desmethyindomethacin (DMI). In addition indomethacin and its desmethyl metabolite are *N*-deacylated via non-microsomal enzymes to *N*-deschlorobenzoylindomethacin (DBI) and *O*-desmethyl, *N*-deschlorobenzoylindomethacin (DMBI). Indomethacin and these metabolites are excreted in the urine (Duggan *et al.*, 1972; Flower *et al.*, 1985). Allopurinol, a drug which inhibits mixed function oxidase enzymes (Vesell *et al.*, 1970) is often used along with indomethacin and might be expected to inhibit the hepatic microsomal metabolism of indomethacin as has been shown with cimetidine, another inhibitor of this enzyme system (Howes *et al.*, 1983). We have, therefore, examined the effect of allopurinol on the pharmacokinetics of indomethacin in man.

Methods

Approval for the study was obtained from the Leeds Western District Ethics Committee and all patients gave their informed consent. Eight

rheumatology inpatients (four with rheumatoid arthritis, three with soft tissue rheumatism and one with osteoarthritis) aged 26–62 years were studied. Patients were given, in single-blind fashion, indomethacin 50 mg 8 hourly and allopurinol placebo each morning for 5 days followed by a similar course of indomethacin but with active allopurinol 300 mg each morning. On day 5 of each treatment period, following a light breakfast, 5 ml blood was taken from an indwelling venous catheter before and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 h following the morning dose of indomethacin and allopurinol or allopurinol placebo. An 8 h urine collection was initiated immediately after dosing. Throughout the study the only other medication allowed was paracetamol. The concentrations of indomethacin in serum and urine and of DMI and DBI in urine were measured by h.p.l.c. using the methods of Skellern & Salole (1975) and Terweij-Groen *et al.* (1980), respectively. The area under the serum drug concentration-time curve (AUC) 0–8 h) was calculated using the trapezoidal rule. Maximum serum concentrations ($C_{\max}$) and times to maximum serum concentration ($t_{\max}$) were determined from inspection of the drug

Correspondence: Dr T. Pullar, Clinical Pharmacology Unit, University Department of Medicine, The General Infirmary, Great George Street, Leeds LS1 3EX

concentration-time curves. Steady-state serum concentrations (C_{av}) were calculated using the formula $C_{av} = \frac{AUC(0-8)}{8}$. Statistical analysis

was carried out using Student's paired *t*-test and the Wilcoxon signed-rank test. A value of $P < 0.05$ was deemed significant.

Results

At the concentrations measured the inter-batch and within-batch coefficients of variation (CV) for serum indomethacin were $\leq 8.5\%$ and $\leq 4.8\%$, respectively. For urinary concentrations of indomethacin and its metabolites CVs were all $\leq 5.3\%$. Table 1 shows the pharmacokinetic parameters for serum indomethacin. There was a wide variation between individuals. Allopurinol produced no significant effect on serum concentrations of indomethacin. Table 2 shows the urinary excretion of indomethacin and its metabolites before and during allopurinol co-

administration. Allopurinol produced no statistically significant change in the amounts of indomethacin, DMI or DBI excreted over 8 h. However the urinary excretion ratio of DBI to indomethacin over 8 h fell from 0.144 ± 0.064 (mean $\pm$ s.d.) while taking indomethacin alone to 0.074 ± 0.035 while taking concomitant allopurinol ($P < 0.05$; paired *t*-test and Wilcoxon signed rank test).

Discussion

The published serum half-life of indomethacin ranges from 1.5 to 16 h (Kwan *et al.*, 1976). Thus all our measurements represent steady-state concentrations of indomethacin. Five days treatment with a therapeutic dose of allopurinol did not alter the circulating serum concentrations of total indomethacin. The short duration of allopurinol administration was necessitated by the duration of in-patient stay but previous studies with cimetidine have found that less than 48 h pre-treatment with cimetidine produces a

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d.) for indomethacin in patients taking indomethacin alone and indomethacin + allopurinol ($n = 8$). (t_{max} = time to maximum serum concentration, $C_{ss,max}$ = maximum serum concentration, C_{av} mean steady state serum concentrations, AUC (0–8 h) = area under the concentration time curve over 8 h)

	t_{max} (h)	$C_{max,ss}$ ($\mu\text{g ml}^{-1}$)	C_{av}	AUC (0–8 h) ($\mu\text{g ml}^{-1} \text{ h}$)
Indomethacin alone	2.0 (± 1.1)	2.69 (± 0.82)	1.25 (± 0.48)	10.0 (± 3.8)
Indomethacin + allopurinol	2.1 (± 1.0)	2.64 (± 0.89)	1.25 (± 0.44)	10.0 (± 3.5)
Paired <i>t</i> -test	NS	NS	NS	NS
Wilcoxon matched pairs signed rank test	NS	NS	NS	NS

Table 2 Eight hour urinary excretion (mean $\pm$ s.d.) of indomethacin and its metabolites and the ratio of metabolite: indomethacin in patients taking indomethacin alone and indomethacin plus allopurinol ($n = 8$)

	Indomethacin (mg)	O-desmethylin domethacin (mg)	ratio	N-deschlorobenzoyl indomethacin (mg)	ratio
Indomethacin alone	7.7 (± 3.0)	7.5 (± 4.76)	1.07 (± 0.54)	1.20 (± 0.84)	0.144 (± 0.064)
Indomethacin + allopurinol	10.3 (± 5.1)	8.4 (± 4.4)	0.995 (± 0.59)	0.63 (± 0.31)	0.074 (± 0.035)
Paired <i>t</i> -test	NS	NS	NS	NS	$P < 0.05$
Wilcoxon matched pairs signed rank test	NS	NS	NS	NS	$P < 0.05$

lowered hepatic clearance of various drugs (Klotz & Reimann, 1980; Fee *et al.*, 1987). The duration of any potential effect of allopurinol on indomethacin metabolism was unknown and therefore, to avoid a prolonged wash-out period, the order of administration was not randomised. There is no known effect of prolonged indomethacin administration on its own elimination and thus an order effect was not thought to be likely.

To provide a power of 85% in this study allopurinol would have had to produce a 54% change in the serum indomethacin AUC (0–8) and changes of between 70% and 91% in the urinary concentrations of indomethacin and its metabolites. For the differences observed in this study to achieve statistical significance with a power of 85% would have required measurement of serum concentration time profiles in

over 10,000 patients, urine indomethacin in over 80 patients, urine DMI in 400 patients and urine DBI in 35 patients.

Allopurinol produced a statistically significant reduction in the urinary ratio of DBI to un-metabolised indomethacin. This possible effect on deacylation is of special interest as it involves non-microsomal enzymes.

Thus 5 days treatment with allopurinol produces no change in steady-state concentrations of indomethacin but may cause a statistically significant though clinically unimportant inhibition of the deacylation of indomethacin to N-deschlorobenzoylindomethacin.

We should like to thank Mrs M. E. Smith for typing the manuscript. We thank Professor Wright and Drs Martin and Iveson for allowing us to study their patients.

References

- Duggan, D. E., Hogans, A. F., Kwan, K. C. & McMahon, F. G. (1972) The metabolism of indomethacin in man. *J. Pharmac. exp. Ther.*, **181**, 563–575.
- Fee, J. P. H., Collier, P. S., Howard, P. J. & Dundee, J. W. (1987). Cimetidine and ranitidine increase midazolam bioavailability. *Clin. Pharmac. Ther.*, **41**, 80–84.
- Flower, R. J., Moncada, S. & Vane, J. R. (1985). Drug therapy of inflammation. In *The Pharmacological Basis of Therapeutics*, eds Gilman, A. G., Goodman, L. S., Rall, T. W. & Murad, F., 7th Edition, pp 674–715. New York: McMillan Publishing Company.
- Howes, C. A., Pullar, T., Sourindhrin, I., Mistra, P. C., Capell, H. A., Lawson, D. H. & Tilstone, W. J. (1983). Reduced steady-state plasma concentrations of chlorpromazine and indomethacin in patients receiving cimetidine. *Eur. J. clin. Pharmac.*, **24**, 99–102.
- Klotz, U. & Reimann, I. (1980). Delayed clearance of diazepam due to cimetidine. *New Engl. J. Med.*, **302**, 1011–1014.
- Kwan, K. C., Breault, G. O., Umbenhauer, E. R., McMahon, F. G. & Duggan, D. E. (1976). Kinetics of indomethacin absorption, elimination and enterohepatic circulation in man. *J. Pharmacokin. Ther.*, **4**, 255–279.
- Skellern, G. G. & Salole, E. G. (1975). A high speed liquid chromatographic analysis of indomethacin in plasma. *J. Chromatogr.*, **114**, 483–485.
- Terweij-Groen, C. P., Haemstra, S. & Kraak, J. C. (1980) Rapid determination of indomethacin and salicylic acid in serum by means of reversed-phased liquid chromatography. *J. Chromatogr.*, **181**, 385–397.
- Vesell, E. S., Passananti, G. T. & Greene, F. E. (1970). Impairment of drug metabolism in man by allopurinol and nortriptyline. *New Engl. J. Med.*, **283**, 1484–1488.

(Received 12 November 1987,
accepted 12 February 1988)