Interaction of isoxicam with acetylsalicylic acid

M. ESQUIVEL*, F. CUSSENOT†, R. I. OGILVIE*, D. S. EAST* & D. H. SHAW J.R.*

¹Clinical Pharmacology Division, Montreal General Hospital, Montreal, Quebec, Canada, H3G 1A4

1 Ten healthy male volunteers were given 200 mg p.o. of isoxicam after an overnight fast and the plasma concentrations over time followed for 96 h by h.p.l.c.

2 Five days later enteric coated acetylsalicylic acid (ASA) 650 mg four times daily was started and continued for 10 days producing steady state trough plasma salicylate of 83 mg/l (range 21-133).

3 A second 200 mg isoxicam dose was given 5 days after starting ASA and the plasma concentration time-curve again followed. After ASA, there was no change in lag time (0.54 vs 0.51 h), time to peak concentration (10 vs 10 h), or disappearance $t_{1/2}$ (28.7 vs 31.0 h) however the peak isoxicam concentration and AUC were reduced 18 and 22% respectively ($P < 0.01$).

4 Plasma protein binding of isoxicam studied by equilibrium dialysis was $96 \pm 1\%$ in the absence and $86 \pm 5\%$ in the presence of ASA. The reduction in binding was unrelated to plasma SA concentrations achieved or observed reductions in AUC for plasma isoxicam.

5 ASA decreased plasma isoxicam binding, peak plasma isoxicam concentrations and AUC without altering the apparent disappearance half-life of total plasma isoxicam after a single oral dose.

Keywords isoxicam aspirin protein binding interaction pharmacokinetics normal volunteers

Introduction

In spite of the availability of many new anti-inflammatory agents the most commonly prescribed drug for the treatment of arthritic conditions is still acetylsalicylic acid (ASA). Although it cannot be recommended, newer agents are often added to baseline ASA therapy and it would be useful to know the kinetic consequences of such concomitant therapy. This study investigates the pharmacokinetic interaction between ASA and isoxicam, a new non-steroidal anti-inflammatory benzothiazine derivative.

Present addresses: *Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, Canada, M5T 2S8 and †Faculte de Medecine B, Universite de Nancy, 5400 Nancy, France

Methods

Pharmacokinetic disposition

Ten healthy male volunteers (mean age 24.6 years, range 20-32; mean weight 69.7 kg, range 56.0-90.5) gave informed consent for this study. After an overnight fast, the volunteers came to the laboratory in the early morning in the 12 h post-absorptive state. A venous catheter was inserted retrogradely into an antecubital vein, a baseline blood sample drawn and the catheter kept patent with a heparin/saline solution (10 u/ml). Thirty minutes later a single dose of isoxicam 200 mg (2×100 mg capsules) was administered with 200 ml tap water. The volunteers were asked to sit up or walk about for the rest of the morning. A light meal was offered 3

h later. Ten ml blood samples were taken via the catheter at 1, 2, 4, 6, 8, 10 and 12 h and by venepuncture at 24, 48, 72 and 96 h. Plasma was separated by centrifugation and frozen for subsequent analysis by h.p.l.c. All samples were analysed within a month of the study.

Five days after the last blood sample, two tablets of enteric coated ASA totalling 650 mg four times/day was started and continued for the next 10 days. Compliance was checked by analysis of a plasma sample for salicylic acid content after the third day of ASA dosing. On the fifth day, a second dose of isoxicam 200 mg was administered using identical conditions as with the first dose. Plasma samples were collected over 96 h for determination of isoxicam content.

Plasma protein binding of isoxicam

Equilibrium dialysis was carried out using 2 ml of plasma placed in bags made from Spectropor 1 dialysis tubing suspended in 10 ml of buffered saline (pH 7.4) constantly agitated for 24 h at ambient temperature. Dialysis periods up to 48 h did not alter the results. Drug concentrations were measured in the plasma sample prior to and after dialysis and in the dialysate for the determination of the plasma protein binding of isoxicam.

For *in vivo* studies, pooled plasma from a different panel of normal volunteers was used to study the effects of salicylic acid (100 mg/l) on plasma protein binding of isoxicam 5 to 20 mg/l added *in vitro*. For *ex vivo* studies, plasma obtained from the 10 volunteers in the isoxicam-ASA kinetic study was used. Pooled plasma obtained from each subject after isoxicam with and without ASA ingestion was used to determine the plasma protein binding of isoxicam *in vivo* and the change induced by ASA ingestion. In addition, pooled plasma obtained from each subject before isoxicam ingestion with or without ASA ingestion was used to determine the plasma protein binding of isoxicam added *in vitro* at a concentration of 5 mg/l.

Determination of drug concentrations

Isoxicam in plasma and dialysate was measured by a h.p.l.c. method using piroxicam as internal standard (Keeley *et al.*, 1978). After extraction in toluene and evaporation to dryness under nitrogen, the sample reconstituted in the mobile phase (45% acetonitrile; 55% of a 1% aqueous acetic acid; 5 mM heptanesulphonic

acid as the sodium salt) was passed through a 3 micron C-18 column at a flow of 1.5 ml/min and detected by absorbance at 313 nm. Salicylic acid in plasma was measured by the h.p.l.c. method of Montgomery & Sitar (1981).

Pharmacokinetic and statistical methods

Plasma isoxicam concentrations for individual subjects were fitted to a one-compartment open pharmacokinetic model using an unweighted non-linear least squares procedure using Gauss-Newton and Newton-Raphson techniques. Group values are given as means $\pm$ 1 s.d. and comparisons made with non-parametric statistical methods (Wilcoxon signed ranks test; Kendall's rank correlation test).

Results

Pharmacokinetic disposition

Plasma isoxicam concentrations in the absence or presence of ASA are shown in Figure 1. Following ASA administration, the mean isoxicam concentration at each time point was lower than the corresponding value in the absence of ASA. Kinetic parameters derived from a one-compartment analysis of the plasma isoxicam concentrations over time are given in Table 1. Following ASA administration there was no change in absorption lag time, appearance $t_{1/2}$, time to peak concentrations or disappearance $t_{1/2}$ from values obtained in the absence of ASA. However the peak plasma isoxicam concentration and the area under the plasma isoxicam concentration time curve (AUC) were considerably lower after ASA administration. The steady state trough plasma salicylate concentration in the 10 volunteers averaged 83 mg/l (range 21–133).

Plasma protein binding

Results of the *in vitro* studies of the effect of added salicylic acid (100 mg/l) on the plasma protein binding of isoxicam 5 to 20 mg/l are given in Table 2. In the absence of ASA, plasma protein binding of isoxicam did not exhibit concentration dependency over the range of 5–20 mg/l. The addition of ASA resulted in a 5.1–8.5% reduction in isoxicam binding. Using the plasma obtained from volunteers during the kinetic study, the plasma protein binding of isoxicam added *in vitro* was

Figure 1 Plasma isoxicam concentrations (mean $\pm$ s.d.) in 10 normal volunteers after isoxicam 200 mg p.o. before (○) and during (●) ingestion of ASA 650 mg four times/day.

similar to that observed *ex vivo* for each subject, therefore the two results for each subject were averaged. In the absence of ASA, the mean plasma protein binding of isoxicam was 95.5% (range 94–98%). In the presence of ASA, the binding was 85.5% (range 73–91) after ASA ingestion by these subjects (Table 2). Although the reduction of plasma protein binding of isoxicam after ASA ingestion averaged 10%, considerable variation between subjects (range 3–21%) was observed and there was no apparent relationship to plasma salicylate concentrations in these subjects or to the reduction in total AUC of plasma isoxicam after ASA ingestion (Table 3).

Discussion

In the absence of ASA, the kinetic disposition of a single dose of isoxicam in this group of normal volunteers revealed a long appearance $t_{1/2}$ of 2.5 h, a delayed time to peak concentration (10 h) and a slow disappearance $t_{1/2}$ of 31 h similar to the results of a previous investigation (Accardo *et al.*, 1983). Following ASA ingestion, the plasma concentrations of a single isoxicam dose were consistently reduced as compared to values obtained in the absence of ASA. Peak plasma isoxicam concentrations were reduced an average of 18% whereas the AUC was decreased an average of 21%. Since

Table 1 Effect of ASA 650 mg four times/day on the kinetic disposition of a single dose of isoxicam 200 mg in 10 normal volunteers (mean $\pm$ s.d.)

Kinetic parameter	Without ASA	With ASA	P value*
Lag time (h)	0.5 $\pm$ 0.2	0.5 $\pm$ 0.2	NS
Appearance $t_{1/2}$ (h)	2.5 $\pm$ 0.2	2.6 $\pm$ 1.0	NS
Time to peak (h)	10.0 $\pm$ 2.9	10.0 $\pm$ 2.4	NS
Peak Cp (mg/l)	6.9 $\pm$ 0.7	5.7 $\pm$ 0.6	< 0.01
AUC (mg l ⁻¹ h)	384 $\pm$ 68	295 $\pm$ 48	< 0.01
Disappearance $t_{1/2}$ (h)	31.0 $\pm$ 5.7	28.7 $\pm$ 5.9	NS

* Two-tailed Wilcoxon's signed ranks test

Table 2 Plasma protein binding of isoxicam in the presence and absence of salicylic acid (100 mg/l) added *in vitro* or in normal volunteers ingesting isoxicam and ASA (*ex vivo*)

	Plasma isoxicam (mg/l)	n	% protein binding of isoxicam		Δ
			Without ASA	With ASA	
<i>In vitro</i>	5	5	94.8 $\pm$ 1.5	86.6 $\pm$ 2.7	8.3
	10	5	93.2 $\pm$ 2.0	84.8 $\pm$ 3.6	8.5
	20	5	92.2 $\pm$ 4.4	87.1 $\pm$ 4.2	5.1
<i>Ex vivo</i>	2-5	10	95.5 $\pm$ 1.4	85.5 $\pm$ 5.1	10.0

the lag time, appearance $t_{1/2}$ and time to maximum plasma isoxicam concentrations were unaltered after ASA ingestion, it is unlikely that ASA interfered with the absorption of isoxicam. The calculated isoxicam disappearance $t_{1/2}$ was only slightly reduced (8%) after ASA ingestion. This does not suggest a large effect of ASA on the elimination of isoxicam. The reduction of plasma isoxicam concentrations and AUC after ASA ingestion is most likely due to reduction of plasma protein binding of isoxicam resulting in an increased free fraction, larger apparent volume of distribution and slightly enhanced renal and/or hepatic clearance. The studies of the interaction of ASA on plasma protein binding of isoxicam supports this conclusion. The binding of isoxicam was considerably reduced after the ingestion of ASA or in pooled plasma after the addition of salicylic acid. However the magni-

tude of displacement of isoxicam after ASA ingestion did not correlate with either the plasma salicylic acid concentrations achieved nor with the reduction in AUC for plasma isoxicam after a single dose of isoxicam.

Most non-steroidal anti-inflammatory drugs including ASA are >90% bound to serum albumin so the potential for pharmacokinetic interaction certainly exists during concomitant administration of two members of this class of drugs. For example, serum ibuprofen concentrations were reported to be reduced by concurrent ASA therapy (Grennan *et al.*, 1979) as have concentrations of naproxen (Segre *et al.*, 1973; Wilkins & Segre 1976). The elimination $t_{1/2}$ of ibuprofen was not altered by ASA therapy in Grennan's study. Some authors reported a lowering of serum indomethacin concentrations by salicylates (Jeremy & Towson, 1970; Rubin *et al.*, 1973) whereas others failed to find an

Table 3 Rank order of change in plasma protein binding of isoxicam related to measured plasma salicylic acid concentration and change in AUC of plasma isoxicam after ASA ingestion*

Volunteer	Change in plasma isoxicam protein binding	Plasma salicylic acid (mg/l)	Change in plasma isoxicam AUC after ASA (% Δ)
1	- 3.0	64	-19.0
2	- 4.5	133	-48.7
3	- 5.7	93	-14.2
4	- 8.1	83	-20.2
5	- 8.3	61	-12.2
6	-10.5	104	-13.2
7	-11.8	104	-19.2
8	-13.7	63	-17.7
9	-13.7	101	-31.8
10	-21.2	21	-25.8
Mean	-10.0	83	-22.2
s.d.	5.4	31	11.0

* No significant correlation between change in protein binding, plasma salicylic acid and change in AUC by Kendall's rank correlation test.

effect (Champion *et al.*, 1971; Brooks *et al.*, 1975). Concurrent administration of ASA decreased the plasma protein binding of ketoprofen and increased its plasma clearance at steady state (Williams *et al.*, 1981). However the absorption and disposition of piroxicam was apparently unaffected by concomitant administration of ASA (Hobbs & Twomey, 1979). In contrast aspirin has been reported to markedly reduce the bioavailability of diclofenac as measured by AUC (Fowler, 1979). In none of these studies is it clear that alterations in protein binding, concentrations or elimination of these drugs resulted in an alteration in

clinical effect. A decrease in total plasma drug concentrations with concomitant increase in the free drug fraction could result in no apparent change in clinical efficacy. However, as the potential exists for altered beneficial or adverse effects and dose-requirements, clinical studies of arthritic patients at steady state after dosing with both ASA and non-steroidal anti-inflammatory agents would be useful.

This study was supported in part by a grant from Parke-Davis Canada Incorporated. Dr Cussenot was supported by a France-Quebec residency exchange program.

References

- Accardo, S., Galletti, F., Gallotti, A. & Samanta, E. (1983). Pharmacokinetics and relative bioavailability of isoxicam after oral and rectal administration in man. *Curr. Ther. Res.*, **33**, 976-981.
- Brooks, P. M., Walker, J. J., Bell, M. A., Buchanan, W. W. & Rhymer, A. R. (1975). Indomethacin-aspirin interaction. A clinical appraisal. *Br. med. J.*, **3**, 69-71.
- Champion, G. D., Paulus, H. E., Mongan, E., Okun, R., Pearson, C. M. & Sarkissian, E. (1971). The effect of aspirin on serum indomethacin. *Clin. Pharmac. Ther.*, **13**, 239-244.
- Fowler, P. D. (1979). Diclofenac sodium (Voltarol): drug interactions and special studies. *Rheumatol. Rehab. suppl.* **2**, 60-68.
- Grennan, D. M., Ferry, D. G., Ashworth, M. E., Kenny, R. E. & Mackinnon, M. (1979). The aspirin-ibuprofen interaction in rheumatoid arthritis. *Br. J. clin. Pharmac.*, **8**, 497-503.
- Hobbs, D. C. & Twomey, T. M. (1979). Piroxicam pharmacokinetics in man: aspirin and antacid interaction studies. *J. clin. Pharmac.*, **19**, 270-281.
- Jeremy, R. & Towson, J. (1970). Interaction between aspirin and indomethacin in the treatment of rheumatoid arthritis. *Med. J. Aust.*, **2**, 127-129.
- Keeley, F. J., Daftsios, A. C. & Glazko, A. J. (1978). *High performance liquid chromatography assay of isoxicam (CI-849) in plasma*. Internal report RR740-000709 Warner-Lambert Pharm. Res. Div. Ann Arbor, Michigan.
- Montgomery, P. R. & Sitar, D. S. (1981). Increased serum salicylate metabolites with age in patients receiving chronic acetylsalicylic acid therapy. *Gerontology*, **27**, 329-333.
- Rubin, A., Rodda, B. E., Warrick, P., Gruber, C. M. & Ridolfo, A. S. (1973). Interactions of aspirin with non-steroidal anti-inflammatory drugs in man. *Arthritis Rheum.*, **16**, 635-645.
- Segre, E. J., Chaplin, M., Forschielli, E., Runkel, R. & Sevelius, H. (1973). Naproxen-aspirin interactions in man. *Clin. Pharmac. Ther.*, **15**, 374-379.
- Wilkins, R. E. & Segre, E. J. (1976). Combination therapy with naproxen and aspirin in rheumatoid arthritis. *Arthritis Rheum.*, **19**, 677-682.
- Williams, R. L., Upton, R. A., Buskin, J. N. & Jones, R. M. (1981). Ketoprofen-aspirin interactions. *Clin. Pharmac. Ther.*, **30**, 226-231.

(Received March 16, 1984,
accepted May 20, 1984)