The comparative pharmacokinetics of acemetacin in young subjects and elderly patients

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Single and multiple dose pharmacokinetics of acemetacin in 10 young healthy subjects and 10 elderly patients with osteoarthritis were studied. Peak plasma concentrations of acemetacin and its metabolite, indomethacin, were found between 2.4 and 4 h after an oral dose of the drug. After dosing to steady state (7 days), the mean plasma elimination half-life for acemetacin was 1.1 h and 1.0 h, and for indomethacin 7.1 h and 7.2 h in the young and elderly groups respectively. Statistical analysis of t_{max}, AUC, plasma $t_{1/2}$ and residual drug concentrations for acemetacin or indomethacin revealed no significant differences ($P > 0.05$) between young subjects and elderly patients after acute or chronic dosing. The results suggest that drug accumulation did not occur in the elderly subjects over the time period studied and that, on pharmacokinetic grounds, dose adjustment in the elderly is unlikely to be required.

Keywords   age   acemetacin   osteoarthritis

Introduction

Acemetacin is a glycolic acid ester of the nonsteroidal anti inflammatory drug (NSAID) indomethacin. Acemetacin possesses potent anti-inflammatory activity in animal models of inflammation (Jacobi *et al.*, 1980; Jacobi & Dell, 1980) and clinical studies have shown that the efficacy of acemetacin is similar to that of indomethacin in the treatment of inflammatory and rheumatic disorders. Acemetacin appears to be generally better tolerated than indomethacin in this context; in particular it appears to produce fewer gastrointestinal side effects (Brackertz & Muller, 1982; Heiter *et al.*, 1980; Lonauer & Wirth, 1980). The metabolism of acemetacin is hepatic, the major metabolite being indomethacin which is partly responsible for the overall efficacy of the drug as a NSAID.

It has become evident that NSAIDs are particularly toxic in the elderly, the gut and kidney being especially vulnerable (Walt *et al.*, 1986). Accumulation of these drugs in the elderly may occur because of altered body composition and drug disposition, or because elimination is reduced by decreased renal or hepatic function exacerbating drug toxicity. Acemetacin has been used extensively in the elderly to treat such conditions, yet few pharmacokinetic data for acemetacin exist for such an aged population. An earlier study of the pharmacokinetics of acemetacin after a single oral dose in healthy elderly volunteers suggested that drug accumulation in the elderly

should not be a problem since the kinetics were similar to those for a young population (Jones *et al.*, 1987). The present study has examined the pharmacokinetics of acemetacin and its major metabolite indomethacin at steady state in a relatively elderly population with osteoarthritis, and compared these findings with those from a young healthy population. The object of the experiment was to determine if a reduction of dose was required in elderly patients.

Methods

Subjects

Two groups of subjects were studied, one comprising 10 healthy volunteers, mean age 30.9 years (22–44 years), the other group being 10 relatively elderly patients, mean age 75.9 years (68–80 years), all diagnosed as having osteoarthritis. None of the elderly group suffered from acute organ failure, although five were hypertensive two had Paget's disease, one had 'mild' renal failure and one, diabetes mellitus. Only the patients with hypertension and diabetes were given drug treatment, which was stable and continued through the study. The drugs involved were propranolol, Navidrex K, hydralazine,

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atenolol, bendrofluazide and glibenclamide. The mean body weight of the young volunteers was 74.7 kg (56–105 kg), and the elderly group 74.0 kg (61–92 kg).

Subjects were accepted into the study after a medical examination including ECG, routine haematology, biochemistry and urine analysis, which demonstrated that they did not suffer from any acute or relevant disease. Volunteers and patients were excluded if they had received an anti-inflammatory drug within the previous 7 days. Paracetamol was allowed as an analgesic in the elderly group. All subjects were non-smokers and all reported an alcohol consumption of less than 10 units per week. The study was approved by the local Ethics Committee.

Study protocol

The study was of open design. Each subject was fasted overnight and a sample of venous blood was taken before medication was administered. The subjects were allowed a standard light breakfast of tea and toast, during which they took a single capsule containing 60 mg of acemetacin (Emflex 60 mg, E. Merck Ltd) with 100 ml of water. Thereafter, venous blood samples were taken at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 12 and 24 h post dose. The blood samples were placed into heparinized tubes, centrifuged and the plasma stored at −20° C prior to analysis. Each subject continued to take acemetacin, 60 mg, twice a day for the next 7 days. On the eighth day, the subjects took a final single 60 mg capsule of acemetacin together with the standard breakfast and had venous blood samples taken over the next 24 h, as previously stated.

Analysis

Analyses of the plasma samples for acemetacin and its metabolite, indomethacin, were performed by reverse phase h.p.l.c. using a modification of the method of Notarianni & Collins (1987). Linear regression of the log (concentration) *vs* time was used to calculate the terminal phase half-life $(t_{1/2})$. The area under the curve (AUC 0–∞) was calculated, using the linear trapezoidal rule to the last data point with extrapolation to infinite time. Statistical comparisons of the maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), $t_{1/2}$ and

AUC between the young and elderly group were made using paired and unpaired Student's *t*-test, as appropriate. Statistical significance was set at the 5% level.

Results

Acemetacin was generally well tolerated in this study. The young volunteers did not report any side effects. One subject in the elderly group complained of indigestion, and was replaced by another subject. There were no relevant changes in either haematological or biochemical parameters after the study. There was considerable inter-subject variation in plasma concentrations. The mean plasma drug concentrations of acemetacin and indomethacin at each time point are shown in Table 1. Table 2 shows the mean pharmacokinetic values, derived from individual plasma profiles.

C_{max} for acemetacin was significantly higher $(P < 0.05)$ on day 8 in the elderly group (276.8 ± 1053 ng ml^{-1}: mean ± s.d.) compared with the young (187.0 ± 85.4 ng ml^{-1}). AUC values for acemetacin did not differ between the young and elderly on either study day. There was no significant difference in the $t_{1/2}$ between the groups on either day although few data points were obtained to give an accurate estimate of $t_{1/2}$ in several volunteers. No residual acemetacin was observed 24 h after the last dose in any volunteer.

Mean peak plasma concentrations and AUC of indomethacin were significantly higher $(P < 0.05)$ on day 8 than day 1 for both young and elderly groups. The mean AUC ratio (day 8 : day 1) was 1.38 for the young and 1.77 for the elderly. This reflected steady state concentrations of indomethacin. There was no significant difference between the young and elderly groups in respect of the residual indomethacin concentrations observed prior to the final dose in day 8 (162.3 ± 91.7 *vs* 157.2 ± 83.2 ng ml^{-1} respectively).

Discussion

NSAIDs are often given to elderly subjects to reduce inflammation and pain. Often these phenomena are caused by forms of arthritis, resulting in NSAIDs being

Table 1 Plasma drug concentrations (mean ± s.d.) of acemetacin and indomethacin on study days 1 and 8

| | Acemetacin (ng ml^{-1}) | | | | Indomethacin (ng ml^{-1}) | | | |
| | Young (n = 10) | | Elderly (n = 10) | | Young (n = 10) | | Elderly (n = 10) | |
Time (h)	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
0.0	0.0	0.0	0.0	0.0	0.0	162.3 ± 91.6	0.0	157.2 ± 83.1
0.5	2.7 ± 8.5	1.0 ± 3.16	84.4 ± 141.2	20.0 ± 58.7	4.8 ± 10.1	210.0 ± 113.4	47.2 ± 75.5	203.2 ± 198.7
1.0	15.2 ± 22.7	32.6 ± 47.4	178.0 ± 221.5	79.7 ± 115.6	73.0 ± 91.4	286.0 ± 156.1	233.3 ± 198.4	321.4 ± 291.6
1.5	29.8 ± 29.3	91.4 ± 57.5	201.6 ± 177.9	106.0 ± 140.6	145.3 ± 126.4	423.9 ± 193.0	372.1 ± 186.4	428.9 ± 344.7
2.0	76.7 ± 48.3	138.9 ± 105.8	167.3 ± 97.9	123.9 ± 106.8	273.4 ± 162.1	526.6 ± 185.1	441.9 ± 139.3	496.2 ± 303.6
2.5	170.5 ± 94.8	158.4 ± 91.9	143.4 ± 80.2	138.8 ± 74.8	430.0 ± 157.3	627.3 ± 151.6	482.4 ± 136.8	554.7 ± 229.7
3.0	225.2 ± 158.6	143.1 ± 53.7	118.7 ± 71.7	215.3 ± 143.7	574.4 ± 168.7	687.3 ± 211.4	471.9 ± 138.7	658.4 ± 153.5
4.0	133.9 ± 110.6	80.8 ± 55.9	76.6 ± 48.6	114.5 ± 82.4	552.4 ± 186.4	574.6 ± 207.2	421.9 ± 183.2	586.7 ± 147.2
6.0	20.4 ± 40.7	9.4 ± 18.9	18.6 ± 26.5	43.1 ± 70.4	285.8 ± 153.5	326.6 ± 113.7	221.2 ± 93.2	422.1 ± 108.3
12.0	0.0	0.0	0.6 ± 1.8	0.6 ± 1.8	135.6 ± 78.3	148.7 ± 63.8	101.4 ± 42.0	203.0 ± 63.5
24.0	0.0	0.0	0.0	0.0	44.2 ± 15.8	71.3 ± 41.3	40.4 ± 23.3	155.0 ± 222.4

Table 2 Pharmacokinetic parameters (mean ± s.d.) for acemetacin and its metabolite indomethacin

| | Acemetacin | | | | Indomethacin | | | |
| | Young (n = 10) | | Elderly (n = 10) | | Young (n = 10) | | Elderly (n = 10) | |
	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
Mean t_{max} (h)	3.2 ± 1.8	2.6 ± 2.3	1.9 ± 1.0	2.5 ± 0.9	3.4 ± 0.7	3.1 ± 0.4	2.5 ± 0.9	2.9 ± 0.9
Mean C_{max} (ng ml^{-1})	245 ± 160	187 ± 85	268 ± 174	277 ± 105*	632 ± 178	705 ± 212**	555 ± 152	804 ± 189**
Mean AUC (ng ml^{-1} h)	589 ± 404	483 ± 286	664 ± 357	712 ± 489	4596 ± 1778	6349 ± 2511**	4296 ± 1452	7586 ± 2421**
Mean $t_{1/2}$ (h)	1.03 ± 0.44 (n = 7)	1.10 ± 0.60 (n = 7)	1.03 ± 0.66 (n = 7)	2.27 ± 4.14 (n = 10)	601 ± 0.70 (n = 10)	7.07 ± 1.80 (n = 10)	6.12 ± 2.18 (n = 10)	7.20 ± 2.44 (n = 10)
C residual (ng ml^{-1})	—	—	—	—	—	162 ± 92	—	157 ± 83

* $P < 0.05$ compared with young group
** $P < 0.05$ compared with day 1

given to elderly patients over long periods. The present investigation was carried out to investigate the relative pharmacokinetics of acemetacin in young healthy volunteers and elderly patients with osteoarthritis.

Repeat dosing produced steady state plasma concentrations of the metabolite, indomethacin, which were higher than those obtained after a single dose of acemetacin. AUC levels of acemetacin and indomethacin did not differ significantly between the young and elderly groups although there was a difference in the AUC and C_{max} of indomethacin between day 1 and 8, which was greater in the elderly group. Calculated plasma elimination half lives in this investigation were within the range 1–2 h for acemetacin, and 3–12 h for indomethacin. These times were similar for the two groups.

The results of this comparison of the kinetics of acemetacin in young subjects and elderly patients suggest that both groups metabolised the drug similarly. The elderly patients did not have any major organ failure which may have affected their capacity to metabolise drugs. These results demonstrate that age alone is not sufficient to cause clinically relevant differences in the disposition of this drug. In the group of elderly patients studied, it would appear unlikely that toxic accumulation of acemetacin or its major metabolite would occur after prolonged dosing with acemetacin at the level studied.

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