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PHARMACOKINETICS OF FLURBIPROFEN IN MAN I. AREA/DOSE RELATIONSHIPS

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ABSTRACT

Flurbiprofen pharmacokinetics were studied in 15 normal male subjects after four oral doses. Plasma levels of total (bound + free) drug were monitored for 48 h and urine was collected for 96 h after the doses. All subjects demonstrated linear relationships between administered dose and total flurbiprofen AUC, indicating that oral clearance is independent of dose for the dose range evaluated in this study. Urinary recovery data indicated that the efficacy of absorption was dose independent.

KEY WORDS Flurbiprofen Tablets Solution AUC/dose relationship Plasma levels Urinary excretion

INTRODUCTION

Flurbiprofen is DL-2-(2-fluoro-4-biphenylyl)propionic acid. It is a potent nonsteroidal anti-inflammatory drug (NSAID) of the arylacetic acid class. Flurbiprofen is currently undergoing Phase III clinical trials in the United States and has been on the market since 1977 in Europe. The drug is indicated in the long-term oral treatment of rheumatoid arthritis, osteoarthritis, and acute gouty arthritis. It possesses potent antithrombotic activity.[1,2] The pharmacology and metabolism of flurbiprofen in man and other species have been reported.[3–5] In the rat, mouse, and man three major metabolites have been detected. They have been identified as 2-(2-fluoro-4′-hydroxy-4-biphenylyl)propionic acid (metabolite I), 2-(2-fluoro-3′,4′-dihydroxy-4-biphenylyl)propionic acid (metabolite II), and 2-(2-fluoro-3′-hydroxy-4′-methoxy-4-biphenylyl)propionic acid (metabolite III). It has been demonstrated that flurbiprofen is highly bound to plasma proteins (> 99 per cent).[5–7] Many drugs of the same class as flurbiprofen (e.g., ibuprofen and

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naproxen) exhibit nonlinear pharmacokinetics as a result of saturable plasma protein binding.[8,9] The aim of this work was to study the pharmacokinetics of flurbiprofen in 15 normal male volunteers. If the pharmacokinetics were nonlinear, the methods necessary to elucidate the cause of the nonlinearity were incorporated into the study design (e.g., plasma protein binding studies and measurement of the renal excretion of parent drug and metabolites).

METHODS

Fifteen male volunteers ranging in age from 18 to 40 years (mean = 29), body weight 62·3 to 109·1 kg (mean = 76·4 kg), height 1·68 to 1·88 m (mean = 1·77 m), and surface area 1·71 to 2·35 m^2 (mean = 1·94 m^2) were selected to participate in this study. These subjects were selected from respondents to an advertisement based on established criteria, namely subject availability, reliability, medical history, physical examination, and the results of blood and urine analysis. Subjects could not participate if they were taking other medications, had upper gastrointestinal diseases, were renally or hepatically impaired, or were known to be hypersensitive to flurbiprofen. The subjects were asked to refrain from the use of alcohol and any medications during the course of the study. All subjects signed consent forms.

Each group was randomly assigned to one of three treatment groups and received one of three treatments (A, B or C) sequentially over the first 3 weeks of the 4-week study period. Treatments A, B, and C consisted of one, two or three 100 mg ANSAID® Tablets (flurbiprofen, Upjohn) which were administered to the subjects according to a Latin Square experimental design. In the final week of the study, all subjects received Treatment D which consisted of 40 ml flurbiprofen oral solution (2·5 mg ml^{-1} flurbiprofen). The randomization schedule for this study is presented in Table 1. All medication was taken at 7:00 am with 180 ml of water. The tablets were swallowed whole; the oral solution was administered with a calibrated syringe. All subjects were fasted from 10:00 pm the previous night. No food or beverages were permitted until 4 h after the doses were administered. At this time a standard

Table 1. Randomization and treatment schedule for the 15 subjects participating in this study

Group	Subjects/group	Treatment for phase no.			
		I	II	III	IV
1	2, 4, 8, 11, 15	A	B	C	D
2	3, 7, 10, 12, 14	B	C	A	D
3	1, 5, 6, 9, 13	C	A	B	D

clinic lunch was provided. All meals served during the study were the same for each phase.

Assay of the dosage forms indicated that the actual doses administered were as follows: Treatment A, 100·55 mg; Treatment B, 201·1 mg; Treatment C, 301·65 mg; and Treatment D, 99·4 mg. These assay doses were utilized in the calculation of clearance and urinary recovery.

Blood samples were drawn by sequential venipuncture into Vacutainer tubes containing sodium heparin as an anticoagulant. For Treatments A, B, and C, 5 ml blood samples were drawn pre-dose (0 h) and at 0·5, 1, 1·5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h post-dose. Following Treatment D, 5 ml blood samples were drawn pre-dose (0 h) and at 0·167 (10 min), 0·333 (20 min), 0·5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 h post-dose. The sampling scheme for Treatment D, the oral solution, was different to that used for Treatments A, B, and C since the absorption of flurbiprofen from the solution was more rapid than from tablets. An additional 5 ml of blood was collected following Treatments A, B, and C at 1, 1·5, 2, 4, 6, 12, and 24 h. These samples were utilized in protein binding experiments.

All blood samples collected were immediately separated into plasma and cellular components by centrifugation. Plasma harvested from these samples was immediately frozen and kept in a frozen state until such time as they were assayed for flurbiprofen. Total urine samples were collected over the 0–12, 12–24, 24–36, 36–48, 48–72, and 72–96 h intervals post-dose. The volume of each sample was recorded and a 50 ml aliquot was frozen until such time as it was assayed for amounts of flurbiprofen and metabolites. All plasma samples were subjected to specific assay for flurbiprofen using a reversed phase HPLC method with fluorescence detection. The lower limit of quantitation for this method was 0·01 $\mu g\,ml^{-1}$.

Urine samples were analysed using a similar HPLC method utilizing UV detection. The concentrations of conjugated and unconjugated drug and metabolites were obtained by assaying the samples twice. Unconjugated drug and metabolites were determined directly. Total (conjugated + unconjugated) drug and metabolites were determined by first incubating the urine samples in 0·5N HCl, and then analysing these hydrolysed samples by HPLC. Concentrations of conjugated drug and metabolites were then obtained by difference (conjugated moiety = total moiety − unconjugated moiety).

An estimation of free (unbound) flurbiprofen concentrations in plasma were gained by subjecting selected plasma samples from five of the 15 subjects to equilibrium dialysis experiments and then using these data and the HPLC assays on the remaining samples to estimate free drug concentrations for all samples obtained from these five subjects. A technique similar to this was used to evaluate ibuprofen data.[9,10] A detailed account of the HPLC assay methodology employed, as well as results of protein binding experiments, will be presented in future reports.

RESULTS

Mean plasma concentrations of total (bound + free) flurbiprofen at each time point following the administration of each of the four treatments are presented in Table 2. Table 3 lists mean kinetic parameters obtained from total flurbiprofen plasma concentrations following Treatments A, B, C, and D. It should be recognized that these parameters were not derived from the mean plasma concentration data shown in Table 2, but from individual subject plasma concentration data. Areas under the plasma concentration–time curve from time 0 to time T (AUC 0-T) were calculated using the

Table 2. Mean plasma concentrations ($\mu g\,ml^{-1}$) of total flurbiprofen following treatments A, B, C, and D

Time (hours)	Mean plasma concentration ($\mu g\,ml^{-1}$) A	B	C	D
0·167	–*	–	–	11·4 (5·29)†
0·333	–	–	–	14·1 (3·05)
0·5	6·63 (6·36)	14·1 (10·8)	19·6 (11·3)	14·2 (2·04)
1·0	8·51 (5·75)	21·4 (9·97)	24·8 (12·61)	13·4 (2·00)
1·5	10·6 (5·40)	21·0 (7·50)	27·6 (10·41)	–
2·0	10·7 (5·19)	19·8 (5·80)	29·5 (8·51)	10·5 (1·72)
3·0	9·23 (2·82)	18·2 (3·61)	26·1 (6·17)	8·00 (1·71)
4·0	7·86 (3·21)	14·9 (3·52)	21·2 (7·07)	6·57 (1·56)
6·0	4·92 (1·51)	8·96 (2·66)	13·7 (4·47)	4·29 (1·04)
8·0	3·28 (1·16)	6·10 (2·09)	9·60 (3·12)	3·01 (0·740)
12·0	1·72 (0·694)	3·23 (1·40)	5·05 (2·23)	1·81 (0·728)
24·0	0·435 (0·238)	0·901 (0·533)	1·22 (0·700)	0·478 (0·268)
36·0	0·133 (0·083)	0·247 (0·175)	0·374 (0·297)	0·153 (0·111)
48·0	0·051 (0·036)	0·107 (0·087)	0·135 (0·122)	0·058 (0·042)

* Missing values correspond to time points in which no samples were drawn for particular treatment.

† Values in parentheses are standard deviations.

Table 3. Mean kinetic parameters obtained from total flurbiprofen plasma concentrations for the four treatments

	A	B	C	D
Peak total plasma conc. ($\mu g\,ml^{-1}$)	14·2 (4·23)§	25·8 (6·48)	35·5 (6·56)	15·7 (4·15)
Time to peak concentration (h)	1·90 (1·51)	1·73 (0·79)	1·83 (0·94)	0·511 (0·31)
AUC ($0 - T$) ($\mu g\,ml^{-1} \times h$)	82·19 (20·1)	160·2 (42·2)	232·5 (54·5)	83·9 (17·5)
AUC ($0 - \infty$) ($\mu g\,ml^{-1} \times h$)	82·74 (20·4)	161·3 (43·1)	233·9 (55·9)	84·9 (18·2)
Elimination rate constant (λ^1) (h^{-1})	0·0935 (0·011)	0·0965 (0·016)	0·102 (0·013)	0·0947 (0·016)
$t_{1/2}$ (h)*	7·41	7·19	6·81	7·31
Cl ($1\,h^{-1}$)†	1·28 (0·27)	1·32 (0·33)	1·36 (0·31)	1·22 (0·25)
Cl ($ml\,min^{-1}\,kg^{-1}$)‡	0·281 (0·056)	0·292 (0·073)	0·298 (0·060)	0·269 (0·055)

* Harmonic mean elimination half-life.
† Oral clearance, actually Cl/F, where F is the bioavailability.
‡ Oral clearance corrected for body weight, actually Cl/(WF) where W is the body weight in kg, and F is the bioavailability.
§ Values in parentheses are standard deviations.

trapezoidal rule. Corresponding terminal elimination rate constants (λ_1) were calculated by applying equation 1 to data which was in the terminal log-linear phase of the plasma concentration–time profile.

$$\ln C = \ln C_0 - \lambda_1 t \quad (1)$$

The extrapolated areas from time T to infinity [AUC ($T - \infty$)] were then calculated as the quotient of the concentration predicted by equation 1 at time $t = T$ and the least squares estimate of λ_1, the terminal elimination rate constant. Areas from time zero to infinity (AUC $0 - \infty$) were then calculated as the sum of AUC ($0 - T$) and AUC ($T - \infty$). Oral clearances (CL/F), where F is the bioavailability, were calculated using equation 2.

$$CL/F = \text{Dose/AUC}\ (0 - \infty) \quad (2)$$

The observed areas under the plasma concentration–time profiles, AUC ($0 - T$), averaged 99 per cent (range 98·8 to 99·4 per cent) of the estimated AUC ($0 - \infty$). Hence, the areas calculated by extrapolation were only a minor portion of AUC ($0 - \infty$)s. Differences among mean plasma concentrations following Treatments A, B, and C were significant at all sampling times, as would be expected. Likewise, differences among treatment means were also significant for AUC ($0 - \infty$) ($p < 0·001$) and peak

concentration ($p < 0{\cdot}001$) by ANOVA for crossover design. Differences among treatment means for time to peak were not significant ($p > 0{\cdot}25$). Differences among the three mean elimination rate constants following Treatments A, B, and C were not significant ($p > 0{\cdot}2$) by ANOVA for crossover design. Two-way ANOVA indicated that differences among elimination rate constants following all treatments (including Treatment D) were not significant ($p > 0{\cdot}3$). The absolute magnitude of terminal elimination rate constants observed in this study were considerably smaller (with corresponding half-lives averaging 7·2 h) than that previously reported for flurbiprofen in the literature. The explanation for this observation is that the assay methodology developed as part of this work afforded sufficient sensitivity to monitor the time course of flurbiprofen for 48 h post-dose, allowing measurement of the true terminal elimination rate constant.

Unlike iboprofen and naproxen, the AUC $(0 - \infty)$ for total (bound + free) flurbiprofen is a linear function of the administered dose in the ranges examined in this study. Figure 1 is a plot of AUC $(0 - \infty)$ ($\mu g \times h\,ml^{-1}$) for Treatments A, B, and C vs assay dose ($mg\,kg^{-1}$) for the 15 subjects participating in this study. Least squares regression of AUC $(0 - \infty)$ on dose gives the line: AUC $(0 - \infty) = 11{\cdot}0 + 54{\cdot}4$ (dose) ($r^2 = 0{\cdot}747$). The intercept of this regression line is not significantly different from zero ($p > 0{\cdot}2$) by a *t*-test. Hence, the line drawn in Figure 1 is the least squares line forced

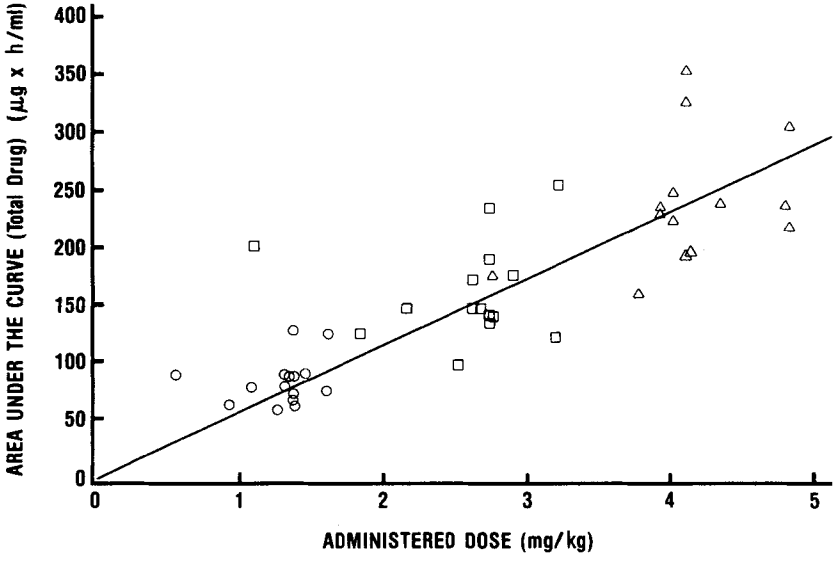


Figure 1. Plot of AUC $(0 - \infty)$ vs dose for the three tablet treatments. Open circles = Treatment A, squares = Treatment B, triangles = Treatment C. Equation of the line is AUC $(0 - \infty) = 57{\cdot}8$ (dose)

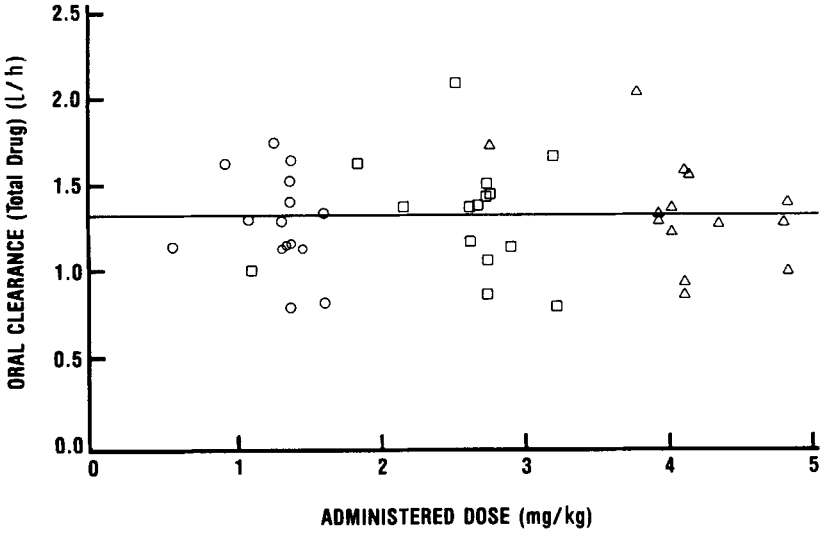


Figure 2. Plot of oral clearance vs dose using data from Treatments A, B, and C. Open circles = Treatment A, squares = Treatment B, triangles = Treatment C. The line drawn in the figure is the mean clearance $1{\cdot}321\,h^{-1}$

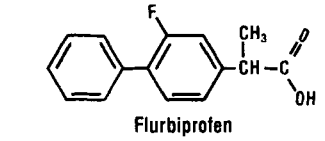
through the origin and has the equation AUC $(0 - \infty) = 57{\cdot}8$ (dose) ($r^2 = 0{\cdot}743$). Since the slope of this regression line is equal to (WF/Cl), where Cl is oral clearance, W is body weight (kg), and F is the bioavailability, the linear area/dose relationship shown in Figure 1 also implies constant clearance of total drug. Figure 2 is a plot of oral clearance based on total drug (uncorrected for body weight) vs assay dose ($mg\,kg^{-1}$). Regression of clearance on dose results in a regression line whose slope is not significantly different from zero ($p > 0{\cdot}2$). Hence, the line drawn in this figure is the line which best describes these data, namely the mean clearance $1{\cdot}321\,h^{-1}$. This observation indicates that clearance is independent of administered dose.

Analysis of free (unbound) and bound flurbiprofen plasma concentrations for the five subjects in which protein binding experiments were conducted indicated that flurbiprofen does exhibit saturable plasma protein binding, but that in the concentration range achieved in this study the binding was essentially linear. Consequently, for these doses, calculations based on total (bound + free) drug are accurate predictors of the pharmacokinetic and biopharmaceutic characteristics of flurbiprofen. As mentioned earlier, the binding of flurbiprofen to plasma proteins will be the subject of another report.

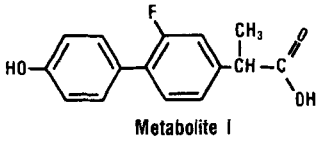
Estimates of bioavailability relative to the oral solution (calculated as ratios of oral clearances based on total drug) averaged 0·96, 0·94, and 0·91, respectively, for one, two, and three tablets. Differences among average bioavailabilities were not significant based on ANOVA ($p > 0{\cdot}1$). The trends

observed in these values (i.e., a decrease in bioavailability with increase in dose) may reflect a slight decrease in the efficiency of absorption as the dose is increased. As will be shown, however, the urinary recoveries of flurbiprofen and its metabolites were consistent from treatment to treatment, demonstrating no dose dependency.

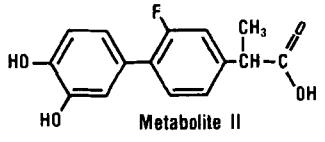
Mean urinary recoveries of conjugated and unconjugated flurbiprofen and its metabolites, expressed as amounts recovered as a percentage of the administered dose, are presented in Table 4. Individual subject data were corrected for differences in molecular weight where applicable. ANOVA for crossover design was applied to amount of total (conjugated + unconjugated) flurbiprofen, metabolite I, metabolite III, and to total recovery values for the 15 subjects. Differences among treatment means were not significant ($p > 0{\cdot}3$). When the ANOVA procedure was applied to amounts of unconjugated and conjugated flurbiprofen and metabolite I, differences among treatment means were also not significant ($p > 0{\cdot}2$). Unconjugated, conjugated, and total amounts of metabolite II were not subjected to the ANOVA procedure



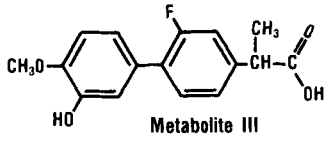
Flurbiprofen



Metabolite I



Metabolite II



Metabolite III

Figure 3. Chemical structures of flurbiprofen and its major metabolites

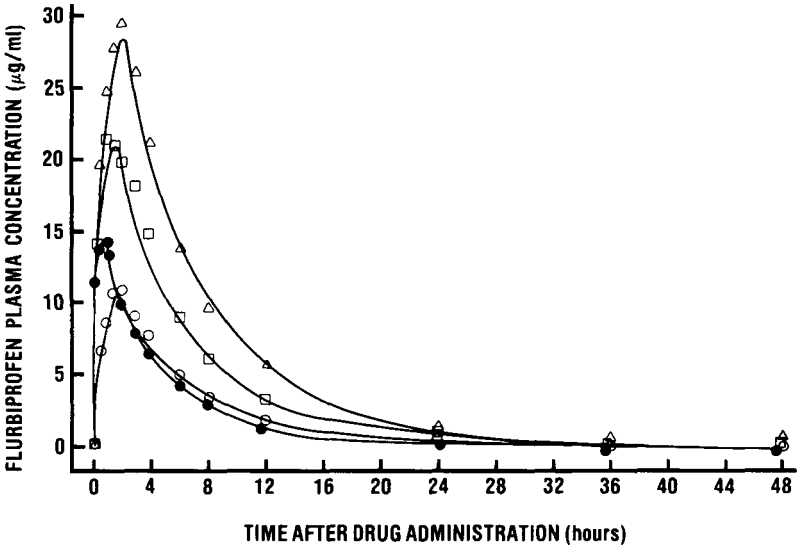


Figure 4. Fits of mean flurbiprofen plasma data following Treatments A, B, C, and D. Open circles = Treatment A, squares = Treatment B, triangles = Treatment C, closed circles = Treatment D

since this metabolite did not achieve detectable concentrations in every subject and also since it was not always detectable in all three treatments in a given subject. The above results indicate that the urinary excretion of flurbiprofen and its metabolites is dose independent and supports the observation that flurbiprofen obeys linear pharmacokinetics. It should be noted that the urinary recovery results described above differ from those obtained by previous investigators,[5] specifically in regard to amounts of metabolite II, metabolite III, and total recovery. Ridsall *et al.*,[5] claim 100 per cent recovery of an administered dose of flurbiprofen in the urine of humans. Of this amount, 24·6 per cent was recovered as metabolite III and 5·1 per cent was recovered as metabolite II. We achieved mean recoveries of 74·8 per cent of the administered dose, of which 6·75 per cent was excreted as metabolite III and 1·18 per cent as metabolite II. Our analytical methods were proven to be accurate and specific, and we are confident that our results are valid. Furthermore, subsequent experiments in which plasma concentrations of metabolite I were monitored were suggestive of biliary cycling of this metabolite. It is entirely possible that some of the administered dose may be excreted in the faeces.

Nonlinear least squares fitting of mean plasma concentration–time data indicated that mean tablet and solution data were adequately described by the two-compartment open model with first order absorption with rate constants ordered as follows: $k_a > \alpha > \beta$ (see Figure 4). These results differ from that obtained by detailed analysis of individual subject concentration–time data.

Table 4. Summary of urinary excretion data

	Mean % (± S.D.) recovery for each treatment							
	Treatment A		Treatment B		Treatment C		Treatment D	
Unconjugated flurbiprofen	2·9	(1·3)	2·4	(0·74)	3·1	(1·2)	2·4	(0·8)
Conjugated flurbiprofen	19·4	(7·0)	18·3	(7·3)	18·9	(8·3)	18·4	(7·4)
Total flurbiprofen	22·3	(7·7)	20·7	(7·8)	22·0	(8·6)	20·8	(7·8)
Unconjugated metabolite I	6·9	(2·9)	6·2	(2·6)	7·2	(3·3)	5·8	(2·1)
Conjugated metabolite I	40·7	(8·2)	39·3	(14·7)	42·4	(13·5)	35·1	(8·7)
Total metabolite I	47·6	(9·8)	45·5	(15·7)	49·6	(13·8)	40·9	(9·2)
Unconjugated metabolite II	0·48	(9·4)	0·3	(0·3)	0·4	(0·41)	0·2	(0·21)
Conjugated metabolite II	0·52	(0·4)	1·0	(0·9)	1·1	(0·7)	0·8	(0·4)
Total metabolite II	1·0	(0·3)	1·3	(1·1)	1·4	0·9)	1·0	(0·5)
Unconjugated metabolite III	0·0		0·0		0·0		0·0	
Conjugated metabolite III	6·6	(2·0)	7·2	(2·4)	6·5	(2·5)	6·7	(1·8)
Total metabolite III	6·6	(2·0)	7·2	(2·4)	6·5	(2·5)	6·7	(1·8)
Total recovery	77·1	(13·7)	74·3	(15·8)	79·1	(15·2)	68·9	(11·8)

When absorption profiles were constructed for individual subjects (not shown), only the oral solution appeared to be absorbed by a first order process. The absorption of flurbiprofen from compressed tablets appears to follow either zero order, or ill-defined kinetics. These observations will be the subject of a future report.

DISCUSSION

Data presented indicate that flurbiprofen obeys linear pharmacokinetics following the doses administered in this study. Plots of total area vs dose were linear, with the regression line passing through the origin as theory would dictate. This observation implies that oral clearance of total drug is independent of dose and is accurately described by the average value, namely $1{\cdot}32\,l\,h^{-1}$.

The consistency of the mean urinary recoveries of flurbiprofen and its metabolites shown in Table 4, coupled with the statistical analysis of these data, indicates that the renal excretion of flurbiprofen is a linear function of dose and is, therefore, dose independent. These urinary excretion results, along with the observation that the clearance of total drug is constant, implies that the efficiency of flurbiprofen absorption is also dose independent.

Terminal elimination rate constants estimated from the tail ends of total flurbiprofen plasma concentration–time curves gave values smaller than previously reported in the literature. These rate constants corresponded to harmonic mean half-lives of 7·41, 7·19, 6·81, and 7·31 h for TreatmentsA, B, C, and D, respectively.

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