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Research Article

Route of Administration and Sex Differences in the Pharmacokinetics of Aspirin, Administered as Its Lysine Salt

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One thousand milligrams of aspirin, as its lysine salt, was administered intravenously, orally, and intramuscularly to nine male and nine female young healthy adult volunteers. After intravenous injection mean (±SD) values of clearance, steady-state volume of distribution, and terminal half-life were 12.2 ± 2.2 ml/min/kg, 0.219 ± 0.042 liter/kg, and 15.4 ± 2.5 min, respectively, with no differences between males and females. Following oral administration aspirin was absorbed more quickly in females than in males (mean absorption times of 16.4 and 21.3 min, respectively) although the bioavailability, 54%, was the same in both groups. In contrast, following intramuscular administration, aspirin was absorbed more slowly in females than males (mean absorption times of 97 and 53 min, respectively) but again the bioavailability, 89%, was the same in both groups. The data suggest that in the female the intramuscular injection is going into fat. Salicylic acid concentration–time profiles showed a less pronounced sex difference and were comparable among the three routes of administration.

KEY WORDS: aspirin; pharmacokinetics; intramuscular; sex differences; rate of absorption.

INTRODUCTION

Aspirin (acetylsalicylic acid), introduced in 1900, is still the most widely used oral medication for the relief of headache, pain, and fever. It is also still widely prescribed for the treatment of rheumatoid arthritis. Initially introduced as a prodrug, to overcome the unpleasant taste and the gastrointestinal irritation associated with salicylic acid, aspirin has subsequently been shown to be a more potent analgesic than salicylic acid (1) and to have a selective antithrombotic activity (2,3). Conventionally aspirin has been given orally. The results of recent studies, however, suggest that the efficacy of aspirin, given intravenously and intramuscularly, is comparable to that of narcotic analgesics, such as oxycodone, for the relief of postoperative pain, without producing any respiratory depressant effect (4,5). Pharmacokinetic data following intravenous and intramuscular administration of aspirin are limited (6,7). Such data are of use in the design of optimal dosage regimens for the intravenous or intramuscular administration of aspirin.

The purpose of the present study was to examine the pharmacokinetics of aspirin after oral, intramuscular, and intravenous administration to human volunteers. Specifically we were interested in determining the rate and extent of aspirin absorption following oral and intramuscular administration.

METHODS

Subjects

The study was performed in 18 (9 male and 9 female) young healthy adult volunteers whose ages ranged from 19 to 40 years (mean, 26 years) and weight from 50 to 89 kg (mean, 68 kg). No subject was receiving medication 7 days prior to and during the period of the study. Four females were taking oral contraceptives. No alcoholic beverage was allowed 12 hr prior to and during each phase of the study. Each subject gave informed written consent to participate in the study and the study received the approval of an Ethics Committee.

Protocol

The study was performed in a randomized three-way crossover design. Each volunteer received, after an overnight fast, a commercial preparation of 1.8 g lysine acetylsalicylate (equivalent to 1000 mg aspirin) orally (Aspegic 1000), intravenously (Aspegic injectable), and intramuscularly (Aspegic injectable) with a 1-week washout period between administrations. The oral dose was dissolved in 100 ml of water and was drunk rapidly. The intravenous dose was given as an infusion over 2.5 min into an antecubital fessa vein and the intramuscular dose was injected into the upper lateral part of the buttock. Serial blood samples (5 ml) were

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collected from an indwelling cannula in a forearm vein immediately prior to the dose and 3, 6, 10, 15, 20, 25, 30, 40, 50, 60, 75, and 90 min and 2, 2.5, 3, 4, 6, 7, 10, and 12 hr after drug administration. In the case of the intravenous dose, in the first 10 min samples were taken from a contralateral vein immediately prior to the dose and at 1, 2.5, 5, 7.5, and 10 min after the start of the infusion. In order to minimize aspirin hydrolysis blood samples were collected in ice-cold tubes containing potassium fluoride (50 mg) and immediately centrifuged, and the plasma was frozen and then stored at −70°C until analyzed; subjects were permitted a light snack 2 hr after drug administration and a normal diet after that.

Analytical Methods

Aspirin and salicylic acid in plasma were measured by high-performance liquid chromatography (HPLC), using a modification of the method of Cham *et al.* (8). To 1 ml of plasma was added 200 μl of an aqueous solution containing 25 mg/liter of 3-hydroxybenzoic acid (internal standard), 500 μl of 0.2 *M* sulfuric acid, and 10 ml of a mixture containing equal volumes of ether and hexane. After shaking for 10 min and centrifuging, the organic layer was recovered by freezing the plasma layer in liquid nitrogen and decanting. The organic phase was then extracted with 500 μl of 0.1 *M* phosphate buffer, pH 8.4, by shaking for 10 min, and after centrifugation, 100 μl was injected onto the HPLC. A 250 × 4.6-mm ODS column (7-μm particle size; Zorbax, DuPont UK) together with a 50 × 4.6-mm guard column (Permaphase ODS, DuPont UK) was used in the analysis. The mobile phase consisted of 34 parts methanol and 10 parts acetonitrile made up to volume with 0.1 *M* phosphate buffer, pH 2.5, and was passed through the column at a rate of 1 ml/min. All reagents were of analytical reagent grade or better. A fixed-wavelength (229 nm) UV monitor (Waters Associates Model 441 with cadmium lamp) was used for detection. Under the conditions of the assay, the retention times for the internal standard, aspirin, and salicylic acid were 6.3, 9.5, and 11.0 min, respectively. Calibrations were linear up to 20 mg/liter for aspirin and to 100 mg/liter for salicylic acid and the assay could detect concentrations down to 0.15 mg/liter for aspirin and 1.0 mg/liter for salicylic acid. Stability studies showed that less than 5% of aspirin was lost due to hydrolysis between sample collection and final analysis.

The residual aspirin in the syringe used for injection and, in the case of the intravenous injection, in the infusion set was assayed. As it has been shown that aspirin pharmacokinetics are dose independent over the range 300 to 1200 mg (6), all concentrations were then normalized to a 1000-mg administered dose of aspirin.

Kinetic Analysis

Intravenous data were analyzed by fitting a biexponential model to the data (9). Clearance (Cl), initial volume of distribution (V_1), volume of distribution at steady state (V_{ss}), and mean residence time (MRT) were calculated using standard procedures (10). The area under the curve (AUC) for the oral and intramuscular data was calculated using the trapezoidal rule and terminal half-lives ($t_{1/2}$) by log-linear regression. The peak concentration (C_{max}) was taken as the maximum observed value and the time to peak concentration (T_{max}) as the time corresponding to this value. MRT was calculated by the method of moments and the mean absorption time (MAT) was calculated as the difference between the MRTs of the oral or intramuscular data and the intravenous data (11). Bioavailabilities (F) of the oral and intramuscular doses were estimated by comparing the respective AUCs with that obtained from the intravenous dose. Absorption rate profiles were estimated by numerical deconvolution using a point-area method (12) with the unit impulse function being estimated from the biexponential model fitted to the intravenous data.

Statistical Analysis

Univariate parameters, such as Cl, were compared between males and females with the aid of Student's t test. Because of the strong correlation between C_{max} and T_{max} these parameters were tested by means of multivariate analysis of variance [MANOVA (13)] and comparisons between sexes made with Hotelling's T^2 test (14), which is the multivariate equivalent of Student's t test. Cumulative absorption–time profiles were compared using a mixed-model analysis of variance (15) and parallelism tested by means of the sex-by-times interaction.

RESULTS

Table I summarizes the disposition kinetics of aspirin following intravenous administration and in Fig. 1 the aspirin concentration–time profile, together with the fitted biexponential equation, is shown for one subject. The mean dose of aspirin administered was 898 ± 24 (SD) mg. No statistically significant sex differences were observed with any of the parameters listed in Table I. The disposition parameters are comparable with those reported in the literature (6).

Table I. Pharmacokinetic Parameters (Mean ± SD) of Aspirin Following an Intravenous Infusion of Lysine Acetylsalicylate to Nine Male and Nine Female Subjects[a]

Sex	Half-life (min)		Cl (ml/min/kg)	V_1 (liters/kg)	V_{ss} (liters/kg)	MRT (min)
	1st phase	2nd phase				
M	3.1 ± 2.3	16.3 ± 2.8	12.0 ± 1.1	0.042 ± 0.007	0.221 ± 0.026	18.6 ± 3.0
F	1.5 ± 1.3	14.5 ± 2.0	12.4 ± 3.0	0.035 ± 0.010	0.218 ± 0.056	17.2 ± 2.9
M&F	2.3 ± 2.0	15.4 ± 2.5	12.2 ± 2.2	0.039 ± 0.009	0.219 ± 0.042	17.9 ± 2.9

[a] No parameter for males is significantly different from females at the 95% confidence level.

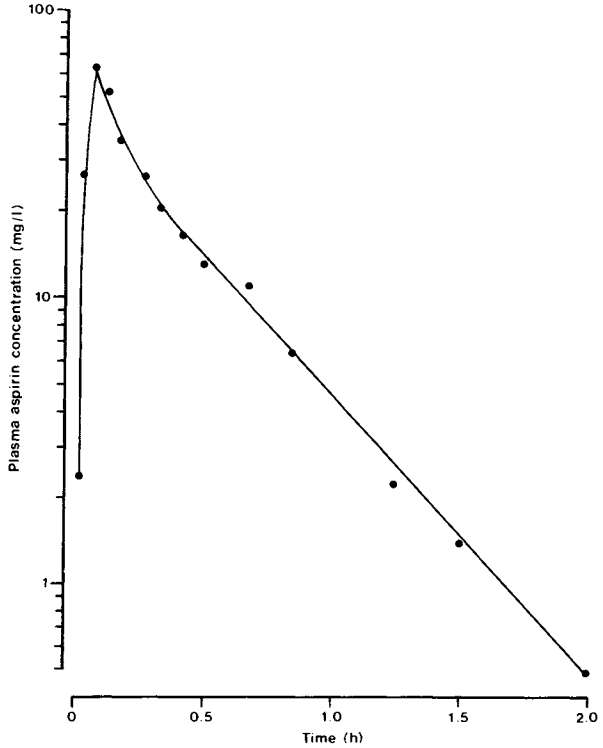

Fig. 1. Aspirin plasma concentration–time profile in a female volunteer following a 10-min intravenous infusion of 897 mg aspirin (as lysine acetylsalicylate). The solid line is the fit of a biexponential model to the data.

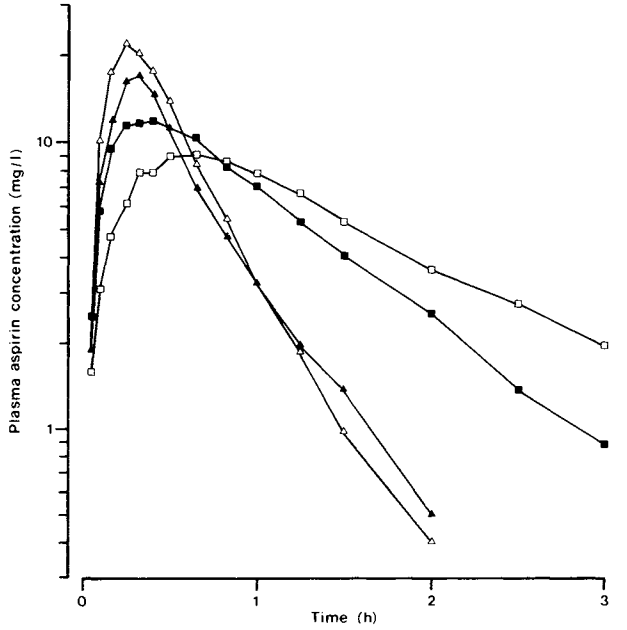

Fig. 2. Aspirin plasma concentration–time profiles following the oral and intramuscular administration of aspirin (as lysine acetyl salicylate) to nine male and nine female subjects (oral dose, 1000 mg; mean i.m. dose, 917 mg). Each point is the mean value for the route of administration and sex: ▲—male, oral; △—female, oral; ■—male, i.m.; □—female, i.m.

A summary of the parameters measured from the aspirin concentration–time profiles obtained after oral and intramuscular administration is given in Table II. The mean aspirin concentration–time profiles for oral and intramuscular administration are displayed in Fig. 2. The mean dose of aspirin administered intramuscularly was 917 ± 76 (SD) mg. Most of the parameters obtained from the oral data show no sex dependence except for the terminal half-life, which is slightly but significantly shorter in females (20.6 min for males versus 16.2 min for females). The terminal half-life from the oral data is also significantly longer than that associated with the second phase from the intravenous data (18.4 vs 15.4 min; $P < 0.005$, paired t test). The MRT is also significantly shorter in females (39.9 min for males vs 33.5 min for females), and although not reaching statistical significance, there is a similar trend for T_{max} and MAT. Only 54% of the oral dose (mean over males and females) reached the systemic circulation.

In contrast to the intravenous data and more marked than the oral data, the aspirin parameters associated with the intramuscular data show a clear sex difference. In particular, the maximum concentration (multiplied by body weight,

Table II. Pharmacokinetic Parameters (Mean ± SD) of Aspirin Following Oral and Intramuscular Administration of Lysine Acetylsalicylate to Nine Male and Nine Female Subjects

Route	Sex	C_{max} (mg/liter × kg)	T_{max} (min)	Terminal $t_{1/2}$ (min)	AUC (mg/liter × kg)	MRT (min)	MAT (min)	F (%)
po	M	1420	19.9	20.6	770	39.9	21.3	51.5
		(±360)	(±9.0)	(±4.5)	(±110)	(±9.2)	(±7.7)	(±3.7)
	F	1590	15.6	16.2	810	33.5	16.4	57.0
		(±340)	(±4.6)	(±3.0)	(±140)	(±5.8)	(±6.8)	(±20.6)
Significance*		ns[a]	ns	$P < 0.025$	ns	$P < 0.05$	ns	ns
im	M	1020	20.0	40.0	1290	71	53	86.2
		(±160)	(±6.6)	(±14.4)	(±230)	(±23)	(±21)	(±9.5)
	F	670	45.8	69.8	1300	116	97	91.4
		(±250)	(±20.6)	(±23.4)	(±180)	(±36)	(±37)	(±26.4)
Significance*		$P < 0.005$	$P < 0.005$	$P < 0.005$	ns	$P < 0.005$	$P < 0.005$	ns

[a] Not significantly different.

* The parameter at the head of the column is significantly smaller or greater than that for females at the probability level given (one sided Student's t test).

which effectively normalizes dose on a body-weight basis) was higher in males (1020 mg/liter × kg) than in females (670 mg/liter × kg) and occurs at an earlier time (20.0 vs 45.8 min). The Hotelling T^2 for the difference between sexes for the bivariate distribution of C_{max} and T_{max} was 19.23 ($P < 0.005$), whereas the corresponding figure for the oral data was 1.47 ($P = 0.45$). A plot of C_{max} × body weight versus T_{max} (Fig. 3) clearly shows the distinction between males and females in the intramuscular data. Furthermore, the terminal $t_{1/2}$, MRT, and MAT were all longer in females (69.8, 116, and 97 min, respectively) than in males (40.0, 71, and 53 min, respectively). These trends are in the opposite direction to those seen in the oral data. However, there was no sex difference in the extent of absorption of aspirin. Significantly more aspirin was absorbed after intramuscular administration, 89% (mean over males and females), than after the oral dose ($P < 0.001$, paired t test). Also, the maximum aspirin concentration was significantly higher in both males (1420 mg/liter × kg) and females (1520 mg/liter × kg) after oral administration than after intramuscular administration (1020 and 670 mg/liter × kg, respectively; $P < 0.001$, paired t test). Whereas the maximum aspirin concentration occurred significantly later in females after intramuscular administration (45.8 min) than after oral administration (15.6 min; $P < 0.001$, paired t test), there were no differences in the time to maximum aspirin concentration in males between the two modes of administration (20.0 and 19.9 min, respectively). The terminal half-life, for both males and females, was significantly longer after intramuscular administration (40.0 and 69.8 min, respectively) than after oral administration (20.6 and 16.2 min, respectively; $P < 0.001$, paired t test).

There is a tendency for the variability in the parameters T_{max}, terminal $t_{1/2}$, and MRT to increase as the parameter increases. For example, the estimated variance in T_{max} for

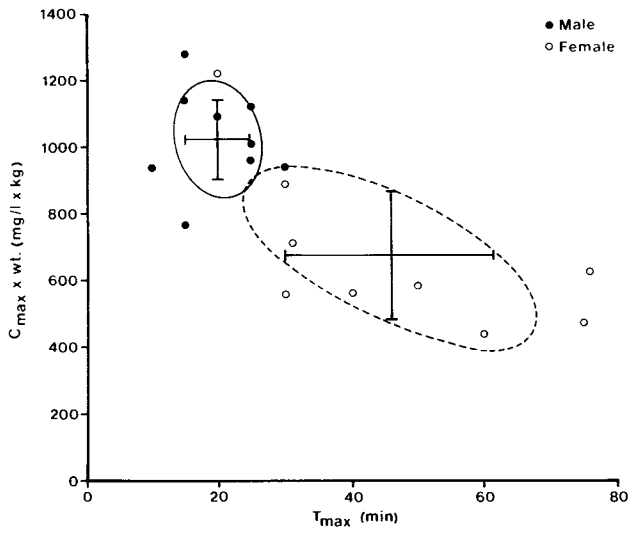

Fig. 3. Plot of the maximum aspirin concentration multiplied by body weight versus the time to reach maximum concentration following the intramuscular administration of aspirin (as lysine acetylsalicylate normalized to 1000 mg of aspirin) to nine male and nine female subjects. The ellipses are 95% confidence intervals for the bivariate distribution of C_{max} × weight and T_{max}. The centers of the ellipses, marked by crosses, are the mean values for the respective groups.

female subjects after intramuscular administration (424.4) is significantly greater than the corresponding figure for males (43.6; $F = 9.74$, $P < 0.01$). The variances become homogeneous by using the logarithms of these values in the statistical comparisons and this transformation was made in all the tests reported here. Also, the variability in bioavailability is greater in females than males for both oral and intramuscular administration ($F = 31.0$ and 7.7, respectively; both P's < 0.01) even though there is no significant difference between the mean values in each case.

The salicylic acid data from the three routes of administration are summarized in Table III and plots of mean concentration–time profiles are shown in Fig. 4. There are no sex differences in the salicylic acid data except for the oral data, in which the AUC (0–12 hr) for females (26,800 mg/liter × hr × kg) is significantly larger than the value in males (23,300 mg/liter × hr × kg). A MANOVA analysis of the C_{max} and T_{max} data indicates a significant effect of route of administration (Wilks' lambda, 0.205; $P < 0.001$). There are no differences between the intravenous and oral routes (mean C_{max} and T_{max}, 4220 mg/liter × kg and 55 min, respectively) but the C_{max} for the intramuscular route (3180 mg/liter × kg) was significantly smaller and the T_{max} (158 min) was significantly longer.

The cumulative absorption–time profiles obtained by deconvoluting the oral and intramuscular data are displayed in Fig. 5. There are clear differences between the oral and the intramuscular data, and as already noted, the total amount of aspirin absorbed from intramuscular administration is significantly greater than from oral administration, although it is absorbed more slowly. There was a significant sex difference in the intramuscular data (sex by time interaction $F = 7.75$; $P < 0.001$), with aspirin being absorbed more slowly from females. However, there were no significant differences between sexes for the oral data ($F = 0.14$). In general the absorption profiles could not be described by a simple function. In the case of the oral data there was a delay of about 2 to 3 min after which the aspirin was absorbed very rapidly with a mean absorption time of about 17 min (no significant difference between males and females). After intramuscular injection aspirin was absorbed in males with a mean absorption time of 44 min, which was significantly different from the value in females, 80 min ($P < 0.01$). The absorption rate–time profile following intramuscular administration was generally biexponential.

DISCUSSION

The bioavailability (extent of absorption) of aspirin following intramuscular injection is high but some aspirin loss, probably due to hydrolysis, evidently occurs at the injection site. Aspirin is absorbed more slowly after intramuscular administration than after oral administration, although the bioavailability from the latter route is significantly less than the former due to presystemic first-pass metabolism (17). As a net result maximum concentrations of aspirin following intramuscular administration are only slightly less than those following oral administration, and while being delayed as compared to the oral route, aspirin concentrations persist for a longer time. The reason the terminal half-life after intramuscular administration is longer than after oral administra-

Table III. Pharmacokinetic Parameters (Mean ± SD) of Salicylic Acid Following Intravenous, Oral, and Intramuscular Administration of Lysine Acetylsalicylate to Nine Male and Nine Female Subjects

Route	Sex	C_{max} (mg/liter × kg)	T_{max} (min)	AUC (0–12 hr) (mg/liter × hr × kg)
iv	M	4090	52	22,200
		(±380)	(±19)	(±1,700)
	F	4330	57	24,800
		(±570)	(±28)	(±4,200)
po	M	4180	52	23,300
		(±220)	(±16)	(±1,600)
	F	4290	60	26,800*
		(±460)	(±17)	(±3,980)
im	M	3380	130	20,500
		(±700)	(±52)	(±4,500)
	F	2970	186	22,100
		(±570)	(±87)	(±5,000)

* Significantly greater than the value in males ($P < 0.05$).

tion is that this terminal half-life reflects the absorption process rather than the elimination process: the "flip-flop" phenomenon (10, p. 35). This is also the probable reason that the terminal half-life following oral administration is slightly greater than after intravenous administration. That is, the terminal half-life from the oral data is "contaminated" with absorption and is not a pure measure of the elimination half-life.

The series of experiments described in this paper demonstrates a clear sex difference in the absorption of aspirin after both oral and intramuscular administration. There is no evidence, from the intravenous data, of a sex difference in the disposition of aspirin. Although subject weight differed by almost twofold in the current study, women being much lighter than men, resulting in differing dose per kilogram body weight, it is unlikely that weight is a major factor in the observed difference in absorption, as the pharmacokinetics of aspirin has been found to be independent of dose (17).

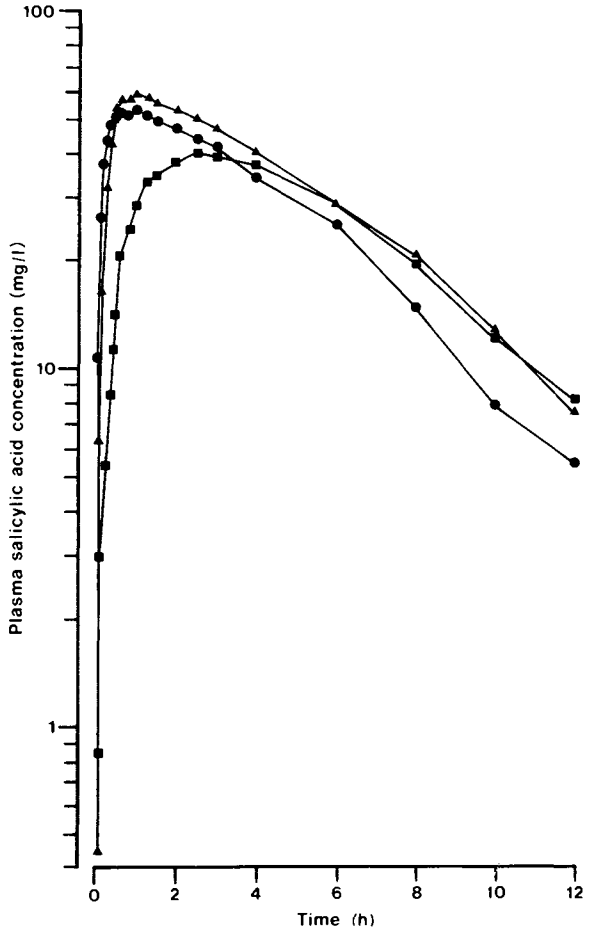

Fig. 4. Plasma salicylic acid concentration–time profiles following the intravenous, oral, and intramuscular administration of aspirin (as lysine acetyl salicylate) to nine male and nine female subjects (mean i.v. dose, 898 mg; oral dose, 1000 mg; mean i.m. dose, 917 mg). Each point is the mean value (averaged over sexes) for the route of administration: ▲—oral; ●—i.v.; ■—i.m.

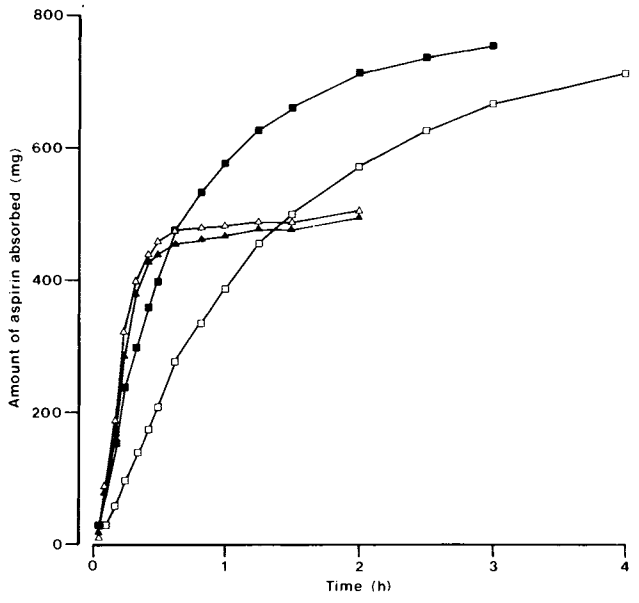

Fig. 5. Cumulative aspirin absorption–time plots following oral and intramuscular administration of aspirin (as lysine acetyl salicylate) to nine male and nine female subjects (oral dose, 1000 mg; mean i.m. dose, 917 mg). Each point is the mean value for the route of administration and sex: ▲—male, oral; △—female, oral; ■—male, i.m.; □—female, i.m.

There have been several reports of sex-related differences in drug disposition (18), particularly for salicylates (19–22). Sechserova *et al.* (21) found that levels of salicylic acid were lower in bulls than heifers after equal doses of aspirin and ascribed this difference to sex-dependent metabolism of both aspirin and salicylic acid. Miaskiewicz *et al.* (20) administered sodium salicylate (9 mg/kg) to male and female volunteers and found that, although there was no difference in maximum salicylate concentrations, the time to maximum concentration was significantly longer in females. In contrast, Trnavska and Trnavska (22) found that after the administration of aspirin (14.3 mg/kg), maximum salicylic acid concentrations were lower and occurred later in males than females. It is difficult to compare the latter two studies, as in one case sodium salicylate (in solution) was administered, whereas in the other aspirin (solid dosage form) was administered.

Ho *et al.* (19) administered 600 mg of aspirin (in solution) to a group of male and female subjects and found, like Trnavska and Trnavska (22), that salicylic acid concentrations were higher in females than males but that there was no difference in the time to reach maximum concentration. These results are in broad agreement with the results presented here. Ho *et al.* (19) also measured aspirin concentrations and observed that much higher concentrations of aspirin were observed in females than males, even after correcting for body weight. This is in contrast to our results, as we did not see any sex difference in the maximum aspirin concentration, the time to maximum concentration, or the area under the curve. Ho *et al.* ascribed the difference in aspirin profiles between males and females to reduced aspirin esterase activity in the female (23). We did not observe any differences in bioavailability, and hence first-pass metabolism, between males and females although the results for females were much more variable. It is possible that too few subjects were used to allow sufficient power to detect a difference. The fact that we observed no difference in the intravenous kinetics between males and females lend support to the proposal that the only difference in oral kinetics is faster absorption in females, presumably due to differences in gastric emptying (24). It is interesting to note that the power of derived statistics such as the MAT and the deconvoluted absorption–time plot is less than parameters such as the terminal half-life, probably due to the added noise produced in deriving these statistics.

The sex difference in the intramuscular data is much more frank. As can be seen from the cumulative absorption–time profiles, females absorb aspirin much more slowly than males after intramuscular injection into the buttock. Sex differences in the intramuscular absorption of cephradine (25) and dapsone (26) have also been reported. Vukovich *et al.* (25) studied the absorption of cephradine from three muscle sites: the gluteus maximus, vastus lateralis, and deltoid. They found that although there were sex differences in the absorption from the three sites, the difference was most pronounced when the drug was injected into the gluteus maximus. Differences in the rate of absorption from the three sites can be partially explained by differences in muscle blood flow between the different muscle groups (27). Absorption of lidocaine is most rapid after deltoid injection, less rapid after injection into the lateral thigh, and least rapid after injection into the gluteus maximus (28). These differences, however, are relatively minor. Accordingly, it is unlikely that differences in blood flow between males and females alone would account for the sex difference in the absorption of aspirin or the other drugs from the gluteus maximus. A more likely explanation is that the drug is being injected into fat in the female rather than into muscle, and consequently, it is absorbed more slowly. The mean gluteal fat thickness increases with weight, but at any given weight, women have 2.5 cm more fat than men (29). The needles used in our study (3.8 cm) would not penetrate to muscle in the case of most of the females on the study. The exception was volunteer 9, who as can be seen from Fig. 3, clearly falls in the "male group." Volunteer 9 was the smallest female on the study at 50 kg and was also very athletic and consequently had a lean frame. Therefore it is likely in her case that the injection actually reached the muscle.

Salicylic acid concentrations peaked later and were lower following intramuscular injection than either intravenous or oral administration. There is a tendency for the time to maximum salicylic acid concentration in females to be longer than in males, which probably reflects the sex difference in the intramuscular absorption of aspirin. Overall the salicylic acid concentration–time profiles from the three routes of administration are relatively similar, which is due to the fact the aspirin is quantitatively converted to salicylic acid (both presystemically and systemically) and the elimination of salicylic acid is much slower than that of aspirin (6). Using the experimental design of the present study, any sex differences in the disposition of salicylic acid are confounded with those due to the absorption of aspirin. Therefore it would be preferable to give salicylate intravenously in order to study any possible sex differences in the disposition of salicylic acid.

CONCLUSION

Intramuscular injection of aspirin is an effective method of delivering aspirin to the systemic circulation. Although maximum concentrations are lower and more delayed than after oral administration, aspirin concentrations are more prolonged and the bioavailability greater. Nevertheless, care must be taken in using the buttocks as an injection site, particularly in the female, where the injection may be made into fat. Perhaps another site such as the thigh or upper arm would be preferable. Finally, as noted by many other workers, the results of this study demonstrate the need to include, rather than exclude, women from volunteer pharmacokinetic studies.

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