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PHARMACOKINETICS OF BENZYDAMINE AFTER INTRAVENOUS, ORAL, AND TOPICAL DOSES TO HUMAN SUBJECTS

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ABSTRACT

The pharmacokinetics of the anti-inflammatory drug benzydamine were determined after intravenous infusion of 5 mg to six healthy male subjects. Benzydamine was characterized as a drug of relatively low systemic clearance (ca. 160 ml min^{-1}) but high volume of distribution (ca. 110 l); the apparent terminal half-life in plasma was ca. 8 h. Benzydamine was well absorbed after oral administration, as indicated by a mean systemic availability of 87 per cent. However, absorption of the drug was low (< 10 per cent of the dose) after its use by male subjects as a mouthwash, or after its application to female subjects as dermal cream and vaginal douche preparations. The data suggest that benzydamine is generally not well absorbed through the skin and non-specialized mucosae, thereby limiting unrequired systemic exposure to this drug when it is used by these routes.

KEY WORDS Benzydamine Human Absorption Pharmacokinetics Intravenous infusion

INTRODUCTION

Benzydamine (1-benzyl-3-[3-dimethylaminopropoxy)-1H-indazole hydrochloride) is a non-steroidal anti-inflammatory agent with local anaesthetic and analgesic properties.[1-4] It is used both topically and systemically for treatment of primary or more active types of inflammation; hence it is formulated for clinical use as oral, mouthwash, vaginal, and topical preparations. It has been reported that local tissue concentrations of benzydamine are higher after topical application of the drug than are those obtained after oral administration;[4-6] plasma concentrations are correspondingly lower. There may, therefore, be advantages to local application of the drug where the desired target site is accessible. However, because it is both well tolerated and effective, with few contra-indications, benzydamine would also appear suitable for intravenous and intramuscular use to control post-operative inflammation.

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Although the pharmacokinetics of benzydamine are well documented after various routes of administration,[4, 5, 7, 8] there is little published information regarding the pharmacokinetics of benzydamine after intravenous doses. The studies described herein were designed to obtain such data, and to assess the degree of drug absorption after oral, mouthwash, dermal, and vaginal douche doses.

MATERIALS AND METHODS

Selection of subjects

Six healthy adult male subjects, age 41–51 years and bodyweight 54–96 kg (70 ± 16 kg; mean ± SD), consented to participate in a study designed to investigate the pharmacokinetics of benzydamine after single intravenous, oral, and mouthwash doses. Six healthy adult females, age 18 – 40 years and bodyweight 53–64 kg (57 ± 4 kg; mean ± SD), consented to participate in a similar study designed to investigate the pharmacokinetics of benzydamine after administration of single oral, vaginal douche, and topical (cream) preparations. Dose levels were selected on the basis of previous clinical experience; doses of up to 50 mg day^{-1} have been reported to be well tolerated after administration by slow intravenous or intramuscular injection.

The two studies were conducted independently; each was approved by the Hospital Ethics Committee. Medical and laboratory investigations indicated that the volunteers were in good health and that drug administration had no detected effect upon their health; the side-effect observed was that of mild headaches but there was no consistent pattern in the occurrence of these with respect to route of administration. On each occasion, the subjects remained under medical supervision for at least 48 h after drug administration; the diet was standardized (ca. 350 g carbohydrate, 175 g fat, and 150 g protein daily, ca. 3750 calories daily) and alcohol was prohibited throughout the period of the study.

Drug formulations

Doses of benzydamine for intravenous administration were supplied as ampoules containing 0·5 per cent (w/v) of benzydamine as the hydrochloride salt in sterile distilled water (Tantum® ampoules, Batch 819), oral doses as a 3 per cent (w/v) solution of the hydrochloride salt in water (Tantum® liquid (drops), Batch 183) and mouthwash doses as a 0·15 per cent (w/v) solution of the hydrochloride salt in water (Tantum® verde mouthwash, Batch 2359). The cream for topical application contained 5 per cent (w/w) of benzydamine hydrochloride (Tantum® cream, Batch 122). The disposable douche for vaginal application contained 0·1 per cent (w/v) benzydamine hydrochloride with benzalkonium chloride (0·02 per cent) (Batch LV 80). A11 formulations used in

the study were supplied by Istituto di Ricerca F. Angelini, Rome, Italy. Oral and intravenous dosing preparations were diluted as necessary.

Dosage schedule and samples

The subjects were fasted overnight prior to dosing and for 4 h afterwards. Drug administration for each study was conducted as a complete three-way crossover in a repeated latin square design, with at least 1 week between doses.

The male subjects received:

(a) Single intravenous infusion doses of nominally 5 mg of benzydamine hydrochloride in aqueous solution, administered into an antecubital vein during 8 min; actual doses administered to individual subjects were determined.
(b) Single oral doses of 50 mg benzydamine hydrochloride in aqueous solution (25 ml, followed by 25 ml water).
(c) Mouthwash doses of 50 mg benzydamine hydrochloride in 33·3 ml solution which were gargled for 15 s, expelled, and a fresh solution (50 mg, 33·3 ml) treated similarly. The subjects were instructed to avoid ingesting the mouthwash. However, relatively high drug concentrations in the plasma of one subject indicated that this individual probably ingested ca. 20 per cent of the dose.

The female subjects received:

(a) Single oral doses of 50 mg benzydamine hydrochloride in aqueous solution (25 ml, followed by 25 ml water).
(b) Single dermal applications of nominally 100 mg benzydamine hydrochloride administered as ca. 2·1 g of cream over an area of the forearm ca. 100 cm^2; the cream was gently rubbed into the treated area which was then occluded (with aluminium foil and a dressing) for 24 h. The residual dose was then washed from the skin.
(c) Single douches of 140 mg benzydamine hydrochloride in 140 ml solution expelled into the vagina during ca. 3 min.

Blood samples (10 ml into heparinized tubes) were taken before dosing and at intervals during 56 h after dosing to male subjects, and during 60 h after dosing to female subjects. However, after administration of the mouthwash dose to males and the vaginal douche to females, blood samples were taken only until 36 h and 30 h after dosing, respectively. Blood was centrifuged to remove the cells, which were discarded, and the plasma was stored at ca. −20° until required for analysis.

During studies in male subjects, urine samples were collected prior to dosing (−12–0 h), and during 0–2, 2–4, 4–8, 8–16, 16–24, 24–36, 36–48, and 48–56 h after intravenous and oral doses. To maintain urine flow, 100 ml of water

was ingested each hour during the first 8 h after dosing. Urine was not collected after mouthwash doses to male subjects nor during studies in females.

Sample analysis

Concentrations of benzydamine in plasma and urine, and its major metabolite, benzydamine *N*-oxide, in urine were determined by high-performance liquid chromatography (HPLC) with fluorimetric detection, using a sensitive and specific assay.[9] Calibration lines of benzydamine in plasma and urine, and benzydamine *N*-oxide in urine were linear over the concentration ranges 0–400 ng ml^{-1}, 0–300 ng ml^{-1} and 0–40 μg ml^{-1}, with limits of reliable determination of 0·5, 1·0, and 50 ng ml^{-1}, respectively; for greater precision of measurement at low analyte concentrations, high- and low-range calibration lines were used for the analysis. The mean standard errors of the fitted (low-range) regression lines were ± 0·5 ng ml^{-1}, ± 0·3 ng ml^{-1}, and ± 20 ng ml^{-1} for benzydamine in plasma and urine and benzydamine *N*-oxide in urine, respectively. Concentrations of benzydamine and benzydamine *N*-oxide in urine were determined after intravenous and oral doses to male subjects only.

Data processing

Terminal rate constants (k) and half-lives of decline of benzydamine concentrations in plasma were calculated after least squares regression analysis of log concentration against time.[10] Areas under the plasma benzydamine concentration–time relationships (AUC) and areas under the first moments of these curves (AUMC)[11] were calculated by the log-linear trapezoidal rule[12] and extrapolated to infinite time. Mean residence times (MRT) were calculated as the ratio AUMC/AUC.

The systemic plasma clearance (CL_s) of benzydamine was calculated[13] as $Dose_{iv}$/AUC. The apparent volume of distribution of benzydamine at distribution equilibrium after intravenous doses (V_{area}) was calculated as Dose/AUC.k and that at steady-state (V_{ss}) as Dose. MRT/AUC.[13]

Input rates and absorption-time plots of benzydamine after oral doses to male subjects were calculated by the numerical deconvolution method of Langenbucher.[14] The unit impulse response (characteristic) functions were derived as transformed biexponential equations fitted to the intravenous plasma level data (normalized for a 50 mg dose) using the program NONLIN84 (Statistical Consultants Inc., Lexington, USA). The 'test' responses were the fitted plasma level data after oral administration. Fractional input rates were calculated at the mid-point of successive 0·5 h intervals chosen for the deconvolution algorithm. Cumulative amounts of benzydamine available to the systemic plasma ('absorption'), were derived by integration of the calculated input rates. The systemic availability (F) of benzydamine after administration of oral and mouthwash doses to male subjects (systemic availability) was calculated as the AUC

ratios compared with those of the intravenous doses. The relative availability of benzydamine after topical and vaginal douche administration to female subjects was calculated as the AUC ratios relative to the oral doses in these subjects. Data were normalized for doses administered as appropriate.

RESULTS

Plasma drug concentrations and derived pharmacokinetic parameters

Mean plasma concentrations of benzydamine obtained after intravenous infusion, oral, and mouthwash doses of benzydamine to six male volunteers and after oral, topical, and vaginal douche doses to six female volunteers are presented in Tables 1 and 2 and Figures 1 and 2, respectively. Mean pharmacokinetic parameters derived therefrom are presented in Table 3.

Table 1. Mean plasma concentrations of benzydamine ($n = 6$) after administration of single intravenous infusion (5 mg), oral (50 mg), and mouthwash (100 mg) doses to male subjects. Results are expressed as ng ml^{-1} with standard deviations in parentheses

Time (h)	Intravenous	Oral	Mouthwash†
0·00	61* (22)	ND (–)	ND (–)
0·08	55 (15)	– (–)	– (–)
0·17	55 (17)	– (–)	– (–)
0·25	54 (13)	29 (25)	5 (2)
0·50	50 (13)	174 (145)	13 (6)
0·75	45 (11)	312 (172)	20 (10)
1·00	44 (12)	392 (156)	24 (12)
1·50	43 (10)	454 (137)	28 (13)
2·00	40 (9)	413 (122)	31 (13)
3·00	34 (7)	347 (92)	37 (12)
4·00	31 (6)	332 (124)	35 (14)
6·00	27 (4)	295 (117)	28 (9)
8·00	22 (3)	232 (101)	22 (8)
12·00	13 (2)	134 (62)	15 (5)
16·00	9 (2)	88 (50)	9 (3)
24·00	6 (2)	61 (47)	7 (2)
36·00	2 (1)	19 (17)	3 (2)
48·00	1 (1)	9 (11)	– (–)
56·00	ND (–)	5 (6)	– (–)

ND: not detected (<0·5 ng ml^{-1}).
* Sample taken at the end of the 8 min infusion.
† Excluding data from one subject who apparently ingested ca. 20 per cent dose.

Studies in male volunteers

After administration of 5 mg intravenous infusion doses of benzydamine hydrochloride to male subjects, the peak of mean concentrations of benzyda-

Table 2. Mean plasma concentrations of benzydamine ($n = 6$) after administration of single oral (50 mg), topical (100 mg), and vaginal douche (140 mg) doses to female subjects. Results are expressed as ng ml^{-1} with standard deviations in parentheses

Time (h)	Oral	Topical	Vaginal douche
0·00	ND (–)	ND (–)	ND (–)
0·25	32 (28)	– (–)	ND (–)
0·50	196 (112)	– (–)	1 (2)
0·75	348 (196)	– (–)	– (–)
1·00	435 (211)	ND (–)	2 (4)
1·50	521 (201)	– (–)	– (–)
2·00	509 (119)	– (–)	3 (4)
3·00	443 (101)	ND (–)	5 (4)
4·00	387 (103)	– (–)	6 (5)
6·00	292 (83)	2 (2)	10 (8)
8·00	217 (67)	– (–)	– (–)
9·00	– (–)	– (–)	9 (8)
10·00	– (–)	4 (4)	– (–)
12·00	138 (30)	– (–)	7 (5)
15·00	– (–)	8 (7)	– (–)
16·00	85 (28)	– (–)	6 (4)
24·00	44 (13)	13 (9)	4 (3)
30·00	– (–)	16 (12)	3 (2)
36·00	14 (9)	12 (6)	– (–)
48·00	7 (5)	7 (4)	– (–)
60·00	2 (1)	4 (2)	– (–)

ND: not detected (< 0·5 ng ml^{-1}).

mine base in plasma of 61 ng ml^{-1} occurred at the end of the 8 min infusion period (Table 1). A short distribution (α) phase, of half-life 0·23 ± 0·13 h (mean ± SD; range 0·05–2·9 h), was identified in the plasma concentration–time profiles of all six subjects, but contributed < 15 per cent to the total AUC. The male subjects did not appear to form a homogeneous group with respect to the distribution phase.

Thereafter plasma concentrations of benzydamine declined with a terminal half-life of 8·1 ± 1·8 h (mean ± SD; Figure 1, Table 3). The calculated mean systemic clearance of benzydamine was 160 ± 35 ml min^{-1} (mean ± SD) and the volumes of distribution (V_{area} and V_{ss}) were 110 ± 23 l and 107 ± 22 l (mean ± SD), respectively. A mean of 14 per cent of the administered dose was excreted in urine as the *N*-oxide, but < 1 per cent was excreted unchanged.

After oral administration of 50 mg doses of benzydamine hydrochloride in aqueous solution, benzydamine was rapidly absorbed. Unchanged drug was detected in the plasma of all six subjects at the first sampling time, 0·25 h after dosing, and peak mean plasma concentrations of 454 ng ml^{-1} occurred at 1·5 h (Table 1). Deconvolution of the plasma level data indicated that the peak of the mean input rates of benzydamine of 73 per cent dose h^{-1} occurred at 1 h and corresponded to a mean mass transfer rate of 610 μg min^{-1} (Figure 3). Plots of drug input rate against time indicated that inter-subject variations

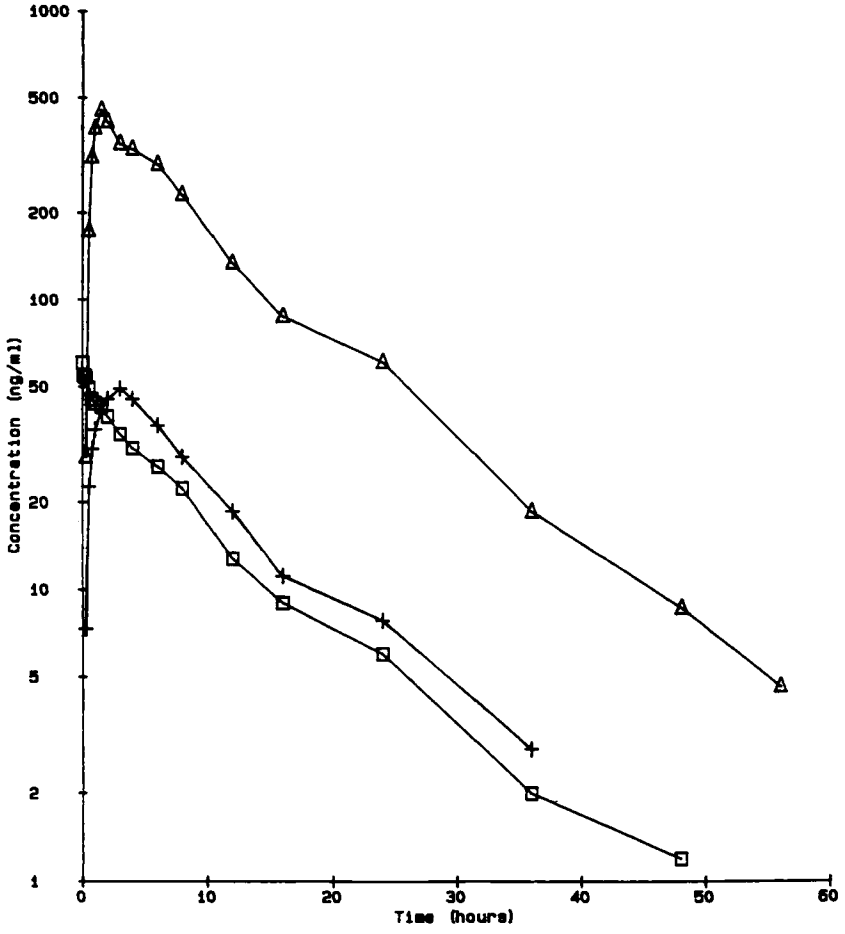

Figure 1. Mean plasma concentrations of benzydamine ($n = 6$) after administration of single intravenous infusion (5 mg □ – □), oral (50 mg △ – △), and mouthwash (100 mg + – +) doses to male subjects

were considerable. Absorption–time profiles obtained by integration of the input rates indicated that approximately 64 per cent of the dose was absorbed by 1 h (Figure 3) and that absorption was essentially complete by 4–6 h. 'Sigma-minus' plots of the proportion of the dose remaining to be absorbed were not linear on a semi-logarithmic scale. Calculated mean residence times of benzydamine in plasma were similar after oral and intravenous doses, thus it was not possible to calculate mean absorption times (MAT). After the oral doses, plasma concentrations of benzydamine declined in parallel with those after the intravenous dose, with a terminal half-life of 7·8 ± 1·7 h (mean ± SD; Table 1). The mean systemic availability of benzydamine after oral doses to male subjects was 87 per cent. The mean urinary excretion of unchanged benzy-

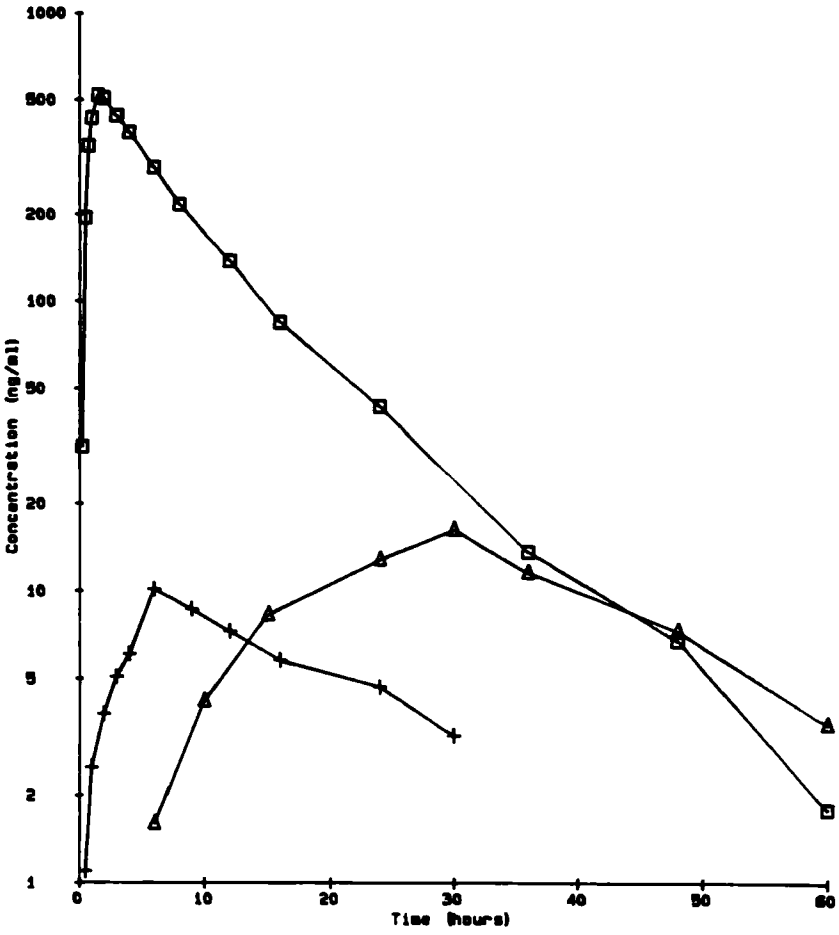

Figure 2. Mean plasma concentrations of benzydamine ($n = 6$) after administration of single oral (50 mg □–□), topical (100 mg △–△), and vaginal douche (140 mg +–+) doses to female subjects

damine was < 1 per cent and that of the *N*-oxide was 12 per cent of the administered dose.

Mouthwash doses of benzydamine were poorly but rapidly absorbed with benzydamine detected in the plasma of all six subjects at the first sampling time (0·25 h). Peak mean plasma concentrations of benzydamine of 37 ng ml^{-1} occurred at 3 h after dosing (Figure 1); plasma benzydamine concentrations thereafter declined in parallel with those obtained after oral and intravenous administration (Figure 1) with a half-life of 9·4 ± 2·9 h (mean ± SD). The mean systemic availability of benzydamine from the mouthwash doses (excluding data from one subject who ingested ca. 20 per cent of the administered dose) was ca. 5 per cent (Table 3).

Table 3. Pharmacokinetic parameters of benzydamine after intravenous, oral, and mouthwash doses to male subjects ($n = 6$), and after oral, topical, and vaginal douche doses to female subjects ($n = 6$). Results are expressed as means with standard deviations in parentheses

	Males						Females			
	Intravenous	Oral	Mouthwash[¶]	Oral	Dermal	Douche
	5 mg	50 mg	100 mg	50 mg	100 mg	140 mg
C_{max} (ng ml^{-1})	68 (19)*	459 (139)	35 (14)	546 (177)	14 (7)	10 (8)
t_{max} (h)	0·07 (0·10)†	1·75 (0·61)	3·60 (0·89)	1·75 (0·27)	31 (5)	7·5 (3·2)
k (h^{-1})	0·09 (0·02)	0·09 (0·02)	0·08 (0·02)	0·09 (0·02)		
$t_{½}$ (h)	8·1 (1·8)	7·8 (1·7)	9·4 (2·9)	7·8 (1·6)		
AUC (ng h ml^{-1})	541 (112)*	4907 (2326)	494 (138)	4994 (1190)	455 (243)[§]	162 (129)[§]
F (%)	100	87 (25)	4·6 (1·5)	100[‖]	5·2 (3·7)[‖]	1·3 (1·3)[‖]
CLs (ml min^{-1})	160 (35)*					
V_{area} (l)	110 (23)					
V_{ss} (l)	107 (22)					
MRT (h)	11·4 (2·6)[‡]	11·4 (2·7)	14·3 (4·2)			
Proportion excreted in urine:						
Benzydamine (%) dose)	0·42 (0·37)	0·29 (0·19)				
Benzydamine N-oxide (% dose)	14·1 (3·6)	12 (2)				

* Data adjusted for dose administered.
† Time after end of infusion.
‡ Adjusted for infusion period.
§ AUC to last measured sample concentration.
‖ Oral dose as reference formulation.
¶ $n = 5$.

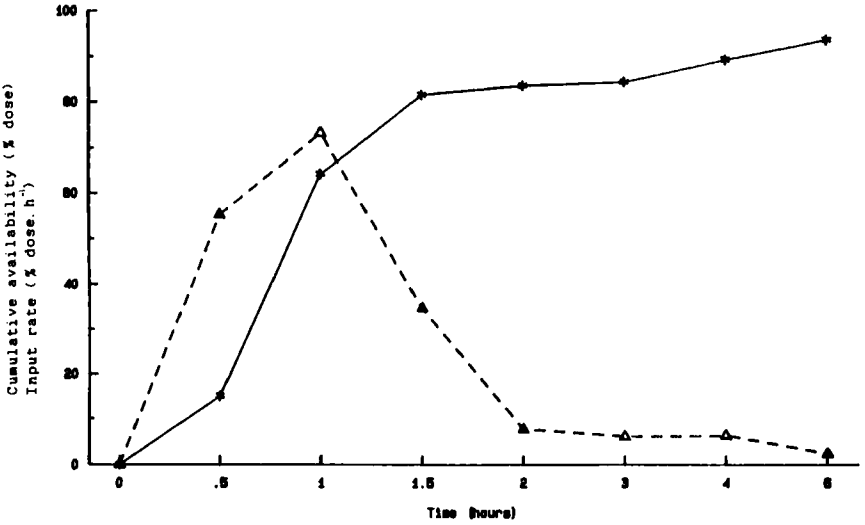

Figure 3. Mean cumulative availability (★ – ★) and input rate (△ – △) of benzydamine after single oral doses of 50 mg to male subjects

Studies in female subjects

After administration of 50 mg oral doses of benzydamine hydrochloride to female subjects, plasma benzydamine concentration–time profiles were generally similar to those obtained after equal doses to male subjects (Tables 1 and 2, Figures 1 and 2). Peak plasma concentrations of benzydamine in female subjects were higher than those in male subjects after equal oral doses; however, this difference was negligible when the data were adjusted for bodyweight. Plasma concentrations of benzydamine after oral doses to female subjects declined with a terminal half-life of 7·8 ± 1·6 h (mean ± SD).

Peak mean plasma concentrations of benzydamine of 16 ng ml^{-1} and 10 ng ml^{-1} after dermal and vaginal douche preparations, respectively, occurred at 30 h and 6 h after dosing, respectively. The terminal decline phases of benzydamine in plasma were inadequately defined after administration by these routes. The mean extent of bioavailability of benzydamine (relative to the oral dose) from the dermal and vaginal douche doses was less than 10 per cent (Table 3).

DISCUSSION

In these studies, benzydamine was characterized as a drug of relatively low systemic clearance but high volume of distribution, the latter being considerably greater than the volume of the total body water. Absorption of benzydamine from the gastrointestinal tract after oral administration was rapid and almost

complete. After mouthwash, vaginal douche, and dermal doses, the proportions of the doses absorbed were lower and peak plasma benzydamine concentrations occurred at progressively later times, possibly reflecting different rates of diffusion through non-specialized mucosae.

Peak plasma concentrations of benzydamine (normalized for dose), times of their occurrence, terminal half-lives, and AUCs (normalized for dose) obtained after oral administration during the course of this study were in good agreement with those previously reported in the literature,[4,5,7] as was the low urinary excretion of unchanged benzydamine. The reported major urinary metabolites of benzydamine are its *N*-oxide and a glucuronic acid conjugate of 5-hydroxybenzydamine.[4,5] The low availability of benzydamine after mouthwash, vaginal, and topical application and the slower absorption after vaginal and topical application are also consistent with previously published data.[4,5,7,8]

The mean systemic availability of benzydamine (87 per cent) after oral administration to male volunteers indicated that the drug was well absorbed, with little evidence of extensive pre-systemic elimination. However, the extent of availability in individual subjects ranged between 58 and 124 per cent. Since the systemic clearance of benzydamine (160 ml min^{-1}) was not such as to suggest appreciable pre-systemic elimination of the drug, the lower systemic availability of benzydamine in some subjects may possibly reflect lower absorption from the gastrointestinal tract. Plasma concentrations of benzydamine and areas under the plasma benzydamine concentration–time relationships in female subjects after oral doses were similar to those obtained in males. Assuming drug clearance is not sex-related, it follows that most of the oral dose administered to female volunteers was also absorbed (ca. 90 per cent).

Estimates of the extent of bioavailability of benzydamine from mouthwash doses were low, with 5 per cent or less of the drug either absorbed through the buccal membrane or ingested. Using the oral dose as the reference, only 5·2 per cent of the dermally applied dose and 1·3 per cent of the vaginal douche dose administered to the female subjects were absorbed. These data show that systemic exposure to the drug is low when it is used by these routes.

Although not well absorbed through the skin, peak plasma concentrations of benzydamine after topical application occurred later than 24 h in five of the six female subjects, i.e. after the drug had been removed from the surface of the treated area. It would appear possible, therefore, that benzydamine penetrates and temporarily resides in the deeper dermal layers from whence it is slowly absorbed. Such a property would be useful in the treatment of soft tissue injury.

Plasma drug concentrations of benzydamine in female subjects after vaginal douche doses were 2–5 fold lower than even those after mouthwash doses to male subjects. Presumably most of the douche dose was removed by drainage, with drug entrapped in the vaginal and cervical regions absorbed through the mucosae. The data suggest that, generally, benzydamine is not well absorbed through the skin and non-specialized mucosae. This has the advantage of limit-

ing undesired systemic exposure to the drug, while allowing local therapeutic tissue exposure which is reported to be higher for topical application than after oral administration.[4–6] Evidently, opportunity will also exist for systemic absorption of benzydamine by inadvertent swallowing after mouthwash doses.

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