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Percutaneous absorption of phenylbutazone from ointment bases in rabbits

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Summary

A rapid, sensitive, accurate and reproducible assay procedure for the simultaneous separation and determination of phenylbutazone and oxyphenbutazone is proposed using reversed-phase, high-pressure liquid chromatography and UV detection. Acidified plasma (pH = 5) was extracted with cyclohexane–ether (1 : 1) and indomethacin was used as an internal standard. Plasma phenylbutazone levels after oral and intravenous drug administration were described by the two-compartment model. A pharmacokinetic model, similar to the percutaneous absorption of indomethacin, was developed to test concepts regarding the percutaneous absorption of phenylbutazone from topical ointment bases. A reasonably good agreement between experimental and calculated values was obtained by taking into account such factors as the absorption rate constant (k_a), the drug release rate constant (k_r) and the fraction of drug absorbed (F). The ointment bases selected for study were solution-type and suspension-type ointment bases. The good percutaneous absorption of phenylbutazone after the topical administration was obtained by using the absorption base.

The optimal effect with additives in the absorption ointment base was finally attained with the addition of 1% urea. The changes in site and size of application of the phenylbutazone ointment was also investigated and the following was found: dorsal site > abdominal site > thigh site. Increasing the size of the application area increased the percutaneous absorption of phenylbutazone.

Introduction

In previous studies (Naito and Tsai, 1981), the percutaneous absorption of indomethacin from ointment bases in rabbits was investigated, and the factors

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involved in the percutaneous absorption from the applied condition of the drug on the skin were clarified by measuring the amount of the drug in the plasma. Where the percutaneous absorption of indomethacin had an identical pharmacokinetic parameter, such as absorption rate constant (k_a) and drug release rate constant (k_r), and only fraction (F) of the indomethacin absorbed was changed by adding some additives to the total indomethacin in the ointment base. Recently, the topical administration of drugs has been tentatively studied as a delivery route to overcome the side-effects following an oral administration. Indeed, for certain drugs, percutaneous absorption produces comparable or better results than the oral administration in terms of clinical effectiveness (Reichek et al., 1974; Karsh et al., 1978). The anti-inflammatory and analgesic effects of phenylbutazone regarding oral administration are well known, but such side-effects as irritation of the gastrointestinal mucosa and production of erosion are easily provoked (Japanese Pharmacopoeia, 1981). The authors, therefore, attempted to design a phenylbutazone ointment and to obtain a clinical therapeutic purpose. However, the degree of percutaneous absorption is dependent primarily on physiologic factors of the skin and physical-chemical factors due to the penetrant and somewhat secondarily concerning the vehicle or formulation (Idson, 1975). The mechanisms of percutaneous absorption remain to be clarified.

It was the primary aim of this paper to examine the influence of the type of ointment bases, various additives and the change of the anatomical site of skin treated and the size of the application area regarding the percutaneous absorption of phenylbutazone in the rabbits. In addition, a pharmacokinetic model for elucidating the percutaneous absorption of phenylbutazone was developed.

Materials and Methods

Materials

The following reagents were used: indomethacin[1], phenylbutazone, oxyphenbutazone, cetyl alcohol, stearyl alcohol, propylene glycol [2], methyl alcohol, acetic acid, ethyl ether, sodium phosphate dibasic 12-hydrate, sodium citrate, sodium bicarbonate, urea, cyclohexane, Brij-35, salicylic acid [3], sodium lauryl sulfate, lecithin [4], simple ointment (Ch.P), hydrophilic ointment (Ch.P), macrogol ointment (Ch.P), white vaselin [5] (Ch.P), hydrophilic vaselin (J.P) [6], taurine and sorbitan sesquioleate [7].

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Phenylbutazone solution for intravenous administration

The phenylbutazone solution was prepared by dissolving 120 mg of the dry powder in 1 ml of distilled water containing 80 mg of sodium bicarbonate by heating at about 60°C and stirring for 2 h.

Suspension-type ointment

Phenylbutazone powder was incorporated into an ointment base representing each of the 4 physical types. The bases selected were: simple ointment (JPX), an oleaginous base; hydrophilic ointment (JPX), an oil-in-water base; absorption ointment (JPX), a water-in-oil base; and macrogol ointment (JPX), a water-soluble base. The phenylbutazone ointment was prepared so as to contain 5% of the active ingredient.

Solution-type ointment

The water phase of the absorption ointment base (6 g) was prepared by dissolving 300 mg of phenylbutazone in 2.27 ml of distilled water containing 200 mg of sodium bicarbonate, and an additive if necessary was then incorporated into it. The oil phase contained 33.3% white vaseline, 15% cetyl alcohol, 5% sorbitan sesquioleate and 0.5% Brij-35. The aqueous and oil phase were heated separately to about 75°C in a water bath, and the aqueous phase was added to the oil phase with appropriate stirring. After formation of an emulsion, the stirring was continued until the temperature of the ointment reached 30°C. Materials such as urea, taurine, salicylic acid and lecithin were used as additives.

The preparation of the phenylbutazone hydrophilic ointment solution-type followed the same method as that of the absorption ointment described above except for the oil phase. This contained 2.08% white vaseline, 18.3% stearyl alcohol, 10% propylene glycol and 1.6% sodium lauryl sulfate.

In vivo absorption study

White male rabbits weighing 1.8–2.2 kg were used and were made to fast for 24 h before the experiment, but water was given to them freely. Each group consisted of 5 rabbits for each experiment. For the topical administration, the hair of rabbits was removed 24 h prior to application of the ointment by electric hair clippers from the skin of the region used. An accurately weighed 6 g sample of the ointment was spread uniformly over a sheet of cloth. This was then applied to the shaved surface of the rabbit. Occlusive dressing techniques (ODT) were used to ensure adequate contact between the ointment and the skin. The cloth was covered with a thin plastic film and fastened with the aid of adhesive tape around the edges. However, in case ODT was not employed, the cloth was fastened only with the aid of adhesive tape around the edges. The composition, type and phenylbutazone concentration of various ointment bases are summarized in Table 1 along with its applied condition in the topical administration. The intravenous administration of phenylbutazone solution (30 mg/kg) was injected into an auricular vein of rabbits over a period of 15 s. In the case of oral administration, a dose of 75 mg/kg of phenylbutazone powder suspended in water was put into the stomach of the rabbits with a Nelaton

TABLE 1

COMPOSITION OF PHENYLBUTAZONE (PBZ) SOLUTION-TYPE OINTMENT AND ITS APPLIED CONDITION

Serial no.	Ointment base	Concentration of PBZ (%)	Quantity of PBZ applied (μmol/kg)	Additives	Applied area (cm^2)	Applied site
1	Simple *	5	486.43	None	60	Abdomen
2	Hydrophilic vaseline *	5	486.43	None	60	Abdomen
3	Hydrophilic *	5	486.43	None	60	Abdomen
4	Macrogol *	5	486.43	None	60	Abdomen
5	Hydrophilic	5	486.43	None	60	Abdomen
6	Absorptive	2.5	243.21	None	60	Abdomen
7	Absorptive	5	486.43	None	60	Abdomen
8	Absorptive	10	972.86	None	60	Abdomen
9	Absorptive	5	486.43	1% salicyclic acid	60	Abdomen
10	Absorptive	5	486.43	1% lecithin	60	Abdomen
11	Absorptive	5	486.43	1% taurine	60	Abdomen
12	Absorptive	5	486.43	0.5% urea	60	Abdomen
13	Absorptive	5	486.43	1% urea	60	Abdomen
14	Absorptive	5	486.43	2% urea	60	Abdomen
15	Absorptive	5	486.43	1% urea	30	Abdomen
16	Absorptive	5	486.43	1% urea	90	Abdomen
17	Absorptive	5	486.43	1% urea	60	Thigh
18	Absorptive	5	486.43	1% urea	60	Dorsal Surface
19	Absorptive	5	486.43	1% urea	60	Abdomen (without ODT)

* Suspension-type ointment.

Catheter No.10 tube. The inside of the tube was then rinsed 5 times with 5 ml of water.

All blood specimens were withdrawn from the carotid artery using heparinized syringes at designated intervals after the dosing. The blood samples were centrifuged at 300 rpm for 5 min. The plasma layer was taken into stoppered glass tubes and frozen until assays were carried out.

Analytical method

The concentrations of phenylbutazone and its metabolite, oxyphenbutazone, were measured simultaneously by modifying, the method described previously (Pound and Sears, 1975; Alvinerie, 1980). A 1-ml aliquot of the plasma sample was pipetted into a 15 ml glass-stoppered centrifuge tube, along with 1 ml of the Na_2HPO_4–citric acid buffer (pH = 5) and 50 μl of the indomethacin methanol solution (500 μg/ml) as the internal standard. The mixture was mixed for 10 s and extracted with 7 ml of a cyclohexane–ethylether (1 : 1, v/v) solvent by mechanical shaking for 20 min after centrifugation for 5 min at 3000 rpm, 5 ml of the organic layer was transferred to another tube and evaporated to dryness in a water bath at 37°C in vacuo. The residue was redissolved in 200 μl of methanol and 10 μl of this solution was injected into the HPLC column. From the ratio of the peak height of a drug to that of the internal standard, the concentration of the drug was routinely obtained. Analytical condition for HPLC: A Water Model 6000 A High-Pressure Liquid Chromatograph equipped with a UV detector, a U6K universal injector and μ-Bondapak C_{18} (3.9 mm i.d. × 30 cm) column was used. The mobile phase consisted of a methanol–0.05% acetic acid (65 : 35 v/v) mixture. The operating temperature was ambient, and the flow-rate was 1.5 ml/min. The column effluent was monitored continuously at 254 nm with a full-scale deflection of 0.2 aufs, and the chart speed of the recorder was maintained at 5 mm/min.

Results and Discussion

The linearity of chromatographic method was tested by injecting 10 μl volume of phenylbutazone (4–40 μg/ml) and oxyphenbutazone (4–40 μg/ml). The correlation coefficients of 0.9998 and 0.9997 were found for the linear relationship between the peak height ratio and amount of phenylbutazone and oxyphenbutazone, respectively.

The extractions of phenylbutazone and oxyphenbutazone with cyclohexane–ether (1 : 1) were pH dependent. As shown in Fig. 1, it was found that the recovery of phenylbutazone and oxyphenbutazone could be improved when the plasma was adjusted to pH 5 with a Na_2HPO_4–citric acid buffer solution. Identical curves were found for the extraction of phenylbutazone and oxyphenbutazone from plasma and an equal portion of deproteinized plasma in which 5 N HCl was previously added, incubated at 37°C for 2 h and adjusted to pH 7 with 5 N NaOH. This result suggests that the determination of the plasma levels of phenylbutazone and oxyphenbutazone shows concentration of free drug, respectively. The recovery and reproducibility are

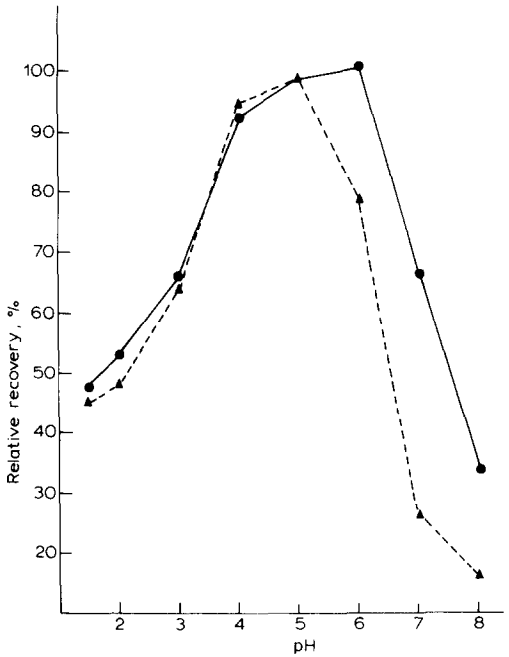


Fig. 1. effect of pH on the extraction of phenylbutazone and oxyphenbutazone from rabbit plasma. The pH of the plasma was adjusted by the addition of different McIlvaine buffers. Key: ●, phenylbutazone; ▲, oxyphenbutazone.

summarized in Table 2. The coefficient of variation (C.V.) for these results was less than 5% for all concentrations investigated.

It is well known that phenylbutazone rapidly metabolizes in the body and its

TABLE 2

ASSAY RECOVERY AND REPRODUCIBILITY

Compound	Concentration in rabbit plasma (μg/ml)	n	Concentration found (μg/ml)		
			Mean ± S.D.	range	CV (%)
Phenyl-butazone	4	4	4.31 ± 0.01	3.80–4.52	0.23
	8	4	7.82 ± 0.28	7.41–8.03	3.58
	16	4	15.89 ± 0.24	15.68–16.20	1.51
	24	4	23.94 ± 0.27	23.58–24.20	1.13
	32	4	31.59 ± 0.62	30.78–32.19	1.96
	40	4	40.37 ± 0.72	39.47–41.23	1.78
Oxyphen-butazone	4	4	4.18 ± 0.46	3.51–4.50	1.10
	8	4	7.90 ± 0.27	7.52–8.13	3.42
	16	4	16.04 ± 0.17	15.99–16.28	1.06
	24	4	23.78 ± 0.76	22.68–24.38	3.20
	32	4	31.62 ± 0.88	30.39–32.45	2.78
	40	4	40.33 ± 0.87	39.39–41.31	2.16

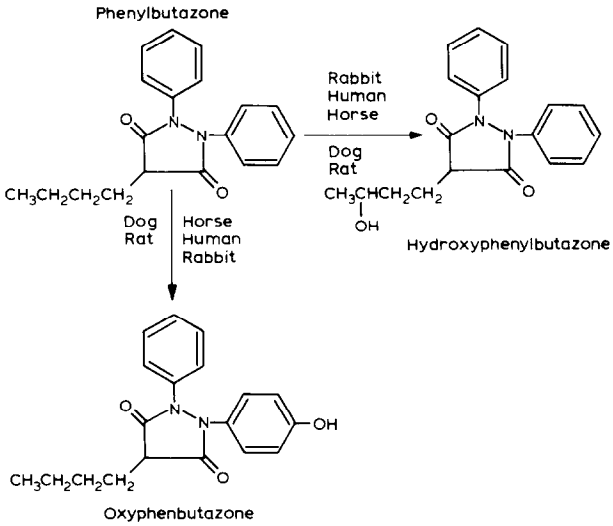


Fig. 2. Phenylbutazone metabolic pathway.

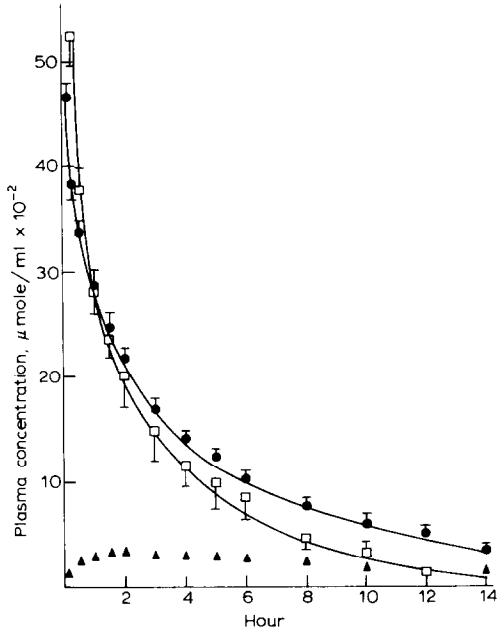


Fig. 3. Phenylbutazone (●) and its metabolite of oxyphenbutazone (▲) in rabbit plasma following intravenous administration of 97.286 μmol/kg of phenylbutazone and oxyphenbutazone (□) in rabbit plasma following intravenous administration of 92.487 μmol/kg of oxyphenbutazone. Solid line shows calculated curve for phenylbutazone from the equation $C_P = 0.2589e^{-0.953t} + 0.2296e^{-0.134t}$, and for oxyphenbutazone from the equation, $C_P = 0.5613e^{-1.93t} + 0.2901e^{-0.23t}$.

main metabolite, oxyphenbutazone, also has an anti-inflammatory activity (Japanese Pharmacopoeia, 1981). In order to investigate the relationship between phenylbutazone and its metabolites after administration through various routes, knowledge about their metabolic pathways is required. Fig. 2 shows which phenylbutazone and its main metabolites, oxyphenbutazone and hydroxyphenylbutazone have been found in the plasma of many species of animals (Bruce et al., 1974; Marunaka et al., 1980; Kaisetsusho for Japanese Pharmacopoeia, 1981).

Time courses for the concentration of phenylbutazone and its metabolites, oxyphenbutazone, and of oxyphenbutazone in the plasma of rabbits treated with 30 mg (97.286×10^{-3} mmol) of phenylbutazone/kg and 30 mg (92.487×10^{-3} mmol) of oxyphenbutazone/kg i.v. are given in Fig. 3, respectively. The plasma levels of phenylbutazone and oxyphenbutazone appear to be consistent with a two-compartment model, respectively. Table 3 summarizes the pharmacokinetic parameters obtained by using a conventional method. The parameters obtained indicated that the disposition of phenylbutazone in the plasma followed a first order process with an initial rapid phase lasting for up to 14 h after dosing. For a comparison of the bioavailability, an oral administration of phenylbutazone was carried out to determine whether phenylbutazone was well absorbed in rabbits with the maximum mean peak concentration in the plasma being reached within 3 h. The equation expressing the amount of oral absorption could be derived from the model shown in Scheme I in relation to the plasma–time data for phenylbutazone. The good agreements obtained for the calculated lines compared with the experimental data before the mean t_{max}, 3 h, suggest that the two-compartment model is sufficient to describe the disposition of phenylbutazone in rabbits (Fig. 4). The calculated line compared with the experimental data cannot fit after the mean t_{max}, because the

TABLE 3

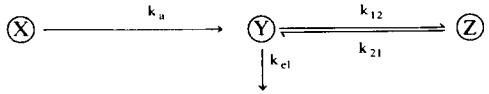
PHARMACOKINETIC PARAMETERS OF PHENYLBUTAZONE AND OXYPHENBUTAZONE (INTRAVENOUS ADMINISTRATION)

Parameter	Value	
	Phenylbutazone	Oxyphenbutazone
α (h^{-1})	0.95	1.93
β (h^{-1})	0.13	0.23
$t_{1/2\beta}$ (h)	5.18	3.02
k_{el} (h^{-1})	0.24	0.55
k_{12} (h^{-1})	0.32	0.80
k_{21} (h^{-1})	0.52	0.81
V_c (ml)	401	217
V_T (ml)	247	214

α and β are hybrid first-order rate constants and $t_{1/2\beta}$ is the half-life associated with the terminal exponential process; k_{el} = elimination rate constant from the central compartment; k_{12} = rate constant from the central to tissue compartment; k_{21} = rate constant from the tissue to central compartment; V_c = distribution volume of the central compartment; and V_T = distribution volume of the tissue compartment.

Scheme I. Mathematical model for oral administration of phenylbutazone

Drug in the G-I tract Drug in the plasma Drug in tissue



$$Y = Pe^{-\alpha t} + Qe^{-\beta t} + Re^{-k_a t}$$

$$P = \frac{k_a FD}{V_c}\left[\frac{(k_{21} - \alpha)}{(k_a - \alpha)(\beta - \alpha)}\right]$$

$$Q = \frac{k_a FD}{V_c}\left[\frac{(k_{21} - \beta)}{(k_a - \beta)(\alpha - \beta)}\right]$$

$$R = \frac{k_a FD}{V_c}\left[\frac{(k_{21} - k_a)}{(\alpha - k_a)(\beta - k_a)}\right]$$

Y, drug concentration in plasma; D, oral dose; F, fraction of drug absorbed to oral dose, equal to 0.041; k_a, absorption rate constant, equal to $0.28h^{-1}$; α, β, k_{12}, k_{21}, k_{el} and V_c, pharmacokinetic parameters.

phenylbutazone metabolizes simultaneously to oxyphenbutazone and hydroxyphenylbutazone in the rabbits and many factors had an effect on the elimination rate constant from the central compartment.

In order to explain the plasma–time data for phenylbutazone after the topical administration, in the previous studies (Naito and Tsai, 1981), the pharmacokinetic

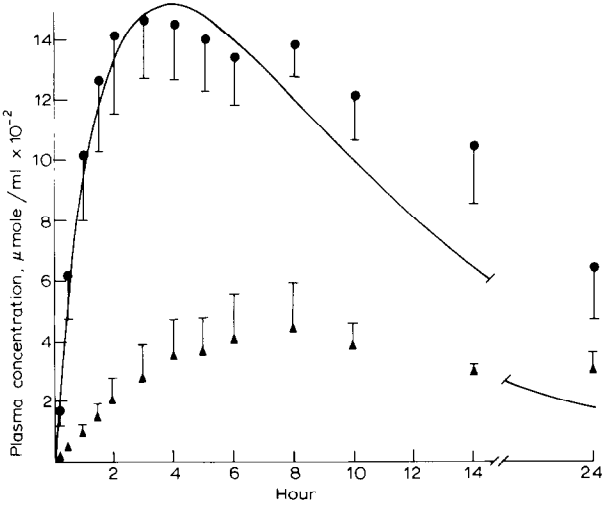
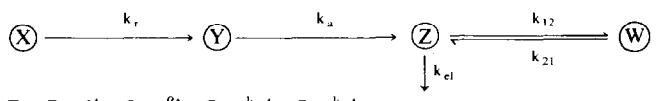


Fig. 4. Plasma concentration time curve of phenylbutazone and its metabolite of oxyphenbutazone following single oral dose of 243.21 μmol/kg of phenylbutazone. Key: ●, phenylbutazone; ▲, oxyphenbutazone. Solid line shows calculated curve obtained from the equation in Scheme I. Each point represents the mean of 5 rabbits with the standard error.

Scheme II. Phermacokinetic model for percutaneous absorption of phenylbutazone



$$Z = Pe^{-\alpha t} + Qe^{-\beta t} + Re^{-k_r t} + Se^{-k_a t} \quad (1)$$

$$P = \frac{k_r k_a FD}{V_c}\left[\frac{(k_{21}-\alpha)}{(\beta-\alpha)(k_r-\alpha)(k_a-\alpha)}\right]$$

$$Q = \frac{k_r k_a FD}{V_c}\left[\frac{(k_{21}-\beta)}{(\alpha-\beta)(k_r-\beta)(k_a-\beta)}\right]$$

$$R = \frac{K_r k_a FD}{V_c}\left[\frac{(k_{21}-k_r)}{(\alpha-k_r)(\beta-k_r)(k_a-k_r)}\right]$$

$$S = \frac{k_r k_a FD}{V_c}\left[\frac{(k_{21}-k_a)}{(\alpha-k_a)(\beta-k_a)(k_r-k_a)}\right]$$

Z, drug concentration in plasma; D, topical dose; F, fraction of drug absorbed to topical dose; k_a, absorption rate constant; k_r, drug release rate constant; α, β, k_{12}, k_{21}, k_{el} and V_c, pharmacokinetic parameters.

model for determining the plasma concentration of indomethacin after the topical administration was applied and is shown as Scheme II. All the curves for percutaneous absorption were calculated from Eqn. 1 of Scheme II.

The phenylbutazone and its metabolite, oxyphenbutazone, in rabbit plasma were found after the intravenous, oral and topical administration. Where the indomethacin and its metabolites, N-deschlorobenzoylindometacin and O-desmethylindomethacin, were found only after the intravenous administration. (Tsai and Naito, 1982). In general, the equation of Michaelis-Menten was used to explain the relationship between the drug and its metabolites. When the metabolizing rate (k_m) was constant, however, the plasma concentration time curves for oxyphenbutazone were not similar to each other after intravenous, oral and topical administrations of phenylbutazone. In the intravenous administration, the oxyphenbutazone curve rose rapidly in the initial stage. However, that curve rose slowly in the oral and topical administrations. The metabolizing rate of phenylbutazone to oxyphenbutazone was not constant in the various administration routes so that the metabolic mechanism of phenylbutazone was not explained by the Michaelis-Menten hypothesis (Levy, 1965; Levy, 1966). The relationship between phenylbutazone and its metabolites, oxyphenbutazone, was compared by the AUC after the oral and topical administrations (Table 4). The percents of the AUC ratio of oxyphenbutazone to phenylbutazone plus oxyphenbutazone were found to be from 11.3% to 26.5% for the topical administration of the 19 selected phenylbutazone ointments containing 2.5–10% of the drug in the six ointment bases, 23.7% for the oral administration and

TABLE 4

PHARMACOKINETIC PARAMETER ON PERCUTANEOUS ABSORPTION FROM PHENYLBUTAZONE OINTMENT

Serial no.	F	k_a	k_r	AUC of phenylbutazone * (μmol·h/ml)$\times 10^{-3}$	AUC of oxyphenbutazone * (μmol·h/ml)$\times 10^{-3}$	Ratio (%) **
1	0.014	0.072	0.2	118.52 ± 29.39	26.90 ± 4.23	18.50
2	0.029	0.072	0.3	256.64 ± 20.22	56.11 ± 6.35	17.9
3	0.009	0.072	0.2	73.52 ± 30.89	16.98 ± 2.14	18.76
4	0	0	0	0	0	0
5	0.989	0.07	0.02	2702.06 ± 330.45	646.43 ± 89.61	19.3
6	0.338	0.072	0.07	177.44 ± 92.18	29.95 ± 5.27	14.4
7	0.577	0.06	0.09	3380.00 ± 747.71	832.23 ± 101.36	19.8
8	0.474	0.05	0.25	2087.30 ± 601.45	264.92 ± 83.06	11.3
9	0.577	0.072	0.03	786.97 ± 357.18	198.13 ± 38.92	20.1
10	0.196	0.072	0.03	766.16 ± 299.91	240.53 ± 70.26	23.9
11	0.989	0.04	0.02	2165.13 ± 704.40	326.82 ± 103.51	13.1
12	0.577	0.04	0.02	1162.11 ± 413.63	325.74 ± 99.28	21.9
13	0.908	0.06	0.04	3710.56 ± 583.03	619.73 ± 77.61	14.3
14	0.338	0.072	0.03	669.15 ± 221.78	89.87 ± 25.40	11.8
15	0.577	0.08	0.06	3165.32 ± 679.18	685.17 ± 136.58	17.8
16	0.742	0.08	0.1	5175.91 ± 894.69	1133.57 ± 225.96	18.0
17	0.495	0.08	0.04	2324.77 ± 577.95	821.60 ± 127.11	26.1
18	0.536	0.10	0.12	4109.51 ± 433.15	783.84 ± 69.82	16.0
19	0.618	0.06	0.09	3297.13 ± 636.52	1186.83 ± 80.61	26.5
i.v.				1688.06 ± 150.90	309.74 ± 30.18	15.5
p.o.				2583.48 ± 408.97	800.87 ± 170.26	23.7

* Obtained by the trapezoidal rule technique.

** Ratio is AUC of oxyphenbutazone/AUC of phenylbutazone + AUC of oxyphenbutazone.

k_a, absorption rate constant; k_r, drug release rate constant; F, fraction of drug absorbed to the total drug in the ointment base.

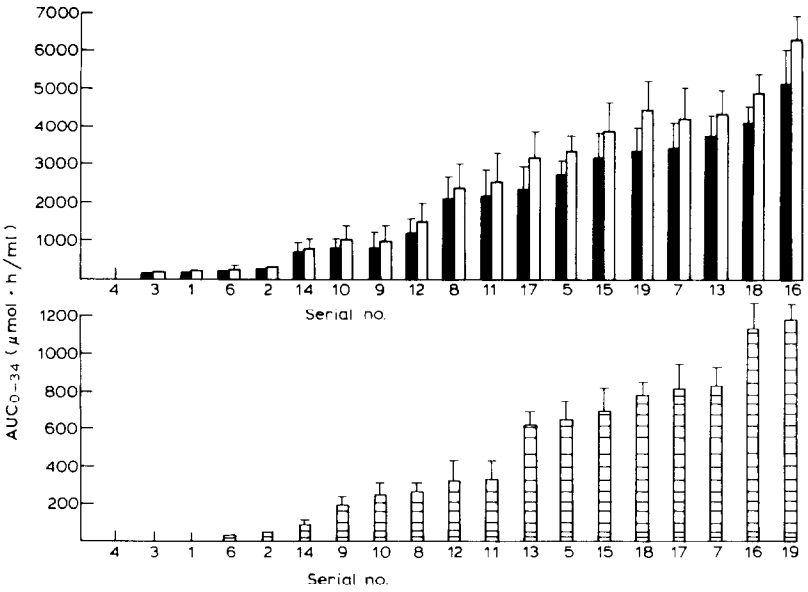


Fig. 5. AUC_{0-34} of phenylbutazone, oxyphenbutazone and total of phenylbutazone plus oxyphenbutazone after topical administration of 19 phenylbutazone ointment. Key: ■, phenylbutazone; ▥, oxyphenbutazone; □, phenylbutazone plus oxyphenbutazone.

15.5% for the intravenous administration. This result obtained indicated that these ratios for the oral and intravenous administrations were found in the range of that for the topical administration. Fig. 5 shows the comparisons of the AUC of phenylbutazone and oxyphenbutazone for the topical administration of the 19 selected phenylbutazone ointments. Serial No. 16 showed the most percutaneous absorption in the 19 selected bases by comparison with the AUC of phenylbutazone and phenylbutazone plus oxyphenbutazone, respectively. However, the AUC of oxyphenbutazone was the highest for serial No. 19, followed by serial No. 16.

Fig. 6 shows the type of ointment base selected to investigate the variations in the percutaneous absorption of phenylbutazone. The solution-type absorption ointment base was found to yield the highest plasma concentration of phenylbutazone compared to the hydrophilic ointment and other suspension-type ointment bases. This phenomenon indicates that the ionized form of phenylbutazone can penetrate the skin and appears similar to the percutaneous absorption of indomethacin (Naito and Tsai, 1981). The solubility of phenylbutazone in a simple ointment, hydrophilic ointment and hydrophilic vaseline was so little that the percutaneous absorption of phenylbutazone was small. However, phenylbutazone that can be readily dissolve in the macrogol ointment base was found to be so strong that drug release was difficult through the vehicle to the skin (Washitake et al., 1975).

Fig. 7 shows the effects of various additives on the percutaneous absorption of phenylbutazone from the absorption ointment base. In this series of experiments on the enhancement of the percutaneous absorption of phenylbutazone by additives,

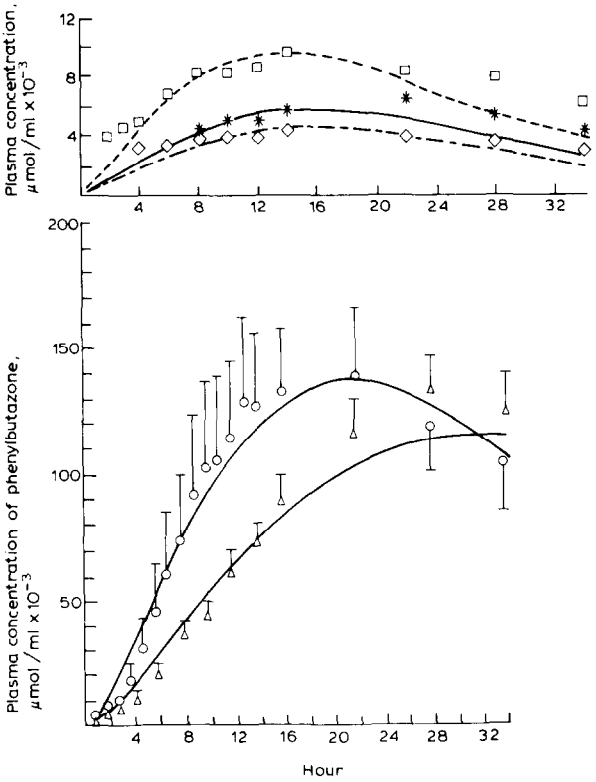


Fig. 6. Effect of type of ointment base on the percutaneous absorption of phenylbutazone. Key: solution-type ointment — ○——○, absorption ointment; △——△, hydrophilic ointment; suspension-type ointment — □·····□, hydrophilic vaseline; ◇-·-◇, simple ointment; *——*, hydrophilic ointment; ○, macrogol ointment. All curves (solid and broken lines) for phenylbutazone were calculated from Eqn. 1 of Scheme II.

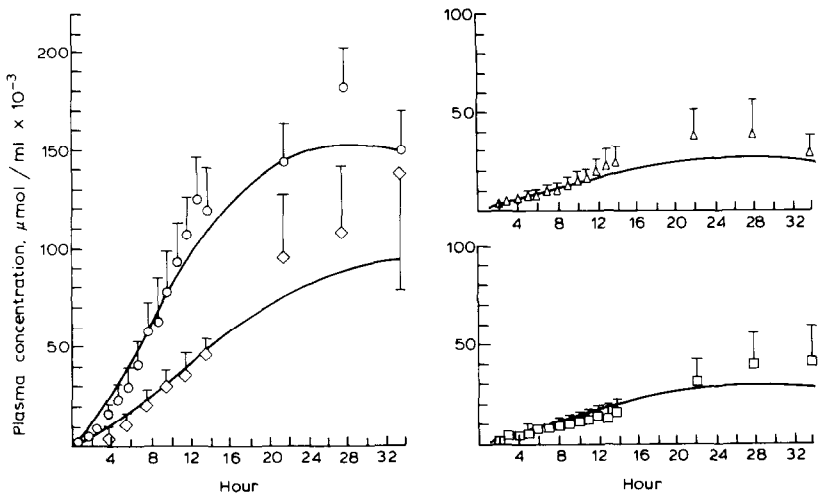


Fig. 7. Effect of various additives on the percutaneous absorption of phenylbutazone from absorption ointment base. Key: ○——○, 1% urea; ◇——◇, 1% taurine; □——□, 1% lecithin; △——△, 1% salicylic acid. All curves (solid and broken lines) for phenylbutazone were calculated from Eqn. 1 of Scheme II.

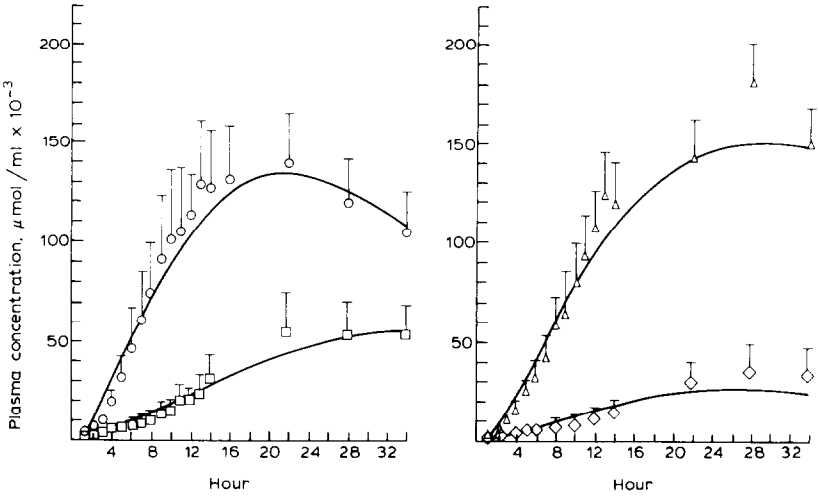


Fig. 8. Effect of various urea concentration on the percutaneous absorption of phenylbutazone from absorption ointment base. Key: ○———○, 0%; □———□, 0.5%; △———△, 1%; ◇———◇, 2%. All curves (solid and broken lines) for phenylbutazone were calculated from Eqn. 1 of Scheme II.

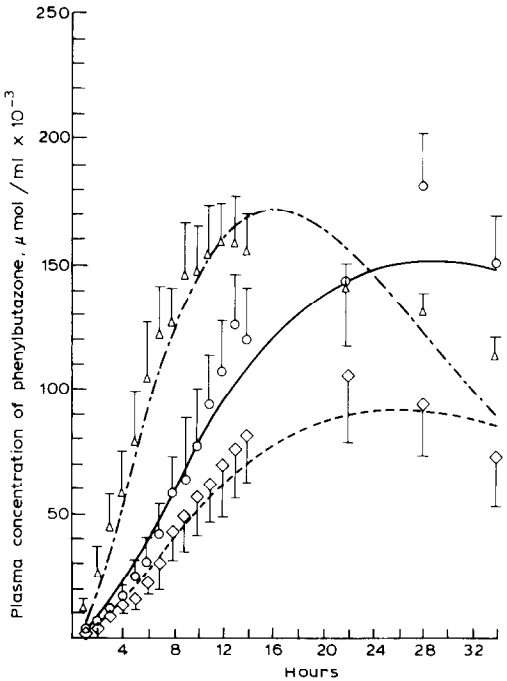


Fig. 9. Effect of treated skin site (60 cm^2) on the percutaneous absorption of phenylbutazone from absorption ointment base containing 1% urea. Key: △- · -△, dorsal surface; ○———○, abdomen; ◇· · · · · ·◇, thigh. All curves (solid and broken lines) for phenylbutazone were calculated from Eqn. 1 of Scheme II.

the changes in the plasma concentration were influenced by all the additives tested. Urea was found to be the only accelerant.

Fig. 8 shows the effects of various urea concentrations on the percutaneous absorption of phenylbutazone from the absorption ointment. The result obtained indicated that the presence of urea in the absorption ointment base may increase, decrease or exert no effect on the extent of the absorption of phenylbutazone. A marked increase in drug absorption occurred at a concentration of 1% urea.

The effects on the site of treated skin regarding the percutaneous absorption of phenylbutazone in rabbits were studied using an absorption ointment base containing 1% urea. The results of these experiments are summarized in Fig. 9. Application of phenylbutazone absorption ointment to the shaved dorsal surface showed rapid drug absorption into the systemic circulation. The present data suggest the presence of a site dependence for the topical absorption of phenylbutazone in rabbits (i.e. dorsal surface > abdomen > thigh). The relationships between plasma concentration–time curve of phenylbutazone and changes in the size of the application area in the abdomen are shown in Fig. 10. Increasing the size of the skin surface area increased the percutaneous absorption of phenylbutazone (Tsai and Naito, 1982).

The effect, with or without ODT, on the percutaneous absorption of phenylbutazone is illustrated in Fig. 11. The results indicate that the percutaneous absorption

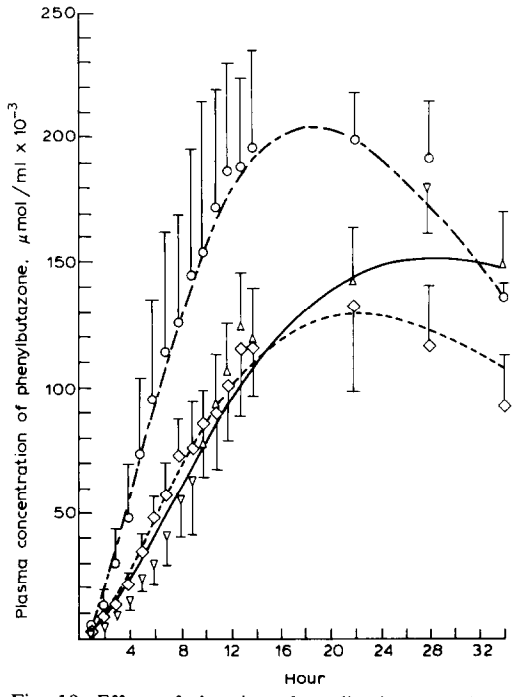


Fig. 10. Effect of the size of application area in the abdomen on the percutaneous absorption of phenylbutazone from absorption ointment base containing 1% urea. Key: O–··–O, 90 cm^2; △———△, 60 cm^2; ◇·····◇, 30 cm^2. All curves (solid and broken lines) for phenylbutazone were calculated from Eqn. 1 of Scheme II.

was scarcely affected by ODT and was a little greater than that obtained without ODT. This phenomenon is different from the percutaneous absorption of the indomethacin ointment. In the previous investigation, the percutaneous absorption of indomethacin depended upon the F-value. However, in the present investigation as shown in Table 4, all the calculated curves have almost similar pharmacokinetic parameters as k_a (absorption rate constant, 0.04–0.1), and changes by k_r (drug release rate constant) and F (fraction of drug absorbed to topical dose). The variation of k_r from 0.03 to 0.3 in the present series of experiments does not demonstrate a different formulation for the phenylbutazone ointment. However, the solution-type phenylbutazone ointment has a higher F-value than that of suspension-type. It was shown that the suspension-type phenylbutazone ointment was apparently not releasing a large enough quantity of its dose immediately. All the curves for the percutaneous absorption were calculated from Eqn. 1 of Scheme II. The calculated lines were in agreement with the experimental data in the plasma concentration of phenylbutazone following the topical administration of all the phenylbutazone ointments in the study. The results suggest that both the release and absorption rate were first-order processes at the dosage levels studied.

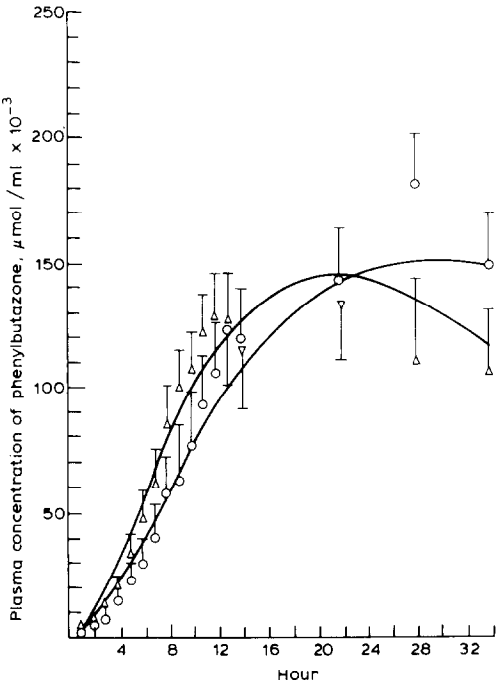


Fig. 11. Effects of with or without occlusive dressing technique (ODT) on the percutaneous absorption of phenylbutazone from absorption ointment containing 1% urea. Key: ○——○, with ODT; △——△, without ODT. All curves (solid and broken lines) for phenylbutazone were calculated from Eqn. 1 of Scheme II.

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