Effect of Water Deprivation on Aspirin Disposition Kinetics

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Abstract □ Temporary water deprivation results in serious stress causing significant physiological, hormonal, and enzymatic changes in the body which can affect the disposition kinetics, toxicity, and activity of drugs. This study attempts to recognize the effect of water deprivation on drug disposition kinetics using aspirin. No significant effects were noted following 36-hr water deprivation in rats on the metabolism of aspirin; there was also no effect of heparinization on aspirin disposition kinetics. The disposition of salicylic acid, however, was altered significantly, with the half-life increased by ~72% concomitant with decreased total body clearance. The effect of two dose levels, 5 and 10 mg/kg, was also studied to elucidate nonlinearity in the disposition kinetic model. Almost complete urinary recovery of aspirin was obtained in the intact form or as metabolites. At the 10-mg/kg dose, the fraction of salicyluric acid excreted decreased significantly compared with the 5-mg/kg dose. However, the effect of water deprivation was uniform at the two dose levels without any effect on the excretion of salicyluric acid. It is suggested that, in view of the significant changes in the disposition characteristics of salicylates with water deprivation, due care must be exercised in adjusting doses giving proper consideration to body hydration levels.

Keyphrases □ Aspirin—disposition kinetics in rats, effect of water deprivation on metabolism □ Kinetics—aspirin metabolism, rats, effect of water deprivation □ Metabolism—of aspirin, effect of water deprivation in rats, kinetics

Dehydration in the body occurs due to circumstantial water deprivation, excessive sweating, and various disease states such as polyuria and diarrhea. A number of physiological and biochemical changes have been attributed to the short-term stress of water deprivation; these can significantly modify the disposition of drugs in the body.

The most prominent manifestations of water deprivation are loss of body weight and decrease of both blood and plasma volumes (1–6). This results in increased plasma osmotic pressure, plasma protein concentration, and hematocrit, while the pH and the acid–base status of blood remain essentially constant (1–10). The volume of the urine and the amount of electrolytes excreted in the urine also decrease significantly in water-deprived rats (5), with corresponding morphological and histochemical changes in the renal medulla (11).

The effects of starvation and nutrition on the drug-metabolizing enzymes of liver microsomes have been extensively investigated (12–22), but kinetic studies of drug disposition with short- and long-term water deprivation in humans or animals are almost nonexistent. Some empirical data exist indicating that water deprivation may influence the pharmacological effect of some drugs (23–27).

The fate and pharmacokinetics of aspirin (acetylsalicylic acid) and salicylic acid in human and animals have been extensively investigated (28–34). However, specific *in vivo* data on aspirin metabolism by rats and other common laboratory animals are lacking. The desert rodents, hopping mice (*Notomys alexis*, Family: Muridae), conserve body water with extreme economy and show high papillary-to-cortex ratios of salicylates along with longer biological half-lives of salicylates (100–120 min) when compared with nondesert mice (55 min). Also, only 9% of the salicylate in desert mice is metabolized to salicyluric acid, compared with 80% in humans and 50% in rats (35, 36). Thus water economy and species differences determine the biological half-life of circulatory salicylate and the nature and extent of its metabolites.

The primary purpose of this study was to investigate the effect of a 36-hr water deprivation on the disposition kinetics of aspirin. Aspirin was selected as a model drug because of its extensive protein binding, several pathways for metabolism and excretion, variable dose-dependent disposition, and clinical importance. Since *in vivo* heparinization of the circulatory system was done to facilitate the withdrawing and handling of blood samples from the rats, the effect of heparin on the pharmacokinetics of aspirin was also investigated.

EXPERIMENTAL

Animal Preparation—Male rats[1] weighing between 300 and 450 g were used. The rats were housed in individual cages[2] and allowed to become accustomed to the laboratory conditions for at least 7 days. The rats were cannulated in the right jugular vein as described in the previous paper (37) at least 3 days before the pharmacokinetic study began, thus allowing sufficient time for recovery from the surgery. The cannula was kept patent by flushing with heparinized (20 U/ml) sterile normal saline for injection[3] twice a day. Each study group was comprised of six rats, selected randomly.

For the treatment group of rats, water deprivation started at 7:00 pm, and the drug was given 36 hr later. During this 36-hr water deprivation, the rats had access to food all the time. The rats were weighed prior to the administration of aspirin to calculate the proper dose; they were also weighed before and after water deprivation to calculate the percent weight loss.

Preparation and Administration of the Aspirin Dose—One gram of aspirin was dissolved in 20 ml of polyethylene glycol 400[4] with constant shaking and diluted with sterile normal saline for injection to 100 ml, so that the final concentration of aspirin in the solution was 10 mg/ml. The resultant solution was passed through a sterile 0.22-μm filter for the removal of any particles or microorganisms. Each solution was freshly prepared due to the instability of aspirin in solution (38).

The sterilized, particle-free solution was aspirated into a 1-ml disposable hypodermic syringe[5], and the dose was administered intravenously through the jugular vein cannula. The dead volume in the cannula was flushed immediately with ~0.2 ml of heparinized (50 U/ml) sterile normal saline. When the effect of heparin on the pharmacokinetics of aspirin was studied, the cannulas of the control (nonheparinized) rats were flushed with sterile normal saline instead of heparinized normal saline.

Collection of Blood and Plasma Samples—For the pharmacokinetic study of intact aspirin, 200 μl of blood was collected in a 1-ml syringe containing 400 μl of acetonitrile[6] prior to the administration of the dose. The contents of the syringe were mixed gently, and this mixture served

[1] Sprague–Dawley strain, King Animals, Madison, Wis.
[2] Nalgene Metabolic Cage, Nage Co., Rochester, N.Y.
[3] Abbott Laboratories, North Chicago, Ill.
[4] BASF, Wyandotte, Mich.
[5] Becton, Dickinson and Co., Rutherford, N.J.
[6] Burdick and Jackson Laboratories, Muskegon, Mich.

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Table I—Effects of Heparin on the Disposition Kinetics (Single Compartment) of Salicylic Acid in Rats [a]

Parameter	Control Rats[b] Mean ± *SEM*	Control Rats[b] Range	Heparinized Rats[b] Mean ± *SEM*	Heparinized Rats[b] Range
Body weight, g	363.0 ± 9.0	327.0–434.0	359.0 ± 10.0	332.0–426.0
Half-life, hr	2.38 ± 0.11	1.62–2.82	2.36 ± 0.15	1.63–3.05
Volume of distribution (V_d), ml/kg	146.8 ± 5.6	124.0–189.0	138.0 ± 6.0	106.0–176.0
Total body clearance, ml/kg·hr	45.4 ± 2.4	33.9–61.1	41.0 ± 2.4	26.6–52.1
AUC, μg·hr/ml	227.3 ± 11.1	162.8–290.3	244.3 ± 15.9	187.7–337.8

[a] Salicylic acid dose = 10 mg/kg; $n = 6$. [b] Rats received 0.3 ml of physiological normal saline (control) or physiological normal saline containing 6 U of heparin (treatment) as a replacement for each 0.3-ml blood sample drawn.

Table II—Effects of Water Deprivation on the Disposition Kinetics (*In Vivo* Hydrolysis) of Aspirin in Rats [a]

Parameter	Control Rats[b] Mean ± *SEM*	Control Rats[b] Range	Water-Deprived Rats[c] Mean ± *SEM*	Water-Deprived Rats[c] Range
Body weight, g	325.0 ± 20.0	285.0–420.0	350.0 ± 6.0	328.0–361.0
Half-life, min	1.8 ± 0.4	0.8–3.2	2.0 ± 0.4	1.6–3.9
Volume of distribution (V_d), ml/kg	994.0 ± 95.0	714.0–1285.0	794.0 ± 43.0	644.0–939.0
Total body clearance, ml/kg·min	465.0 ± 96.0	166.0–736.0	299.0 ± 29.0	166.0–364.0
AUC, μg·min/ml	31.0 ± 8.6	13.9–68.8	37.6 ± 5.5	27.3–64.4

[a] Aspirin dose = 10 mg/kg; $n = 6$. [b] Rats received food and water *ad libitum*. [c] Rats were deprived of water for 36 hr, but received food *ad libitum*.

as the blank. After administering aspirin intravenously through the jugular vein cannula, blood samples were collected every 1 min for 5 min and then every 2 min for another 6–10 min.

For the pharmacokinetic study of salicylic acid in the rats, ~200- to 300-μl blood samples were collected every 15 min for the first hour after the administration of the intravenous dose, every 30 min for the next 2 hr, and then every hour for the next 4 hr. Thereafter, blood samples were collected every 2 hr for another 4–6 hr. The volume of each blood sample collected from the rat was replaced with an equal volume of heparinized (50 U/ml) sterile normal saline.

When the effect of heparin itself on the pharmacokinetics of salicylic acid was investigated, the blood samples for the control (nonheparinized) group of rats were replaced with sterile normal saline rather than heparinized normal saline. Blood samples were collected from each rat for each pharmacokinetic study before administering the aspirin dose and were used as blanks.

Collection of Urine Samples—Rats were placed in metabolism cages, which allowed the collection of urine and feces in separated receptacles that could be removed without disturbing the animal. The urine deposited in the receptacle was collected every 12 hr, pooled, and stored in the refrigerator. The pooled urine was analyzed within 24 hr after the end of the collection. Urine samples from control rats (receiving food and water *ad libitum*) were collected for a total of 48 hr; samples for water-deprived rats were collected for 60 hr. The volume of the pooled urine and its pH were measured at the end of collection. Urine samples were also collected from each rat prior to the administration of aspirin; these samples served as blanks.

Analytical Procedure—*Blood*—The blood–acetonitrile (1:2) mixture was transferred to a 500-μl polypropylene microcentrifuge tube and centrifuged[7] for 5 min at 15,000 rpm. Twenty microliters of the supernatant was analyzed by the high-performance liquid chromatographic (HPLC) method described previously (39).

Plasma—Blood samples collected in the syringe were transferred to 250-μl polyethylene microcentrifuge tubes and centrifuged for 2 min at 15,000 rpm to separate the plasma from the cellular fraction. Aliquots of the separated plasma layer (100 μl) were transferred to a 500-μl polypropylene microcentrifuge tube and precipitated with 200 μl of acetonitrile. The mixture was vortexed for 30 sec, then centrifuged for 8 min (15,000 rpm). Twenty microliters of the supernatant was analyzed using the HPLC method described previously (39).

Urine—The refrigerated pooled urine was warmed to room temperature and mixed by shaking. A portion of the mixture was clarified by centrifugation for 10 min at 2500 rpm. One milliliter of the clarified urine was acidified with 0.5 ml of 6 *N* HCl[8] and extracted with 6 ml of ether[9]. Five milliliters of the ether extract were re-extracted with 1 ml of phosphate buffer (0.1 *M*, pH 7.0), and 20 μl of the buffer extract was analyzed by HPLC (39). The urine samples were prepared in duplicate, and each sample was chromatographed twice so that each analytical value reported was an average of four determinations.

[7] Eppendorf Microcentrifuge Model 5412, Brinkmann Instruments, Westbury, N.Y.
[8] J. T. Baker Chemicals Co., Phillipsburg, N.J.
[9] Mallinckrodt, St. Louis, Mo.

RESULTS AND DISCUSSION

Effect of Heparin on the Pharmacokinetics of Salicylic Acid—Table I lists the pharmacokinetic data for the 22 rats (11 rats in each group) used to study the effect of heparin on the disposition of salicylic acid administered intravenously as a solution of sodium salicylate. The elimination of salicylate by the body was described by first-order kinetics, as is evident from the excellent linear correlation coefficients obtained for each of the pharmacokinetic studies. Figure 1 shows the disposition kinetics of salicylic acid in two representative rats, one from the heparinized and the other from the nonheparinized groups of rats. No statistical significance was observed in the disposition kinetic data between the two study groups.

Similar findings were made at much higher doses of heparin (500–1000 U/kg). This finding is important since heparin decreases plasma protein binding of neutral and basic drugs and increases the binding of acidic drugs (40), except for salicylates where a decreased binding is noted at a 500-U/kg dose (41). The present finding suggests that the decrease in plasma protein binding of salicylate, as observed by Weigand and Levy (41), will not affect the disposition characteristics of salicylic acid.

Disposition of Aspirin in Control and Water-Deprived Rats—Table II lists the disposition kinetic parameters for aspirin after an in-

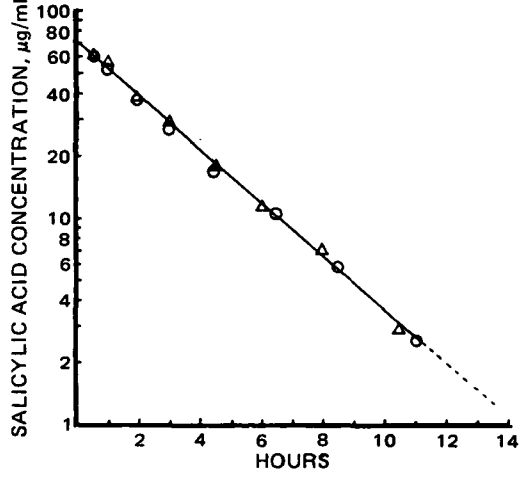

Figure 1—*Typical first-order plots for salicylic acid concentration in plasma* versus *time, after an intravenous dose of 10 mg of aspirin/kg of body weight in rats. Key: (○) control rats, 0.3 ml blood samples were replaced by 0.3 ml sterile normal saline; (△) heparinized rats, 0.3 ml blood samples were replaced by 0.3 ml sterile normal saline containing ~ 6 U of heparin.*

Table III—Effects of Water Deprivation on the Disposition Kinetics of Intravenously Administered Aspirin in Rats [a]

Parameter	Control Rats[b]		Water-Deprived Rats[c]	
	Mean ± *SEM*	Range	Mean ± *SEM*	Range
Body weight, g	393.0 ± 9.0	353.0–422.0	337.0 ± 13.0	270.0–381.0
Half-life, hr	2.1 ± 0.09	1.71–2.44	3.62 ± 0.41	2.39–5.81
Volume of distribution (V_d), ml/kg	176.3 ± 21.9	135.2–326.4	179.4 ± 5.6	160.4–205.5
Total body clearance, ml/kg·hr	50.7 ± 3.3	41.2–70.3	37.0 ± 3.6	24.5–50.9
AUC, μg·hr/ml	101.9 ± 6.2	66.5–121.7	166.4 ± 21.5	93.1–257.6

[a] Aspirin dose = 5 mg/kg; n = 6. [b] Rats received food and water *ad libitum*. [c] Rats were deprived of water for 36 hr, but received food *ad libitum*.

Table IV—Effects of Water Deprivation on the Disposition Kinetics of Salicylate in Rats [a]

Parameter	Control Rats[b]		Water-Deprived Rats[c]	
	Mean ± *SEM*	Range	Mean ± *SEM*	Range
Body weight, g	373.0 ± 6.0	341.0–405.0	374.0 ± 8.0	342.0–410.0
Half-life, hr	2.59 ± 0.15	1.86–3.22	4.37 ± 0.46	2.98–7.07
Volume of distribution (V_d), ml/kg	175.7 ± 7.0	141.0–196.1	178.2 ± 9.1	137.1–232.9
Total body clearance, ml/kg·hr	47.5 ± 1.5	40.8–52.7	30.1 ± 2.7	20.7–44.7
AUC, μg·hr/ml	207.4 ± 13.9	143.3–243.6	369.1 ± 38.9	235.3–555.8

[a] Salicylate dose = 10 mg/kg; n = 6. [b] Rats received food and water *ad libitum*. [c] Rats were deprived of water for 36 hr, but received food *ad libitum*.

travenous dose of 10 mg/kg of body weight in two groups of rats: a control group which had free access to food and water and a 36-hr water-deprived (treatment) group which had free access to food only. Figure 2 shows the first-order disposition kinetics of of aspirin in two rats which represent the control and treatment groups. The disposition constants for aspirin in the control group of rats were not statistically significant ($p < 0.05$) compared with the treatment group.

Therefore, in short-term water deprivation, the activity of the aryl esterases in blood and other organs, such as liver and kidneys, is not significantly altered. Based on the volume of distribution, the contribution of blood to the clearance of aspirin in rats is insignificant (<1%) compared with humans (~20%), despite the fact that the hydrolysis of aspirin in rat blood is faster than in human blood ($t_{1/2}$ = 30 and 12 min, respectively).

Disposition of Salicylic Acid in Control and Water-Deprived Rats—Since no detectable level of aspirin in the blood is found after 10 min following intravenous administration of aspirin, the blood samples collected 15 min after the administration of the intravenous dose and all subsequent sampling times represent the disposition kinetic study of salicylic acid. The two dose levels of aspirin (5 and 10 mg/kg) were selected to study the linearity of kinetics and the effect of dose on the disposition of salicylic acid both in the control and treatment groups.

Figure 3 shows the disposition of salicylic acid after an intravenous 5-mg/kg dose of aspirin in typical control and treatment rats. The disposition kinetics follow a first-order process (Table III). The time zero concentrations of salicylic acid in plasma were similar in both control and treatment rats (30.2 and 31.6 μg/ml, respectively). This implies that short-term water deprivation has little effect on the volume of distribution of salicylic acid.

Although the volume of distribution in both groups of rats was essentially the same (176 and 179 ml/kg), the biological half-life of salicylic acid in the treatment group of rats was 72% higher than the half-life in the control group. This increase in biological half-life is also reflected in the higher value of area under the curve (AUC) (166 *versus* 102 μg·hr/ml) and lower total body clearance (37 *versus* 51 ml/kg/hr).

The results obtained after the administration of a 10-mg/kg aspirin dose in control and treatment rats are listed in Table IV. The typical first-order plots for the disposition of salicylic acid are shown in Fig. 4. The disposition of salicylic acid at this dose level also follows apparent first-order kinetics in rats.

The biological half-life of salicylic acid in 36-hr water-deprived rats was ~70% higher (4.37 *versus* 2.59 hr) than in control rats, although the volume of distribution in both groups was essentially the same (176 and 178 ml/kg). The higher biological half-life of salicylic acid in treatment rats is consistent with the observed lower value (37%) of total body clearance (30.1 *versus* 47.5 ml/kg/hr) and higher value (78%) of the AUC (369.1 *versus* 207.4 μg·hr/ml).

The overall results for the two dose levels suggest that the biological half-life of salicylic acid in both groups of rats increases significantly (p

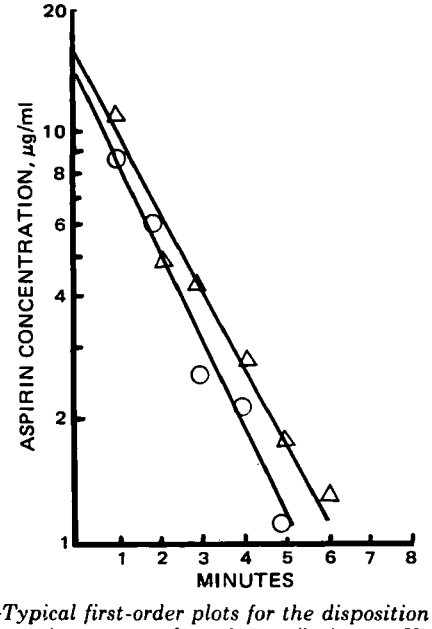

Figure 2—*Typical first-order plots for the disposition of aspirin in plasma after an intravenous dose of 10 mg/kg in rats. Key: (○) control rats (received food and water* ad libitum*); (△) treatment rats (deprived of water for 36 hr, but received food* ad libitum*).*

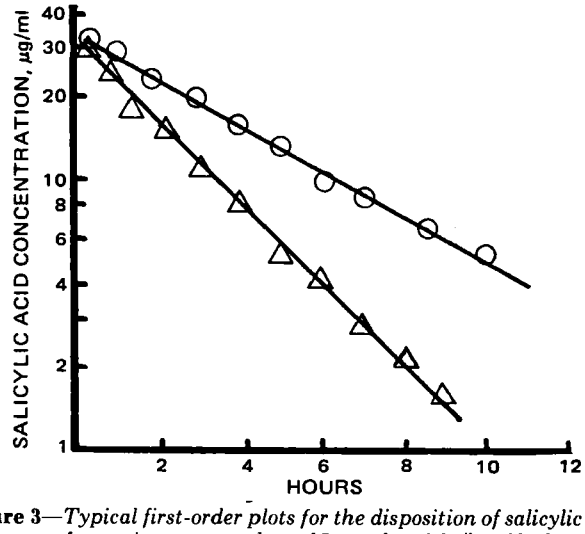

Figure 3—*Typical first-order plots for the disposition of salicylic acid in plasma after an intravenous dose of 5 mg of aspirin/kg of body weight in rats. Key: (△) control rats (received food and water* ad libitum*); (○) treatment rats (deprived of water for 36 hr, but received food* ad libitum*).*

Table V—Recovery of Aspirin Metabolites Salicylic Acid, Salicyluric Acid, and Gentisic Acid in Urine After Intravenous Administration of Aspirin in Two Doses to Control and Water-Deprived Rats

Aspirin Dose, mg/kg	Group	Recovery in Urine, % of Aspirin Dose						
		Salicylic Acid		Salicyluric Acid		Gentisic Acid		
		Mean ± *SEM*	Range	Mean ± *SEM*	Range	Mean ± *SEM*	Range	Total
5	Control[a]	48.6 ± 3.7	40.0–63.1	46.0 ± 3.0	34.9–55.2	—	—	94.6 ± 4.2
5	Water Deprived[b]	44.2 ± 5.7	24.5–65.0	53.6 ± 7.1	30.4–81.9	—	—	97.8 ± 1.8
10	Control	58.3 ± 5.0	31.2–81.3	38.0 ± 4.9	25.7–72.4	—	—	96.3 ± 4.0
10	Water Deprived	50.3 ± 1.7	40.6–55.6	36.9 ± 2.3	29.8–48.2	6.5 ± 0.9	3.6–10.8	93.6 ± 2.1

[a] The control group of rats (n = 6) received food and water *ad libitum*. [b] The rats (n = 9) were deprived of water for 36 hr, but received food *ad libitum*.

< 0.05) when the dose is doubled. This confirms the earlier finding in humans (28), that the disposition of salicylic acid is dose dependent. When the dose was doubled in the control rats, the half-life increased from 2.1 to 3.6 hr, an increase of ~72%. In water-deprived rats, the corresponding increase was 69% (2.59 to 4.37 hr).

The significant increase in the biological half-life of salicylic acid with water deprivation has important implications in the salicylate therapy of rheumatoid arthritis and inflammatory diseases, where aspirin is administered chronically at high dosages and where effective therapeutic levels of salicylate in these conditions approach toxic levels. Accumulation of salicylate due to increased biological half-life, as a result of short-term water deprivation, may produce toxic, possibly fatal effects.

Metabolites of Aspirin in Control and Water-Deprived Rats—Urine samples were analyzed for the major aspirin metabolites, salicylic and salicyluric acids, which account for >90% of the administered dose, and also for the minor metabolite, gentisic acid. The results are shown in Table V for a 5-mg/kg dose of aspirin in control and water-deprived (treatment) rats. The total recovery of aspirin in control rats is ~95% as compared with 97% for the treatment group. There was no significant difference in recovery of aspirin metabolites in these two groups of rats, and there also was no detectable gentisic acid in any of the urine samples. In both groups, approximately half of the aspirin was excreted as salicyluric acid. The fraction of aspirin excreted in the urine as salicyluric acid decreased significantly ($p < 0.05$) as the dose was increased from 5 to 10 mg/kg in both groups of rats. However, no effect of water deprivation was observed on the total percentage of aspirin metabolized to salicyluric acid. This finding is very interesting, since it would be expected that the percentage of salicyluric acid formed would increase in water-deprived rats because the long half-life of salicylic acid gives the liver more time to form salicyluric acid under conditions of metabolic saturation.

Since water deprivation produces no significant change in the excretion of salicyluric acid, the situation may be explained by one or both of two phenomena:

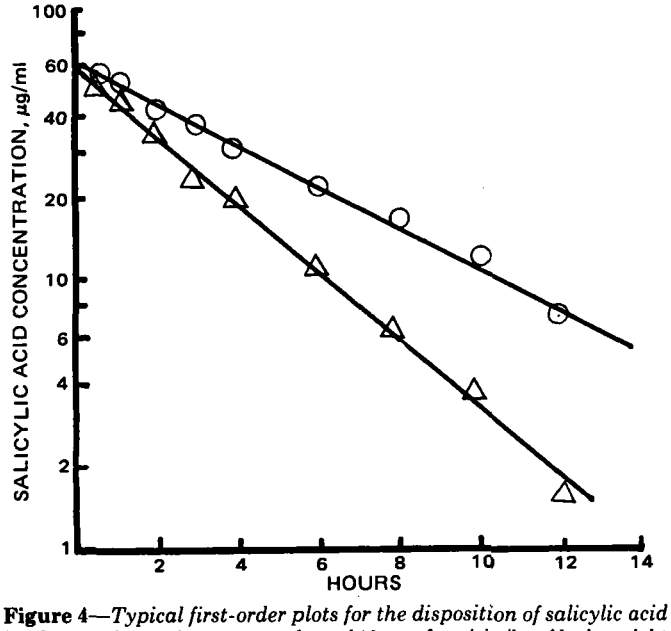

Figure 4—*Typical first-order plots for the disposition of salicylic acid in plasma after an intravenous dose of 10 mg of aspirin/kg of body weight in rats. Key: (△) control rats (received food and water* ad libitum*); (○) treatment rats (deprived of water for 36 hr, but received food* ad libitum*).*

1. If it is assumed that the drug-metabolizing enzymes are inhibited to some extent by water deprivation, the longer circulating half-life of salicylic acid could be balanced by the slower rate of formation of salicyluric acid. In the first step, the carboxylic group of salicylic acid binds with CoA to form the activated complex. In the second step, glycine conjugates with the reactive complex with the help of glycine-*N*-acylase. It is not presently known if one or both of these enzymes is inhibited by water deprivation.

2. The renal tubular conversion of salicyluric acid to salicylic acid (42) is a significant factor. The salicyluric acid formed in the liver from salicylic acid is transferred to the tubule cells of the kidneys, where it is metabolized back to salicylic acid and reabsorbed, thus prolonging the biological half-life of salicylic acid without increasing the proportion of salicyluric acid in the urine. Since with water deprivation, rats are more likely to conserve body water by reducing the formation of urine, the conversion of salicyluric acid to salicylic acid is more likely to occur.

Another interesting finding from the urinary studies is that at higher aspirin doses (10 mg/kg), ~6.5% of aspirin was metabolized to gentisic acid in water-deprived rats, suggesting that the enzyme system responsible for the hydroxylation of the aromatic ring (microsomal mixed-function oxidase) is somewhat stimulated by short-term water deprivation. No gentisic acid was found in the urine of control rats.

In conclusion, it might be stated that although there is no dramatic change in the excretion pattern of different metabolites of aspirin in the urine, the half-life of salicylic acid is significantly increased with water deprivation at both dose levels studied. This increased biological half-life of salicylic acid may have significant clinical impact in the treatment of rheumatoid arthritis and other diseases where the differences between the effective and toxic blood levels of salicylate are extremely narrow.

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Effect of Dosage Form and Formulation Factors on the Adherence of Drugs to the Esophagus

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Abstract □ In recent years, many case reports concerning esophageal injuries caused by drugs have been published. The primary cause has apparently been the adherence of the drug product to the esophagus. In the present study, the adherent tendency of a number of types of tablets and capsules were tested *in vitro* using a recently developed isolated porcine esophagus preparation. The results showed that the tendency of products to adhere to the esophageal mucosa can be modified to a great extent by shape and formulation. Products with low adherence can be obtained by film coating with aqueous dispersions or by sugarcoating. In contrast, gelatin capsules and some cellulose films appear to have a high tendency to adhere to the esophagus.

Keyphrases □ Tablet coatings—effect on adherence, isolated porcine esophagus, potassium chloride □ Potassium chloride—adherence to isolated porcine esophagus, effect of tablet shape, formulation, and coatings □ Drug formulations—effect of additives and coatings on adherence, isolated porcine esophagus

In recent years, many reports concerning esophageal injuries caused by drugs (*e.g.*, doxycycline, emepronium bromide, and potassium chloride) have been published (1–9). The primary cause has apparently been adherence of the drug product to the esophageal mucosa. The tendency to adhere has obviously been greatest for hard gelatin capsules, but differences between various tablet formulations have also been evident. In a previous paper, a study of the tendency of drug products to adhere to the esophageal wall, using the isolated porcine esophagus, was published (10). In the present investigation the effect of the pharmaceutical characteristics of dosage forms on the adherence was studied.

EXPERIMENTAL

Isolated Esophagus Preparation—The isolated porcine esophagus preparation and its usefulness has been described previously (10). Pigs of both sexes were of the Landrace or Yorkshire breeds, weighing 90–100 kg. Immediately after slaughter, the esophagi were removed and transported to the laboratory in Tyrode's solution. Segments (6–7 cm long) were cut from the esophagus and mounted in a classic organ bath for isolated preparations.

Recording of Adherence—A hole was drilled in the products to be tested. The product was attached to a copper wire and placed in the esophageal preparation for 2.0 min (gelatin capsules, 1.0 min). The force needed to detach the product was then measured using a modified prescription balance (10); the force used was taken as a measure of adherence.

Drug Products—Hard gelatin capsules[1] sizes 1, 2, 3, 4, and 5 were filled with lactose. Oval soft gelatin capsules[2] (length 12 or 15 mm) were left empty. The round soft gelatin capsule formulation studied was a commercially available product[3] (diameter 7 mm). The uncoated placebo tablets were compressed from a mixture of basic granules (96%), talc (3%), and magnesium stearate (1%). The basic granules contained 78% lactose, 19% cornstarch, and 3% gelatin. Potassium chloride tablets were compressed from pure potassium chloride. To obtain products with low adherent properties metal tablets were compressed from an alloy of bismuth, lead, tin, and cadmium (5:3:1:1). The shapes, diameters, and areas of all formulations are given in Tables I–III.

The sugar-coated tablets were all commercially available products[3]. The coating suspension used contained 47 g of sucrose, 4 g of polyethylene glycol 6000, 8 g of calcium sulfate, 2 g of titanium dioxide, 30 g of purified water, and 3 g of other ingredients. The dusting powder contained calcium sulfate and talc (1:1). The coating suspension and powder were used in an approximate ratio of 9:5.

To investigate the effect of film coatings on the adherence of drugs to the esophagus, biconvex tablets were coated with different film coatings. The compositions of the hydroxypropyl methyl cellulose-containing solutions (I–V) are given in Table I. The other coating solutions were as follows: VI, 10.0 g of cellulose acetate phthalate, 0.5 g of castor oil, and 89.5 g of acetone; VII, 14.0 g of polyethylene glycol 6000, 6.0 g of cellulose acetate phthalate, 1.0 g of stearic acid, 0.3 g of castor oil, 0.3 g of sorbitan

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