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A flip-flop model for nitrofurantoin disposition in the rabbit following oral administration

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Summary

The influence of route of administration on the absorption of nitrofurantoin and the effect of factors influencing the absorption, such as water volume taken with the drug, change of gastric emptying rate, and effect of particle size, were investigated in rabbits. To clarify the absorption behavior of nitrofurantoin, the Martis-Levy method analogous to the Wagner-Nelson method was used to obtain the absorption kinetics of the drug. Moment analysis was also used to estimate the absorption behavior of the drug.

The rate constants of absorption following oral administration of the drug were significantly smaller than those of elimination following intravenous administration. The results of moment analysis (based on a linear approximation) showed that the mean residence time following intravenous administration was much less than the mean absorption time of any oral dosage form. These results clearly show that the pharmacokinetic profile of nitrofurantoin following oral administration is of flip-flop type. Although this result was obtained in the rabbit, the implications of a flip-flop situation for the human case are discussed on the basis of the available published data.

Introduction

Nitrofurantoin, 1-((5-nitrofurfurylidene)amino)hydantoin, is widely used to treat urinary tract infections. It was reported that during the normal oral therapeutic

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regimen (1.25–1.75 mg/kg), blood or plasma levels of nitrofurantoin are usually very low compared with those obtained after intravenous or intramuscular administration (Paul et al., 1960; Cadwallader and Jun, 1976), and that a significant fraction of the drug is saturably secreted by the renal tubules (Paul et al., 1959; Buzard et al., 1962).

To clarify these phenomena, the gastrointestinal absorption, hepatic first-pass effect and renal excretion of the drug were investigated in rabbits. The disposition of nitrofurantoin could be described by a one-compartment model with simultaneous first-order and Michaelis-Menten type elimination kinetics for the tubular secretion, and bioavailability was estimated by non-linear assessment (Watari et al., 1983). The absolute *F*-value for oral administration was approximately 0.3 irrespective of dose. However, *F*-values following intraduodenal administration and portal vein infusion were nearly unity, and it was concluded that the reduction of bioavailability following oral administration could not be attributed to metabolism by intestinal microflora or to the hepatic first-pass effect. Thus, the reduction of *F*-value following oral administration is probably due to gastric degradation of the drug, because this drug is hydrolyzed to 5-nitro-2-furaldehyde and 1-aminohydantoin by azomethine bond cleavage in acidic media at body temperature (Inotsume and Nakano, 1981). Further, at the low dose of 1.25 mg/kg (approximately linear region), the half-life of the elimination phase after oral administration was significantly larger than that after intravenous administration, though the total plasma clearances were almost constant irrespective of route of administration. This phenomenon is of particular interest in relation to the absorption kinetics of nitrofurantoin, on which little work has been reported.

In the present study, we used the Martis-Levy method (1973) analogous to the Wagner-Nelson method (1963) to obtain the absorption kinetics of the drug. Moment analysis was also used to estimate the absorption behavior of the drug. Derived absorption kinetic parameters were compared to the elimination ones to identify the rate-limiting step, which is of great importance in relation to the development of drug delivery systems, etc.

Materials and Methods

Materials

Nitrofurantoin was used as supplied (Yamanouchi Seiyaku, Tokyo). The particle size grades were obtained by sieving through a Ro-Tap testing sieve shaker, using Japan Industrial Standard (JIS) sieves. The mean diameter of the sieved particles is taken as the arithmetic mean diameter of the sieve openings. A triturated sample was obtained by trituration. The volume-surface diameter of this sample was about 1.81 μm, as determined by the air permeability method (Martin et al., 1973). All other chemicals were of reagent grade.

Animal studies and drug administration

The effects of 4 separate factors on the absorption were studied: the route of

administration, the volume of water taken, the gastric emptying rate, and the nitrofurantoin particle size. Male Japanese white rabbits weighing nearly 2.5 kg were divided at random into 4 groups of 8 animals each and one group of 4 animals. Rabbits were allowed water ad libitum, but were fasted for 48 h before drug administration so as to reduce interference by the gastric contents and to obtain a uniform urinary pH (Fujimoto and Donnelly, 1968), because the renal clearance of nitrofurantoin is dependent on urinary pH since this drug is a weak acid with a pK_a of 7.2 (Woodruff et al., 1961). Consequently, urinary pH was measured prior to and after each experiment and it was confirmed that the urinary pH remained between 5 and 6 under the present conditions. Therefore, the effect of urinary pH on the unionized fraction of the drug is less than 10%, and may be neglected (Paul et al., 1960). The numbers of animals used differed from the numbers in the tables because some animals were dropped from the experiment due to problems of surgery or severe diarrhea during the experimental period.

In the first experiment, route of administration (Table 1), nitrofurantoin was given to one group of 8 rabbits at a dose of 1.25 mg/kg. A second group of 8 rabbits was given 10 mg/kg. In each group one dose of the drug was given to each animal each week by the 4 routes successively; i.v. (intravenous), p.o. (oral), i.d. (intraduodenal), $p.v._{inf}$ (portal vein infusion), and $i.v._{inf}$ (intravenous infusion). In the second experiment, effect of water volume (Table 2), 8 animals were given nitrofurantoin at 4 different levels of dilution with water (4, 7, 10 and 25 ml) in successive weeks at a dose of 1.25 mg/kg. In the third experiment, effect of gastric emptying rate (Table 2), a group of 4 animals was used with a cross-over design at intervals of 1 week at the dose of 10 mg/kg: week 1, two were given atropine injected intraperitoneally 30 min prior to oral administration of nitrofurantoin and two were given normal saline; week 2, the reverse treatments were administered. In the fourth experiment, particle size effect (Table 2), a group of 8 rabbits was given the drug at various particle sizes in the form of an aqueous suspension with 10 ml of water at 1-week intervals at a dose of 10 mg/kg.

The drug solutions were freshly prepared with diethanolamine solution (0.25–0.5%) before each experiment. Diethanolamine used as a solvent is not likely to have an appreciable effect on the pH of gastric absorption of the drug, since it did not affect the pH of the gastric contents, which were found to be stable at pH 1.2 before and immediately after administration of the drug solution when the pH of the gastric juice was measured visually by means of pH test paper.

I.v. administration was carried out by bolus injection or first-order infusion ($k_a = 2.7\ h^{-1}$) into the marginal vein of the ear opposite to that used for collecting blood samples. P.o. administration was carried out by oral intubation. I.d. administration was carried out by bolus injection, and $p.v._{inf}$ was performed in a first-order manner ($k_a = 2.7\ h^{-1}$) via a mesenteric catheter by using an infusion pump after abdominal incision. The first-order rate of infusion was obtained by ensuring a first-order change of the infused volume.

Heparinized venous blood samples (0.5 ml) were collected prior to drug administration and at arbitrary times (10–13 samples) thereafter.

Assay

The concentrations of nitrofurantoin in plasma and urine were measured by fluorometric analysis (Watari et al., 1980a).

Kinetic studies

As the disposition of nitrofurantoin could be described by a one-compartment model with simultaneous first-order and Michaelis-Menten type elimination kinetics for the tubular secretion (Watari et al., 1983), the fraction of the dose absorbed up to time t can be calculated by the following equation (Martis and Levy, 1973).

$$A_t/V = C + \int_0^t [KC + V_{max}C/(K_m + C)]dt \quad (1)$$

where A_t is the amount of drug absorbed at time t, V is the distribution volume, C is the drug concentration in plasma at time t, K is the overall apparent first-order rate constant, V_{max} is the theoretical maximum velocity of the capacity-limited process, and K_m represents the Michaelis constant. The kinetic parameters of nitrofurantoin disposition were determined by the non-linear least-squares method (Watari et al., 1983) from the mean plasma concentration data of each group following i.v. administration. The estimated mean values of K, V_{max} and K_m were 0.0156 min^{-1}, 0.248 μg/ml/min and 4.42 μg/ml, respectively. The estimated errors in the values for K, V_{max} and K_m ranged from 5 to 10%. The estimated parameters for each group were used to calculate the fraction of dose absorbed from the mean plasma concentration data.

The mean residence time (MRT) was also calculated by using the area under the curve and the area under the moment curve from the mean plasma nitrofurantoin concentration data for each group (Yamaoka et al., 1978; Rigelman and Collier, 1980).

Results and Discussion

Influence of route of administration on the absorption

Rabbit plasma nitrofurantoin levels following p.o. administration were appreciably low compared with those after administration by the other routes (Fig. 1). This result is consistent with those in rats (Paul et al., 1960) and man (Cadwallader and Jun, 1976). Semilogarithmic plots of amount unabsorbed versus time, obtained from the mean plasma concentration data, are shown in Fig. 2. The plot for p.o. administration of aqueous solution of 1.25 mg/kg was approximately linear, whereas those for i.d. administration and p.o. administration of aqueous solution of 10 mg/kg were biphasic with concave-descending curves. This was also the case when amount unabsorbed versus time plots were prepared from individual subject data. Therefore, these time course data were approximated by a biexponential equation. Although the plots of $p.v._{inf}$ at the dose of 1.25 mg/kg were slightly curvilinear, in the present study we approximated them to linear form because the administration was performed in a first-order manner ($k_a = 2.7\ h^{-1}$).

TABLE 1

INFLUENCE OF ROUTE OF NITROFURANTOIN ADMINISTRATION ON THE MEAN RESIDENCE TIME ((MRT), MEAN ABSORPTION TIME (MAT), ABSORPTION RATE CONSTANT (k_a), ELIMINATION RATE CONSTANT (λ_1), AND THE FRACTION OF DOSE ABSORBED (F) AT DOSES OF 1.25 AND 10 mg/kg

Dose (mg/kg)	Route	MRT (min)	MAT (min)	k_a (min^{-1})	λ_1 [a] (min^{-1})	F [b]
1.25	i.v. (n = 8)	18.6			0.0424	1.00
	p.o. (n = 8)	74.3	55.7	0.0292(103.3) [c]	0.0155	0.36
	i.d. (n = 7)	50.8	32.2	0.2576(29.7), 0.0276(70.4)	0.0207	1.00
	$p.v._{inf}$ (n = 5)	33.2	14.6	0.0551(86.7)	0.0359	1.05
10.0	i.v. (n = 8)	28.2			0.0392	1.00
	p.o. (n = 6)	116.5	d	0.0365(16.6), 0.0110(85.2)	0.0085	0.32
	i.d. (n = 7)	69.7	d	0.0957(43.8), 0.0135(56.7)	0.0152	1.03
	$p.v._{inf}$ (n = 6)	46.6	d	0.0493(89.2)	0.0287	1.03
	$i.v._{inf}$ (n = 5)	45.7	d	0.0499(92.5)	0.0287	1.01

i.d. = intraduodenal administration; $p.v._{inf}$ = portal vein infusion; $i.v._{inf}$ = intravenous infusion.

[a] Elimination rate constants except for i.v. administration were obtained from the last 3 or 4 points of the time course data.

[b] Cited from Watari et al. (1983).

[c] Values in parentheses represent calculated constant (t = 0) obtained by fitting to an appropriate equation (see text).

[d] Mean absorption time was not calculated because of nonlinear region (see text).

For fitting to an appropriate equation for calculating absorption rate constant, at the initial time (t = 0) the percentage unabsorbed was set at 100 except for p.o. administration, because absolute *F*-values of the other administration routes were nearly unity (Table 1). The calculated absorption rate constant and mean residence time (MRT) are shown in Table 1. The mean absorption times (MAT) were also calculated by subtracting the MRT of i.v. administration (MRTiv) from the MRT of the other administration routes.

The calculated absorption rate constants for a first-order infusion of 10 mg/kg were 0.0493 min^{-1} (2.96 h^{-1}) for $p.v._{inf}$ and 0.0499 min^{-1} (2.99 h^{-1}) for $i.v._{inf}$. These values are in reasonable agreement with the 2.7 h^{-1} infused value. The

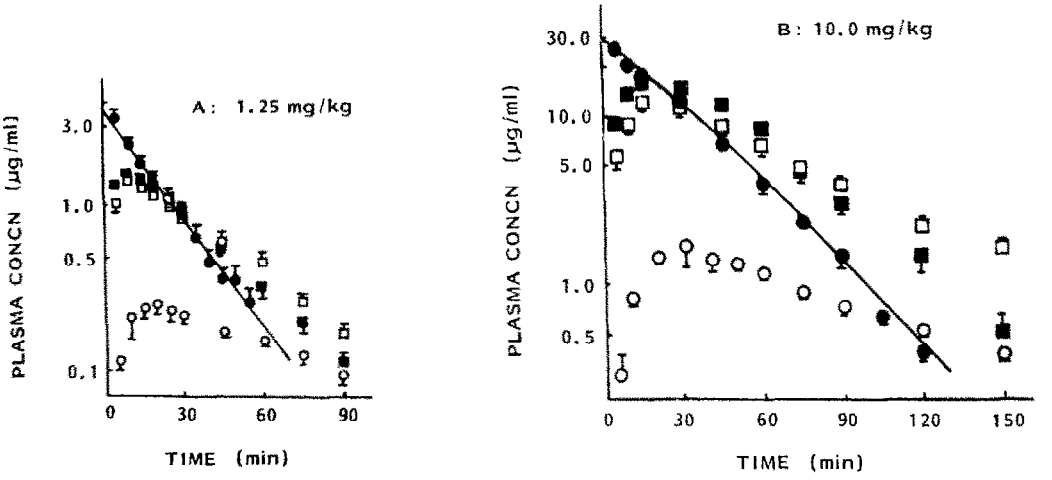

Fig. 1. Plasma concentrations of nitrofurantoin in rabbits following administration by various routes: ○, oral; □, intraduodenal; ■, portal vein infusion; ●, intravenous. The dose was 1.25 mg/kg (A) or 10 mg/kg (B). Solid lines represent the calculated values. Points represent mean values with S.E. Numbers of animals are given in Table 1. Plasma levels following intravenous infusion of 10 mg/kg are omitted because the time course was very similar to that following portal vein infusion.

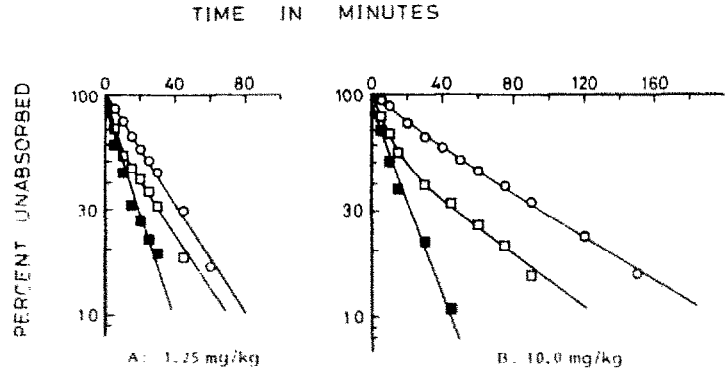

Fig. 2. Semilogarithmic plots of percent unabsorbed versus time following administration by various routes: ○, oral; □, intraduodenal; ■, portal vein infusion. The dose was 1.25 mg/kg (A) or 10 mg/kg (B). The percent-unabsorbed time course following intravenous infusion of 10 mg/kg is omitted because this time course was very similar to that following portal vein infusion.

calculated absorption rate constant for $p.v._{inf}$ of 1.25 mg/kg was 0.0551 min^{-1} (3.31 h^{-1}) and differed from the 2.7 h^{-1} infused value. Further, the calculated initial value (t = 0) was 86.7% because this time course of amount unabsorbed was somewhat curvilinear. Although the reason for this discrepancy between the calculated and infused values for $p.v._{inf}$ of 1.25 mg/kg is not clear, at the dose of 10 mg/kg there was reasonable agreement between the calculated and infused values for both $p.v._{inf}$ and $i.v._{inf}$ administrations. Thus, the estimated kinetic parameters of nitrofurantoin disposition are considered to be appropriate.

The time course of amount unabsorbed for i.d. administration became biphasic, but this result might be explained partly by the passage of the drug through the intestine, because the highest rates of passage occur in the proximal small gut; the rates then diminish continuously until, in the distal small intestine, they are lower by a factor of almost 20 (Marcus and Lengeman, 1962). Similar observations were also suggested in the rabbit (Watari et al. 1980b). Further, the available surface area for the absorption decreases with descent along the intestine, and the fall in surface area from the jejunum to the ileum is remarkable (Creamer, 1974). Therefore, the absorbability of the drug would be a function of both the residence time of the drug at the absorption site and the available surface area. Based on these considerations, the site of the initial very large absorption rate constant in the biexponential equation is suggested to be the duodenum or the duodenum plus some part of the upper jejunum, and the site of the second phase may be the lower jejunum and ileum. These absorption rate constants of i.d. administration were different at doses of 1.25 and 10 mg/kg. This result may be simply due to the difference in dose; at the very low dose of 1.25 mg/kg, the drug may not be spread widely over the gut and may be absorbed completely in the proximal small gut.

In a previous report (Watari et al. 1980b), the time courses of amount unabsorbed after p.o. administration of aqueous solutions of sulfa drugs became biphasic and were similar to the time course data after i.d. administration of nitrofurantoin. The results for aqueous solutions of sulfa drugs were also explained in similar terms, based on the facts that the absorption of sulfa drugs from the stomach is negligibly small compared with that from the small intestine, and that the transport rate of aqueous solution in the stomach is much faster than that of solid material (Marcus and Lengeman, 1962). It was also reported that the major site of absorption of nitrofurantoin is the small intestine (Buzard et al., 1961). Therefore, it is suggested that the time courses of amount unabsorbed after p.o. administration of aqueous solutions of nitrofurantoin would be biphasic for the same reasons as in the case of aqueous solutions of sulfa drugs. As can be seen in Fig. 2, the time course of amount unabsorbed for the aqueous solution of nitrofurantoin of 10 mg/kg became slightly biphasic but differed greatly from that after i.d. administration. This difference between p.o. and i.d. administrations may be partly due to the gastric residence of the drug in the case of p.o. administration. However, the second absorption rate constants in the biexponential equations were almost the same for p.o. and i.d. administrations, indicating that the sites of absorption of the drug in both routes are the same during this period (Table 1). On the other hand, the time course of amount unabsorbed for the aqueous solution of 1.25 mg/kg was essentially linear and

differed from the biphasic time course data after i.d. administration. This may be due to the difference in dose and to the gastric residence of the drug after p.o. administration, i.e. the absorption of the drug given orally is rate-limited by the gastric emptying rate and the drug is completely absorbed in the proximal small intestine due to the very low amount administered, so that absorption of the drug is apparently a first-order process because the drug is mainly absorbed in the small intestine (Buzard et al., 1961).

As the Michaelis constant for the tubular secretion was 4.42 μg/ml, the elimination rate constant of i.v. administration was calculated from the approximately linear phase at plasma concentrations below 1 μg/ml. The elimination rate constants for the other routes were also calculated from the last 3 or 4 points of the plasma time course data, where the plasma concentrations were below 1 μg/ml, except in the cases of i.d., $p.v._{inf}$, and $i.v._{inf}$ of 10 mg/kg. The absorption rate constant of p.o. administration was significantly smaller than the elimination rate constant of i.v. administration (Table 1). The elimination rate constant of i.v. administration was 2- or 3-fold larger than those of p.o. and i.d. administrations at both doses (1.25 and 10 mg/kg). These results clearly demonstrate a flip-flop model of nitrofurantoin absorption. Thus, the second absorption rate constant in the biexponential equation for i.d. administration reflected the elimination and became almost equal to the elimination rate constant at both doses (Table 1).

The markedly reduced absolute *F*-value following p.o. administration was suggested to be due to gastric degradation of the drug (Watari et al., 1983), based on the facts that the absolute *F*-values following administration by other routes were nearly unity, and azomethine bond cleavage of the drug occurs in acidic media in vitro at body temperature (Inotume and Nakano, 1981). This azomethine bond cleavage of the drug in vitro was a first-order process. Therefore it is considered that gastric degradation of the drug may also be a first-order process. The initial absorption rate constant in a biexponential equation for p.o. administration of 10 mg/kg differed from and was much less than that of i.d. administration. This result strongly suggests that the initial absorption rate for p.o. administration is rate-limited by the gastric emptying rate, because the major site of absorption of the drug is the small intestine. If this is the case, simultaneous occurrence of degradation and movement of the drug down the GI tract in the stomach must be considered. Goto et al. (1973) reported this movement to be a first-order process. Therefore, the true initial absorption rate constant for oral administration can be obtained by multiplying the apparent rate constant by the fraction (F) of the orally administered dose absorbed (Notari et al. 1972). Consequently, the true values of the initial absorption rate contant for p.o. administration may be considered to be much smaller, further emphasizing the flip-flop nature of the kinetics of the drug absorption. In addition, in the case of moment analysis, if parallel first-order drug loss from the site of administration occurred, the true value of MATsoln would be obtained by dividing the apparent MATsoln by the fraction (F) of the orally administered dose absorbed because there is an inverse relationship between MAT and the absorption rate constant.

As can be seen in Fig. 1, at the dose of 1.25 mg/kg the nitrofurantoin concentrations following i.v. administration declined approximately monoexponen-

TABLE 2

EFFECT OF VARIOUS FACTORS RELATED TO NITROFURANTOIN ADMINISTRATION ON THE MEAN RESIDENCE TIME (MRT), MEAN ABSORPTION TIME (MAT), ABSORPTION RATE CONSTANT (k_a), ELIMINATION RATE CONSTANT (λ_1), AND THE FRACTION OF DOSE ABSORBED (F)

Dose (mg/kg)	Dosage form			MRT (min)	MAT (min)	k_a (min^{-1})	λ_1 [a] (min^{-1})	F [b]
1.25	Solution	i.v.	(n = 8)	19.4			0.0453	1.00
		(4 ml) [c]	(n = 8)	75.3	55.9	0.0246(103.4) [f]	0.0163	0.26
		(7 ml)	(n = 8)	74.0	54.6	0.0262(105.8)	0.0169	0.25
		(10 ml)	(n = 8)	73.7	54.3	0.0294(100.7)	0.0150	0.30
		(25 ml)	(n = 8)	71.7	52.3	0.0292(103.3)	0.0165	0.30
10.0	Solution	i.v.	(n = 8)	28.6			0.0405	1.00
		(Atropine) [d]	(n = 4)	185.5	156.9	0.0036((98.4)), 0.0106((87.9))	0.0061	0.30
		(Control)	(n = 4)	116.4	87.8	0.0343(23.7), 0.0102(77.6)	0.0085	0.33
	Solution		(n = 6)	113.8	85.2	0.0359(16.6), 0.0110(85.2)	0.0089	0.32
		(Trit.) [e]	(n = 8)	114.2	85.5	0.0113(104.7)	0.0114	0.25
	Suspension	(81 μm)	(n = 8)	263.3	234.7	0.0061((105)), 0.0144((53.8))	0.0044	0.27
		(163 μm)	(n = 8)	252.2	223.6	0.0067((104)), 0.0126((51.4))	0.0043	0.15

[a] Elimination rate constants except for i.v. administration were obtained from the last 3 or 4 points of the time course data.

[b] Cited from Watari et al. (1983).

[c] Drug diluted with the indicated water volumes.

[d] Effect of the gastric emptying rate.

[e] Administered particle size.

[f] Values in parentheses represent calculated constant (t = 0) obtained by fitting to an appropriate equation. The values in double parentheses represent calculated constant at time t = 0 (initial parentheses) and t = T. Here, T is the time corresponding to the intersection of the two lines (see text).

tially with time, indicating moment analysis to be applicable. The MAT for p.o. or i.d. administration is approximately 2- or 3-fold larger than the MRTiv. If simultaneous first-order drug loss from the stomach occurred, the true value of MATsoln would be obtained by multiplying by the reciprocal of the absolute *F*-value of 0.3 as described above and would be increased further. In either case, this result is also consistent with a flip-flop pharmacokinetic profile of nitrofurantoin following p.o. administration.

At the dose of 10 mg/kg, elimination of the drug after i.v. administration was non-linear and the non-linearity of i.v. administration was the most marked among the various routes of administration. Therefore, the MAT calculated by subtracting the MRTiv would give the minimal value and may be useful as an approximate index of the absorption.

Factors influencing the absorption

The influence of various factors on the absorption of nitrofurantoin was investigated. The factors were the volume of water taken, gastric emptying rate, and the nitrofurantoin particle size. The time courses of nitrofurantoin concentration in plasma and bioavailability were reported in a previous paper (Watari et al., 1983). The absolute *F*-values after p.o. administration were below about 0.3 (Table 2). Therefore, nitrofurantoin concentrations in the plasma did not increase above the levels observed after aqueous solution administration of 10 mg/kg (Fig. 1) and

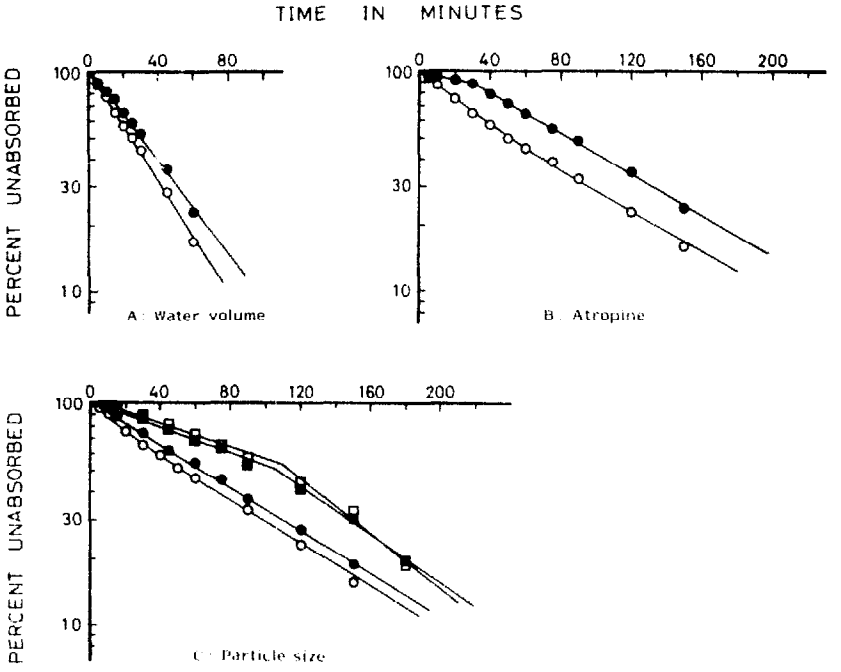

Fig. 3. Semilogarithmic plots of percent unabsorbed versus time following oral administration as affected by various factors: volume of water taken simultaneously (A) (●, 4 ml; ○, 25 ml), change of gastric emptying rate (B) (○, control; ●, atropine treatment), and particle size (C) (○, solution; ●, trituration; □, 81 μm; ■, 163 μm).

generally remained below 1.5 μg/kg. Thus, elimination of the drug may be approximated as a first-order process.

The effects of various factors on the amount unabsorbed versus time plots are shown in Fig. 3. An increase in the volume of water administered tended to improve the rate of absorption (Fig. 3A and Table 2). This observation is in agreement with an earlier report (Watari et al., 1983) in which there was a statistically significant difference between 4 and 25 ml of administered water. One might expect that a large volume of water administered would decrease the concentration of the drug in the GI tract and tend to reduce the rate of absorption. However, oral dilution causes a marked increase in the surface area over which absorption may take place; this factor apparently exerts a more significant effect on GI absorption of the drug than does the factor of concentration of the drug in the GI tract (Henderson et al., 1966). Nitrofurantoin is poorly absorbed from the stomach but is absorbed from the small intestine (Buzard et al., 1961). Hence, hastening the passage of the drug from the stomach into the intestine by oral dilution tends to allow intestinal absorption to start sooner. Consequently, an increase in the volume of water administered tended to improve the absolute *F*-value, because gastric degradation of the drug was reduced.

The influence of a delay in gastric emptying upon the absorption of the drug was investigated by using atropine sulfate. The time course of amount unabsorbed for the group treated with atropine became a biphasic convex-descending curve (Fig. 3B). These time course data were fitted to two lines by the least-squares method. The intersection time of the two lines was 31.3 min. On the other hand, the time course of amount unabsorbed for the control group was a biphasic concave-descending curve and this was fitted by a biexponential equation. The initial absorption rate constant of the group treated with atropine was much smaller (one-tenth) than that of the control group. This difference is caused by the change in gastric emptying rate between the group treated with atropine and the control group, and this result also suggests that the absorption site of the drug is not in the stomach but in the intestine. However, in spite of the markedly reduced gastric emptying rate, there is no significant difference between the atropine and control groups in terms of absolute *F*-value (Watari et al., 1983). This can be explained by the characteristic of atropine of reducing not only the gastric emptying rate but also the secretion of gastric juice.

The effect of particle size on the absorption of nitrofurantoin is shown in Fig. 3C and Table 2. These results are in good agreement with those found in rats (Paul et al., 1967) and man (Conklin and Hailey, 1969). The time courses of the amount unabsorbed for the 81 and 163 μm particles became biphasic with convex-descending curves. These time course data were also fitted by two lines. The intersection times of the two lines were 110 min for the 81 μm particles and 105 min for the 163 μm particles. The ratio of the second slope for these particles to the initial slope was about 2 in the amount unabsorbed-time plot (Table 2). Cadwallader and Jun (1976) reported that the solubility of nitrofurantoin increased remarkably with an increase in pH. Therefore, this phenomenon may be explained by the change of the dissolving environment as the particle drug moves to the GI tract (Crouthamel et al.

1975). Consequently, the initial absorption rate constant for the 81 and 163 μm particles is suggested to be due to the dissolution of the particles in the stomach; the aqueous solution produced by the dissolution of the particles moves relatively faster to the small intestine than the suspension and is rapidly transferred to the body, because the transport rate of aqueous solution in the stomach is much faster than that of solid material (Marcus and Lengeman, 1962).

As another possible explanation, the biphasic convex-descending curves of 81 and 163 μm may be due to a zero-order dissolution of the particles during the initial portion of the absorption phase since the dissolution process of the particles was indicated to be rate-limiting for the absorption in Fig. 3C. However, this initial period of the absorption phase can be expected to correspond to the dissolving period of the particles in the stomach, and it is also expected that the particles in the stomach would be emptied into the intestine with time. Based on these speculations, this explanation would be invalid. Although a biphasic convex-descending curve for the absorption of the group treated with atropine was also observed, this may be simply the effect of atropine on the gastric emptying rate because both the atropine and the control groups were administered nitrofurantoin in an aqueous solution form. On the other hand, the time course of the amount unabsorbed for the triturated sample was approximately linear. This may be because the particles of the drug are very fine.

With regard to the absolute *F*-values, significant differences were observed between the 163 μm particles and the other samples, and the *F*-value of 163 μm particles was one-half that of the aqueous solution (Table 2). This was considered to be due to incomplete dissolution of the drug in the GI tract as well as gastric degradation. Further, although the absorption rate constant for 163 μm particles is similar to that for 81 μm particles, the true absorption rate constant of 163 μm particles would be smaller than that of 81 μm particles, because the absolute *F*-value of 81 μm particles is about 2-fold larger than that of 163 μm particles.

From the present results, obtained when the drug was given orally under various conditions, it is clear that a flip-flop model of nitrofurantoin absorption holds (Table 2). In the cases of 81 and 163 μm particles, we also calculated the mean dissolution time (MDT) of particles by subtracting MRTsoln from the MRT of particles (Tanigawara et al., 1982). The MDT was 149.5 min for the 81 μm particles and 138.4 min for the 163 μm particles. Therefore, the mean residence times will be in the following order: MDTparticle > MATsoln > MRTiv. This clearly indicates that dissolution of the drug is a rate-limiting step for the absorption. In calculating MATsoln at 10 mg/kg, however, we used the MRTiv of 10 mg/kg; the levels of nitrofurantoin concentration in plasma after p.o. administration of aqueous solution and particles remained below 1.5 μg/ml, suggesting that elimination of the drug under these circumstances proceeds approximately as a first-order process. Therefore it may be valid to use MRTiv of 1.25 mg/kg instead of that of 10 mg/kg. In this case, the calculated MATsoln will be increased by about 10 min. Even in such a case the order of residence time for p.o. administration of the particles does not change, indicating that dissolution of the drug is rate-limiting in the absorption.

It is very important to know whether the flip-flop situation found in the rabbit is

also applicable to the human case; it should be noted that the gastric emptying rate of rabbits is significantly slower than that of humans (Watari and Kaneniwa, 1981) and intestinal pH values of rabbits are higher than those of humans (Crouthamel et al., 1975). The results on bioavailability of commercial nitrofurantoin tablets in man showed that the rate of absorption was smaller than that of elimination for many products (McGilveray et al., 1973). Furthermore, the biological half-life of nitrofurantoin in man is very fast and appears to be 30 min or less (Cadwallader and Jun, 1976). Based on these considerations, it seems likely that the pharmacokinetic profile in man following oral administration of nitrofurantoin also follows a flip-flop model. If this is so, it has important implications for the design of bioavailability testing and for the development of the drug delivery systems.

References

Buzard, J.A., Bender, R.C., Nohle, E.G., Humphrey, D.T. and Paul, M.F., Renal tubular transport of nitrofurantoin. Am. J. Physiol., 202 (1962) 1136–1140.

Buzard, J.A., Conklin, J.D., O'Keefe, E. and Paul, M.F., Studies on the absorption, distribution and elimination of nitrofurantoin in the rat. J. Pharmacol. Exp. Ther., 131 (1961) 38–43.

Cadwallader, D.E. and Jun, H.W., Analytical Profiles of Drug Substances, Vol. 3, Flory and Klaus (Eds.), Academic Press, New York, 1976, pp. 346–373.

Conklin, J.D. and Hailey, F.J., Urinary drug excretion in man during oral dosage of different nitrofurantoin formulations. Clin. Pharmacol. Ther., 10 (1969) 534–539.

Creamer, B., Biomembranes, Vol. 4A, D.H. Smyth (Ed.), Plenum Press, London, New York, 1974, pp. 1–42.

Crouthamel, W.G., Abolin, C.R., Hsieh, J. and Lim, J.K., Intestinal pH as a factor in selection of animal models for bioavailability testing. J. Pharm. Sci., 64 (1975) 1726–1727.

Fujimoto, J.M. and Donnelly, R.A., Effect of feeding and fasting on excretion of phenobarbital in the rabbit. Clin. Tox., 1 (1968) 297–307.

Goto, S., Yamagata, T., Tsuzuki, O. and Iguchi, S., Rate of gastric emptying of phenol red in a rabbit. Chem. Pharm. Bull., 21 (1973) 2495–2499.

Henderson, M.L., Picchioni, A.L. and Chin, L., Evaluation of oral dilution as first aid measure in poisoning. J. Pharm. Sci., 55 (1966) 1311–1313.

Inotsume, N. and Nakano, M., Reversible azomethine bond cleavage of nitrofurantoin in acidic solutions at body temperature. Int. J. Pharm., 8 (1981) 111–119.

Marcus, C.S. and Lengemann, F.W., Use of radioyttrium to study food movement in the small intestine of the rat. J. Nutr., 76 (1962) 179–182.

Martin, A.W., Swarbrich, J. and Cammarata, A., Physical Pharmacy, 2nd edn., Lea and Febiger, Philadelphia, 1973, pp. 484–485.

Martis, L. and Levy, R.H., Bioavailability calculations for drugs showing simultaneous first-order and capacity-limited elimination kinetics. J. Pharmacokin. Biopharm., 1 (1973) 283–294.

McGilveray, I.J., Mattok, G.L. and Hossie, R.D., The comparison of the bioavailabilities of commercial nitrofurantoin tablets. Rev. Can. Biol., 32 (1973) 99–106.

Notari, R.E., DeYoung, J.L. and Reuning, R.H., Effect of parallel first-order drug loss from site of administration on calculated values for absorption rate constants. J. Pharm. Sci., 61 (1972) 135–138.

Paul, M.F., Bender R.C. and Nohle, E.G., Renal excretion of nitrofurantoin (Furadantin). Am. J. Physiol., 197 (1959) 580–584.

Paul, H.E., Hayes, K.J., Paul, M.F. and Borgmann, A.R., Laboratory studies with nitrofurantoin; relationship between crystal size, urinary excretion in the rat and man, and emesis in dogs. J. Pharm. Sci., 56 (1967) 882–885.

Paul, M.F., Paul, H.E., Bender, R.C., Kopko, F., Harrington, C.M., Ells, V.R. and Buzard, J.A., Studies on the distribution and excretion of certain nitrofurans. Antibiot. Chemother., 10 (1960) 287–302.

Riegelman, S. and Collier, P., The application of statistical moment theory to the evaluation of in vivo dissolution time and absorption time. J. Pharmacokin. Biopharm., 8 (1980) 509–534.

Tanigawara, Y., Yamaoka, K., Nakagawa, T. and Uno, T., Moment analysis for the separation of mean in vivo disintegration, dissolution, absorption, and disposition time of ampicillin products. J. Pharm. Sci., 71 (1982) 1129–1133.

Wagner, J.G. and Nelson, E., Per cent absorbed time plots derived from blood level and/or urinary excretion data. J. Pharm. Sci., 52 (1963) 610–611.

Watari, N., Funaki, T., Aizawa, K. and Kaneniwa, N., Nonlinear assessment of nitrofurantoin bioavailability in rabbits. J. Pharmacokin. Biopharm., 11 (1983) 529–545.

Watari, N., Funaki, T. and Kaneniwa, N., Fluorescence assay of nitrofurantoin with *o*-aminothiophenol in plasma and urine. J. Pharm. Sci., 69 (1980a) 106–107.

Watari, N. and Kaneniwa, N., Dissolution of slightly soluble drugs VIII. In vivo drug dissolution in human subjects and rabbits. Int. J. Pharm., 7 (1981) 307–316.

Watari, N., Kaneniwa, N. and Hanano, M., Comparison of in vivo dissolution of sulfa drugs calculated by deconvolution to absorption rates calculated by multicompartment model method. Int. J. Pharm., 6 (1980b) 155–166.

Woodruff, M.W., Malvin, R.L. and Thompson, I.M., The renal transport of nitrofurantoin. J. Am. Med. Ass., 175 (1961) 1132–1135.

Yamaoka, K., Nakagawa, T. and Uno, T., Statistical moments in pharmacokinetics. J. Pharmacokin. Biopharm., 6 (1978) 547–558.