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Urinary Drug Excretion in Dogs During Therapeutic Doses of Different Nitrofurantoin Dosage Forms

JOHN D. CONKLIN, R. J. SOBERS, and D. L. WAGNER

Abstract □ Nitrofurantoin, a urinary tract antibacterial, was administered daily in different dosage forms to dogs using a multiple-dose regimen and the urinary drug excretion determined. Results are presented which show that two oral dosage forms, microcrystalline drug in a tablet or macrocrystalline drug in a capsule, are well absorbed. Differences observed in urinary drug recoveries and in urinary drug excretion patterns between these dosage forms suggest a slower rate of absorption for the macrocrystals than for the tablet. Data are also provided which indicate that an intramuscular dosage form is very well absorbed and excreted readily in the urine.

Keyphrases □ Dosage forms—nitrofurantoin □ Nitrofurantoin—urinary excretion □ Absorption, nitrofurantoin—parenteral and oral administration

Usually most drugs are administered clinically according to a predetermined daily multiple-dose regimen. Although much effort has been directed recently toward investigating the relationship between the particle size of various drugs and their *in vivo* absorption (1), few of these studies have been conducted using multiple doses in therapeutic amounts. It seems reasonable to assume that a single dose of a drug may not always yield *in vivo* results which reflect accurately those encountered during a multiple-dose regimen. Nitrofurantoin,[1] 1-(5-nitrofurfurylideneamino)hydantoin, is an antibacterial drug effective in the treatment of urinary tract infections (2). Results are presented in this report concerning urinary drug excretion in dogs during daily multiple therapeutic doses of different nitrofurantoin dosage forms.

EXPERIMENTAL

Oral Drug Administration—Four healthy, adult male beagle dogs were selected on the basis of weight (range 13–16 kg.). A crossover design was used in which two of the dogs received one drug dosage form while the other two dogs received the other dosage form. An interval of 15 days during which drug was not administered was maintained between crossovers. Nitrofurantoin either as microcrystalline drug in a tablet (10- and 50-mg. veterinary tablet[2]) or as macrocrystalline drug (80–200 mesh) in a gelatin capsule (10- and 50-mg. veterinary capsule[3]) was administered orally at 4–5 mg./kg. t.i.d. for 10 days (a therapeutic dose and regimen). The drug was administered at 8 a.m., 12 noon, and 4 p.m., either as two 10-mg. tablets plus one 50-mg. tablet or two 10-mg. capsules plus one 50-mg. capsule, respectively, per dose. Heparinized blood samples were collected by venipuncture on Days 1 and 10 at 2 hr. after the second dose of drug. On Days 1 and 10, urine samples were collected (voided and/or by catheterization) from 0–4, 4–8, 8–12, and 12–24 hr. Urine samples were also obtained just before initial drug dosage on Day 1 to serve as controls and on Day 10 to serve as drug residue samples.

Parenteral Drug Administration—Nitrofurantoin sodium[4] as a solution was administered intramuscularly at about 3 mg./kg. b.i.d. for 10 days (a therapeutic dose and regimen) to the same dogs used in the oral drug study. Drug solutions were prepared by dissolving nitrofurantoin sodium in 5 ml. of sterile water to obtain a drug concentration of 36 mg./ml. (pH 9.1). The drug was injected into the left vastus lateralis muscle at 8 a.m. and into the contralateral muscle at 4 p.m. Heparinized blood samples were collected by venipuncture on Days 1 and 10 at 1 hr. after the second dose of drug. Urine samples were collected (voided and/or by catheterization) from 0–4, 4–8, 8–12, and 12–24 hr. on Days 1 and 10. Urine samples were also obtained just before initial drug dosage on Day 1 to serve as controls and on Day 10 to serve as drug residue samples.

In the intravenous drug study, nitrofurantoin sodium as a solution was administered as a single injection at either 3 or 6 mg./kg. to the same dogs used previously. A crossover design similar to the one described in the oral study was utilized. Drug solutions were prepared by dissolving nitrofurantoin sodium in 15 ml. of sterile 5% dextrose solution to obtain a drug concentration of 12 mg./ml. (pH 8.6). The drug was injected into the cephalic vein of one leg and heparinized blood samples then were collected by venipuncture from the contralateral vein at selected intervals. Samples of urine were collected (voided and/or by catheterization) from 0–4, 4–8,

[1] Furadantin, Eaton Laboratories.

[2] Veterinary 50-mg. nitrofurantoin tablet, Furadantin Ora-Bol, Eaton Laboratories.

[3] Veterinary macrocrystalline nitrofurantoin, Dantamacrin, Eaton Laboratories.

[4] Nitrofurantoin sodium, Furadantin sodium, Eaton Laboratories.

Table I—Urinary Excretion of Nitrofurantoin in Dogs During Oral Dosage of Nitrofurantoin Tablets[a]

Dog No.	Av. Dose, mg./kg./day	Nitrofurantoin Excreted, mg. Collection Interval 0–4 hr. Day 1	0–4 hr. Day 10	4–8 hr. Day 1	4–8 hr. Day 10	8–12 hr. Day 1	8–12 hr. Day 10	12–24 hr. Day 1	12–24 hr. Day 10	Dose Recovered, %[b] 0–24 hr. Day 1	Dose Recovered, %[b] 0–24 hr. Day 10
1	13.0	12.8	16.1	25.3	18.6	20.5	25.5	9.6	6.5	32.5	31.8
2	13.1	11.1	7.8	13.1	24.6	20.7	16.0	5.1	10.3	23.8	28.0
3	15.7	14.8	26.4	12.8	19.8	32.6	19.8	5.3	0.9	31.2	31.9
4	15.8	15.0	27.3	16.7	20.5	7.8	19.9	14.9	5.6	26.0	34.9
Av., mg.		13.4	19.4	16.9	20.8	20.4	20.3	8.7	5.8	28.3	31.6
SE, mg.		0.9	4.6	2.9	1.3	5.0	1.9	2.3	1.9	2.0	1.4

[a] Nitrofurantoin as microcrystalline drug in a tablet was administered orally at 4–5 mg./kg. t.i.d. for 10 days. [b] Based on daily dose administered (210 mg.).

Table II—Urinary Excretion of Nitrofurantoin in Dogs During Oral Dosage of Macrocrystalline Nitrofurantoin[a]

Dog No.	Av. Dose, mg./kg./day	Nitrofurantoin Excreted, mg. Collection Interval 0–4 hr. Day 1	0–4 hr. Day 10	4–8 hr. Day 1	4–8 hr. Day 10	8–12 hr. Day 1	8–12 hr. Day 10	12–24 hr. Day 1	12–24 hr. Day 10	Dose Recovered, %[b] 0–24 hr. Day 1	Dose Recovered, %[b] 0–24 hr. Day 10
1	12.6	10.0	11.0	13.6	16.6	7.6	17.0	12.2	10.3	20.7	26.1
2	13.3	8.0	8.3	13.5	8.6	14.3	11.4	13.5	4.4	23.5	15.6
3	15.2	13.3	5.6	11.1	14.2	20.5	16.1	16.5	5.1	29.2	19.5
4	15.7	9.0	15.4	23.6	11.1	14.7	12.9	2.3	4.4	23.6	20.9
Av., mg.		10.0	10.0	15.4	12.6	14.2	14.3	11.1	6.0	24.2	20.5
SE, mg.		1.1	2.1	2.7	1.7	2.6	1.3	3.0	1.4	1.7	2.1

[a] Nitrofurantoin as macrocrystalline drug in a gelatin capsule was administered orally at 4–5 mg./kg. t.i.d. for 10 days. [b] Based on daily dose administered (210 mg.).

and 8–24 hr. Blood and urine samples were obtained just before drug dosage to serve as controls.

Drug Analysis—The urine samples were analyzed for nitrofurantoin by the method of Conklin and Hollifield (3), while the samples of blood were assayed for drug by a modification of this procedure (4). These procedures each have a sensitivity of 2 mg./l. and are considered specific for the determination of unchanged nitrofurantoin (3–5).

Statistical evaluation of the results depended on the mean values acquired with the same animals. The paired Student's t test was applied to determine the significance of differences between means and the probability estimates were recorded. Standard errors were calculated whenever necessary.

RESULTS

Oral Drug Administration—Drug was not detectable in any of the blood samples collected from each animal at 2 hr. after the second dose of the two nitrofurantoin oral dosage forms on either Day 1 or Day 10 (limit of detection, 2 mg./l.). In contrast, the urinary drug excretion data presented in Tables I and II show that nitrofurantoin was consistently present in the urine during the administration of either the tablet or the macrocrystalline drug.

The average urinary drug recovery (0–24 hr.) encountered in the four dogs following 10 days of tablet administration (31.6%) was not significantly different ($p < 0.05$) from that obtained on the first day of tablet dosage (28.3%). An identical comparison revealed that there was also no significant difference ($p < 0.05$) between Day 1 (24.2%) and Day 10 (20.5%) for the macrocrystalline drug.

Illustrated in Fig. 1 are the average (Days 1 and 10 combined) urinary drug excretion patterns obtained in the four dogs for each of the oral dosage forms. During administration of the tablet, greater amounts of drug were present in the urine (0–12 hr.) than were found during dosage of the macrocrystals. In comparison, during the succeeding 12 hr. of the day, a smaller amount of drug was recovered in the urine (12–24 hr.) after dosage of the tablet than following administration of the macrocrystals. The average urinary drug recoveries (0–24 hr.) observed with the tablet (Table I) are significantly greater ($p < 0.05$) than those noted for the macrocrystalline drug (Table II).

An average of about 0.1% of the daily dose of either the tablet or the macrocrystalline drug was present in the urine collected at 16 hr. following the final dose of drug on Day 9. No adjustment was made for this drug residue in calculating the urinary drug recoveries for Day 10 (Tables I and II).

Parenteral Drug Administration—The analysis of blood samples collected from each animal at 1 hr. after the second intramuscular dose of nitrofurantoin sodium on either Day 1 or Day 10 revealed that drug was not detectable (limit of detection, 2 mg./l.). However, as shown by the results in Table III, substantial amounts of nitro-

Table III—Urinary Excretion of Nitrofurantoin in Dogs During Intramuscular Dosage of Nitrofurantoin Sodium[a]

Dog No.	Av. Dose, mg./kg./day	Nitrofurantoin Excreted, mg. Collection Interval 0–4 hr. Day 1	0–4 hr. Day 10	4–8 hr. Day 1	4–8 hr. Day 10	8–12 hr. Day 1	8–12 hr. Day 10	12–24 hr. Day 1	12–24 hr. Day 10	Dose Recovered, %[b] 0–24 hr. Day 1	Dose Recovered, %[b] 0–24 hr. Day 10
1	6.3	14.6	16.4	2.4	0.2	14.8	11.6	1.0	2.9	31.2	29.4
2	6.6	19.9	19.2	0.2	0.4	11.0	7.5	1.5	0.3	31.0	26.0
3	5.9	12.3	14.9	2.2	0.6	13.2	15.3	0.9	0.9	33.5	36.9
4	6.3	16.6	15.6	0.2	0.2	10.7	11.8	1.7	1.2	34.0	33.6
Av., mg.		15.8	16.5	1.2	0.3	12.4	11.5	1.2	1.3	32.4	31.4
SE, mg.		1.6	0.9	0.6	0.1	0.9	1.6	0.2	0.5	0.7	2.3

[a] Nitrofurantoin sodium as a solution in water (pH 9.1) was administered intramuscularly at about 3.0 mg./kg. b.i.d. for 10 days. [b] Based on daily dose administered (101 mg. for Dogs 1, 2; 86 mg. for Dogs 3, 4).

Table IV—Urinary Excretion of Nitrofurantoin in Dogs Following Intravenous Dosage of Nitrofurantoin Sodium[a]

Dose, mg./kg.	Nitrofurantoin Excreted[b], mg. Collection Interval 0–4 hr.	4–8 hr.	8–24 hr.	Dose Recovered, %[c] 0–24 hr.
3.0	15.1 *SE* 1.2	0.8 *SE* 0.2	0.2 *SE* 0.04	36.2 *SE* 3.8
6.0	29.8 *SE* 1.7	1.2 *SE* 0.4	0.3 *SE* 0.08	34.5 *SE* 1.8

[a] Nitrofurantoin sodium as a solution in 5% dextrose (pH 8.6) was administered intravenously as a single injection either at 3.0 or 6.0 mg./kg. [b] Represents an average for four dogs. [c] Based on the single dose administered.

furantoin were excreted readily in the urine under these conditions. The average urinary drug recovery (0–24 hr.) obtained in the four dogs on the first day of intramuscular dosage (32.4%) was not significantly different ($p < 0.05$) from that encountered following 10 days of intramuscular drug administration (31.4%). Only traces of drug were occasionally detectable in the urine collected at 16 hr. after the last dose of drug on Day 9.

For comparison, nitrofurantoin sodium was administered as a single intravenous injection at two different doses to the same dogs. As illustrated in Fig. 2, the blood drug concentrations encountered were dose related. In agreement with this, a drug dose response was obtained in urine (see Table IV). This direct relationship indicates that urinary drug excretion may be used as a reliable indicator for the *in vivo* absorption of nitrofurantoin. Similar half-lives (average for four dogs) for nitrofurantoin in blood were obtained for each of the doses used (3 mg./kg.—27 min., 6 mg./kg.—34 min.). These values agree with half-lives reported previously for equivalent intravenous doses of nitrofurantoin sodium in dogs (6).

An average urinary drug recovery (0–24 hr.) of 36.2% was obtained in the four dogs following the intravenous administration of nitrofurantoin sodium at 3 mg./kg. (Table IV). If it is assumed that this value represents complete *in vivo* absorption for nitrofurantoin in these dogs, then the average urinary drug recoveries encountered during intramuscular drug dosage (Table III) indicate that this dosage form was very well absorbed. An identical comparison of the data acquired with the oral dosage forms (Tables I and II) revealed that both dosage forms were well absorbed and that less drug was absorbed following macrocrystal dosage than after administration of the tablet.

DISCUSSION

Although blood drug concentration is often used to measure the *in vivo* absorption of drug dosage forms, blood drug levels were not detectable in the present study following daily parenteral or oral multiple therapeutic doses of nitrofurantoin. However, the influence of the dosage form of nitrofurantoin becomes apparent when the urinary drug excretion results are examined. As anticipated, the parenteral dosage form was very well absorbed. Both of the oral dosage forms were well absorbed although greater drug absorption occurred following dosage of the tablet than after administration of the macrocrystals.

Greater average urinary drug recoveries (0–24 hr.) were obtained with the tablet dosage form than with the macrocrystalline dosage form (Tables I and II). Less drug was excreted during dosage of the macrocrystals than during administration of the tablet (0–12 hr.), while the drug excretion encountered with the macrocrystals usually became greater than that observed with the tablet during the final 12 hr. (12–24 hr.) of the day (Fig. 1). Similar results concerning drug absorption and subsequent patterns of urinary drug excretion were obtained in a corresponding study conducted recently in humans during a daily therapeutic dose regimen with orally administered nitrofurantoin, either as microcrystalline drug in a tablet or as macrocrystalline drug[5] in a gelatin capsule (7). These data indicate a difference in urinary drug excretion, apparently due to *in vivo* availability differences between the two dosage forms. It has been suggested, on the basis of data obtained previously with single oral doses of nitrofurantoin, that these

[5] Medical macrocrystalline nitrofurantoin, Macrodantin, Eaton Laboratories.

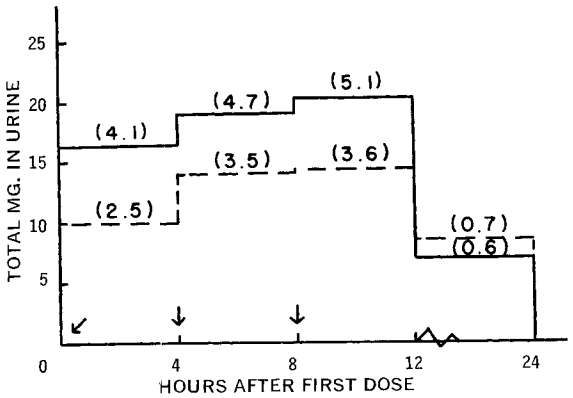

Figure 1—*Urinary excretion of nitrofurantoin in dogs (average for four dogs), average for Days 1 and 10 combined, following oral administration of either nitrofurantoin tablets or macrocrystalline nitrofurantoin at 4–5 mg./kg. t.i.d. Key: —, tablet; ---, macrocrystals. Figures in parentheses represent the average urinary excretion rate in mg./hr. The arrows indicate the time of dose.*

characteristics reflect a slower rate of absorption for the macrocrystals than for the microcrystalline drug (8).

During the present investigation, the average output of urine encountered was about 10 ml./hr. Under *in vitro* conditions, an average minimal inhibitory concentration of 20 mg./l. was obtained for nitrofurantoin against a number of *Escherichia coli* strains. Utilizing these values, it is estimated that a urinary excretion rate of at least 0.2 mg./hr. would be required for nitrofurantoin to provide effectiveness against *E. coli*. Although less drug was absorbed following dosage of the macrocrystals than after administration of the tablet, it should be noted that the urinary drug excretion rates attained with each of these oral dosage forms were usually in considerable excess of 0.2 mg./hr. during a 24-hr. period (Tables I and II). In comparison, consistent urinary drug excretion rates greater than 0.2 mg./hr. were only apparent within the first 4 hr. after administration of the intramuscular dosage form (Table III).

In conclusion, results are presented regarding urinary drug excretion in dogs during daily multiple therapeutic doses of different nitrofurantoin dosage forms. Data are provided which indicate that two oral dosage forms, microcrystalline drug in a tablet or macrocrystalline drug in a capsule, are well absorbed. The differences observed in urinary drug recoveries and in urinary drug excretion patterns between these two dosage forms suggest that there is a slower rate of absorption for the macrocrystals than for

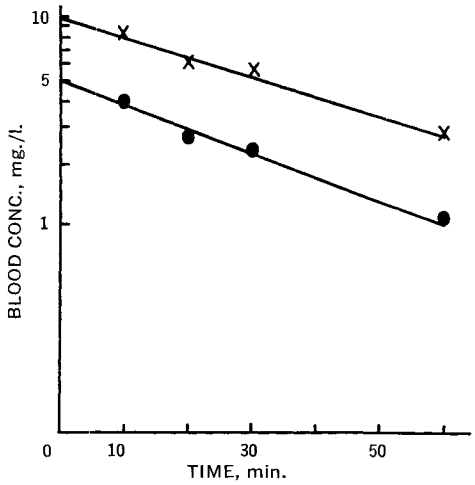

Figure 2—*Disappearance of nitrofurantoin from the blood of dogs (average for four dogs) following intravenous administration of nitrofurantoin sodium. Key: ●, 3 mg./kg., $T^1/_2$ 27 min.; ×, 6 mg./kg., $T^1/_2$ 34 min.*

the tablet. Results are also presented which show that an intramuscular dosage form is very well absorbed and excreted readily in the urine.

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Physiologic Surface-Active Agents and Drug Absorption IV: Effect of Pre-Micellar Concentrations of Surfactant on Dissolution Rate

HOWARD WEINTRAUB* and MILO GIBALDI

Abstract ☐ The influence of a nonionic surfactant and certain physiologic surfactants and components of gastric juice on the dissolution rate of drug powders was examined. In addition, the effects of pre-micellar concentrations of surfactant on the dissolution rate of aspirin from commercial dosage forms were determined. Low concentrations of polyoxyethylene (23) lauryl ether (POE lauryl ether), and lysolecithin markedly enhanced the dissolution rate of salicylic acid powder while pepsin and gastric mucin were without effect. Sodium glycocholate was found to increase considerably the dissolution rate of salicylamide powder in pH 6.0 buffer. Both POE lauryl ether and lysolecithin enhanced the dissolution rate of aspirin from a tablet dosage form but were without effect on the dissolution rate of the drug from a capsule dosage form. Good correlation was observed between the surface tensions of the POE lauryl ether solutions and the dissolution rates of aspirin from the tablet dosage form in these media. The relevance of these data to the design of *in vitro* dissolution tests is discussed.

Keyphrases ☐ Surfactants, physiologic—dosage form dissolution ☐ Pre-micellar surfactant concentration—dissolution rates ☐ Dissolution rates—surfactants, gastric mucin ☐ UV spectrophotometry—analysis

There is a strong likelihood that certain components of the gastrointestinal tract facilitate drug dissolution. Biliary secretion results in relatively large concentrations of highly surface-active materials in the proximal intestine. Components of bile such as conjugated bile salts and lysolecithin have been found to markedly increase the solubility and dissolution rate of various poorly water-soluble drugs (1–4). Pekanmaki and Salmi (5) report a marked decrease in the absorption of poorly soluble phenolphthalein when drainage of bile into the rat intestine is prevented. However, the absence of bile had no effect on the absorption of the water-soluble glucuronide conjugate of phenolphthalein. More recently Meli *et al.* (6) note that endogenous bile influences the rate of intestinal absorption of ethynylestradiol-3-cyclopentyl ether in rats. The rate of absorption of the estrogen is considerably lower in bile duct-cannulated rats than in control animals. Since the drug is relatively water-insoluble, it is reasonable to consider that the presence of bile increases the solubility of the drug in the intestinal lumen and thereby enhances the dissolution and absorption rate.

Finholt and Solvang (7) have suggested the presence of physiologic surfactants in human gastric fluid. Samples of gastric juice obtained from patients under examination for diseases of the stomach manifested rather low surface tenson values (35 to 50 dynes/cm.) and marked wetting activity as judged by powder dissolution studies. The rates of dissolution of phenacetin in diluted gastric juice and in dilute HCl at the same pH and adjusted to the same surface tension as gastric juice with polysorbate 80 were similar but markedly faster than the rates observed in dilute HCl alone.

The influence of surface-active agents on the dissolution rates of relatively water-insoluble drugs may involve several mechanisms. For example, a surfactant may decrease the interfacial energy barrier between the drug and the dissolution medium, allowing the drug to be "wet" more completely and thereby effectively increase the available surface area of the solid. Additionally, concentrations of surfactant above the critical micelle concentration (CMC) may markedly increase the apparent solubility of the drug in the medium by means of micellar solubilization and thereby effect an increase in the dissolution rate, which is a function of diffusional parameters and the hydrodynamics of the system (8–10). While the influence of micellar solubilization on dissolution has been studied rather extensively, the effect of low concentrations (below the CMC) of surface-active agents on the dissolution of drugs from