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ABSORPTION AND DISPOSITION CHARACTERISTICS OF NITROFURANTOIN IN DOGS

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ABSTRACT

This study reports the disposition kinetic properties of nitrofurantoin in dogs following single intravenous and oral administration of various formulations of nitrofurantoin. Also reported here is the effect of delaying gastric emptying by food and atropine on the absorption characteristics of nitrofurantoin. The drug absorption parameters calculated using a deconvolution computer program indicate that the rate and extent of enterohepatic recycling affects the elimination and absorption rate constants and thus confound the bioavailability calculations of nitrofurantoin, heretofore unrecognized in the literature.

The plasma half-life following intravenous administration was 31 min (monoexponential equation) with little effect of enterohepatic recycling noted. Following oral administration, a biexponential equation with lag-time was used to fit the blood levels. The absorption half-lives were higher when nitrofurantoin was administered as a solid dosage form compared to a solution. The absorption half-lives following tablet administration ranged from 30 to 72 min and were not affected by food or atropine. The elimination half-lives following oral administration ranged from 19 to 87 min with significantly prolonged elimination when solid dosage forms were administered compared to solution. The extent of absorption ranged from 38 to 120 per cent. A direct correlation between the absorption and elimination half-lives was established, indicating that increased biliary recycling direct affects the apparent disposition half-life. The three brands of nitrofurantoin tested for bioavailability showed that the use of blood levels without appropriate corrections for biliary recycling are not suitable for bioavailability testing of nitrofurantoin. The use of urinary excretion data in evaluating nitrofurantoin bioavailability is also questioned in the study.

KEY WORDS Nitrofurantoin Absorption Disposition Biliary recycling Deconvolution method Food and drug absorption Bioavailability urinary extraction Effect of delayed gastric emptying

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INTRODUCTION

Nitrofurantoin is a weak acid with poor water solubility (0·2 mg/ml), and as a result, it has potential problems in its bioavailability.[1] To this date, all bioavailability comparisons on nitrofurantoin formulations have been performed by the estimation of intact fractions of nitrofurantoin excreted in the urine.[1] No blood level study has been reported on nitrofurantoin to ascertain its absorption or disposition kinetics, due mainly to the lack of availability of a sensitive analytic methodology.[2] In this study, using a highly sensitive high pressure liquid chromatographic method[3] we report disposition kinetic characteristics of nitrofurantoin following administration of various dosage forms in dogs. These data are applied to bioavailability calculations using a deconvolution technique.

EXPERIMENTAL

Animals

Four healthy female beagle dogs, ages 1·5–2·5 yr and weighing between 10·5 and 12·5 kg, were used in this study. In intravenous studies, the cephalic vein in both the forelegs was cannulated using an indwelling catheter* with a rubber stopper. The drug solution was injected through one cephalic vein and the samples collected from the other cephalic vein. For oral dose studies, only one cephalic vein was catheterized. All studies were performed after 24 h fasting. At least 48 h was allowed to clear the drug from the animals between studies.

Intravenous study

Nitrofurantoin sodium was used as supplied in a commercial dosage form.† A 50 mg dose was injected through the cephalic vein, followed by 10 ml of sterile normal saline; blood samples were collected at 15 min intervals for 1 h and then at 30 min for a period of 3 h.

Oral solution study

A 50 mg dose of nitrofurantoin sodium in 5 ml of normal saline was introduced into the stomach by means of a stomach tube.‡ Prior to the administration of the drug solution, 20 ml of normal saline were introduced through the same tube to dilute gastrointestinal fluids and thus minimize local irritation due to high concentration of the drug. The stomach tube was flushed with 30 ml of normal saline. The blood samples were collected for up to 4 h.

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* Monoject, needle gauge 22, length 2'. St. Louis, MO.
† Invandantin, Norwich-Eaton Pharmaceuticals, N.Y.
‡ 18 french, Davor, N.Y.

Oral tablet study

Studies were performed using commercial* tablets given: (i) whole tablets on fasting, (ii) whole tablets followed by food (400 g of horsemeat†), and (iii) whole tablets followed by 0·2 mg atropine‡ given intramuscularly in the hind leg followed by food. Bioavailability comparisons were made within three commercially available tables§ ‖ of nitrofurantoin on fasting only. The blood samples were collected for up to 8 h.

Drug analysis

The plasma levels of nitrofurantoin were analysed using a high pressure liquid chromatographic technique as described elsewhere.[3] A 50 µl aliquot of the deproteinated plasma sample was injected¶ on the column** and the absorbance monitored at 365 nm, using a dual channel detector.††. The solvent system used was 20 per cent methanol‡‡ in distilled water adjusted to pH 5·0 using 0·1 M sodium acetate.§§ A high pressure pump‖‖ was used to drive the solvent system. A linear recorder¶¶ was used to record the peak heights. The plasma samples were protected from light at all times to avoid possible degradation of nitrofurantoin.[4]

Curve fitting

The absorption rate and extent were calculated by a least square deconvolution method according to the algorithm and computer program described elsewhere.[5]

The concentration of drug in the blood after an intravenous dose, C_{iv}, is approximated by a poly-exponential expression:

$$C_{iv}(t) = \sum_{i=1}^{n} a_i e^{-\alpha_i t} \quad (1)$$

where a is the zero time intercept, and α is the first-order elimination constant.

The intravenous bolus data were adequately approximated by a single exponential expression and the oral data by a two-exponential function with a lag time.

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* Nitrofurantoin 100 mg tablet, Norwich-Eaton Pharmaceuticals, N.Y.
† Evanger's Dog and Cat Food Company, Chicago, IL.
‡ Atropine Sulfate Injection, Abboject®, Abbott, Chicago, IL.
§ Purepac Nitrofurantoin Tablets, NDC 0228-2264-10, Purepac Pharm. Co., N.Y.
‖ Cyantin®, Nitrofurantoin 100 mg tablets, Laderle Labs., N.Y.
¶ U6-K Injector, Water Associates, Milford, MA.
** 440-A Dual Channel detector, Water Associates, Milford, MA.
†† C_{18}-µBondapak reversed phase column, Water Associates, Milford, MA.
‡‡ Methanol, glass distilled, Burdick and Jackson, MA.
§§ Sodium Acetate, Malinckrodt Chemical Works, St. Louis, MO.
‖‖ M-600 A, Water Associates, Milford, MA.
¶¶ Linear Recorder 10 M, Linear Instruments Inc., CA.

The cumulative amount of drug input expressed as percentage of dose, PCT, is given by

$$\mathrm{PCT}(t) = u_0 + u_1 \exp(v_1 t_+) + u_2 \exp(-v_2 t_+) \tag{2}$$

where v_1 and v_2 are absorption and elimination rate constants, and where

$$t_+ = (t - t_{\mathrm{lag}})_+ \tag{3}$$

and

$$u_0 + u_1 + u_2 = 0 \tag{4}$$

The detailed derivation of the above equations is given elsewhere.[5] The curve fittings and parameter estimations were performed using an interactive non-linear regression program FUNFIT.[6] The statistical analysis was made by using analysis of variance.

RESULTS AND DISCUSSION

Intravenous studies

Despite the fact that nitrofurantoin has been in use for a long time, no comprehensive pharmacokinetic data on it have been reported following intravenous administration. Only one study has reported blood levels on nitrofurantoin lasting a few minutes after intravenous administration.[2]

Figure 1 shows typical plasma profiles obtained after administering 50 mg of nitrofurantoin intravenously; the fitted pharmacokinetic parameters are listed in Table 1. The intravenous blood level data were adequately expressed by a monoexponential equation.

The elimination half-lives, volumes of distribution, and total body clearance values are given in Table 2.

The average elimination half-life of nitrofurantoin was 31 min. This value is in agreement with a previously reported half-life of 25 min.[7] The average volume of distribution was 0·46 l/kg suggesting that the drug may readily distribute into the extracellular and intracellular fluids.

Oral solutions studies

The typical plasma levels obtained after administering 50 mg of nitrofurantoin sodium solution are shown in Figure 1. The peak plasma levels ranged from 3·0 to 4·6 μg/ml and the peaks occurred between 30 and 60 min.

The plasma profiles were adequately described by a biexponential equation with a lag time as given by

$$C(t) = b[\exp(-\beta_1(t - t_{\mathrm{lag}})_+ - \exp(-\beta_2(t - t_{\mathrm{lag}+})] \tag{5}$$

where b is the zero-time intercept, and β_1 and β_2 are the first-order elimination and absorption rate constants respectively.

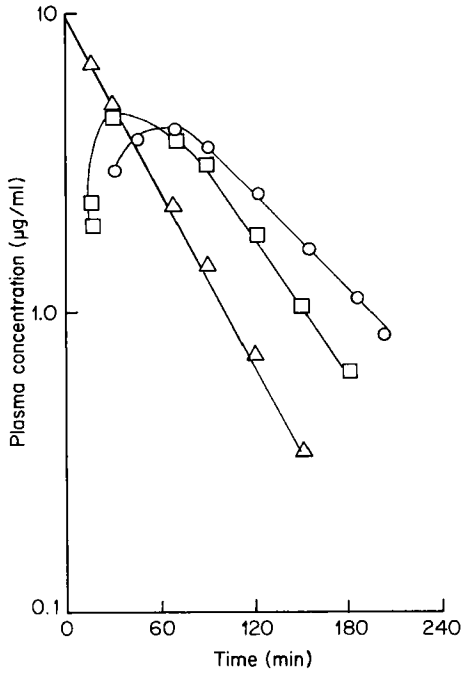

Figure 1. Plasma profiles of nitrofurantoin following intravenous (△), oral solution (□), and oral tablet (○) in a typical dog (#2)

Table 1. Least squares approximation of nitrofurantoin plasma level response from intravenous bolus administration*

Dog	a (μg/ml)	α (min^{-1})	RSS† (μg/ml)
1	11·1	0·0299	0·022
2	9·56	0·0208	0·017
3	10·6	0·0224	0·025
4	7·88	0·0191	0·011

*$ae^{-\alpha t}$.
† RSS = Residual sum of squares.

The parameters of equations (2) and (5) as determined by least square fittings are given in Tables 3 and 4.

For the oral solution studies the elimination half-lives of nitrofurantoin (Table 5) ranged from 19 to 28 min in dogs 1, 2, and 3, and 44 min in dog 4. The absorption half-lives in dogs 1, 2, and 3 ranged from 18 to 26 min but in dog

Table 2. Elimination half-life, volume of distribution, and total body clearance of nitrofurantoin plasma level from intravenous bolus administration

Dog	Elimination $t_{0.5}$ (min)	Volume of distribution (l/kg)*	Total body clearance (l/min/kg)
1	23·1	0·398	0·0119
2	33·3	0·418	0·00869
3	30·9	0·467	0·0104
4	36·2	0·551	0·0105
Mean + S.D.	30·9 ± 5·61	0·458 ± 0·0681	0·0104 ± 0·00131

* Dog #1, 11·3 kg; dog #2, 12·5 kg; dog #3, 10·10 kg; and dog #4, 11·51 kg.

4 the value was 40 min. There was no statistical difference in the half-lives obtained from intravenous and oral solution studies. The percentage of administered dose absorbed ranged from 68 to 107 per cent in dogs 1, 2, and 3 and 117 per cent in dog 4 (Table 5).

Some studies showed a secondary hump after oral solution administration of nitrofurantoin. It is indicative of enterohepatic recycling, previously observed by Conklin and Wagner.[8] The enterohepatic recycling is important because of the unusual biliary excretion properties of nitrofurantoin,[8] which has a bile to blood ratio of 200 and has significant hydrocholerectic effect. In the dose range of 3·0–6·0 mg/kg, about 17–22 per cent of nitrofurantoin is recovered in bile after 6 h with an apparent saturation of the biliary excretion taking place at doses of 24 mg/kg.[7] In this study, a 50 mg dose of nitrofurantoin was given which is significantly above the minimum required to produce hydrocholerectic effect but below the saturation level. Thus, a large amount of bile is expected to be produced and released either continuously resulting in a continuous circulation of nitrofurantoin from the gastrointestinal tract,[9] or released in a discontinuous manner[10] resulting in secondary peaks. The process of continuous or discontinuous re-absorption has been mathematically described elsewhere.[11] On a physiologic basis, however, little recirculation will be possible within 1–2 h of administration. In animals showing significant biliary excretion, the disposition half-life following oral administration was significantly prolonged compared to intravenous administration. This is further reflected in the calculation of total bioavailability (Table 5) wherein more than 100 per cent absorption is noted for animals showing most prolonged elimination half-life. This is due to repeated appearance of nitrofurantoin molecules in the blood as a result of biliary recycling. Thus all bioavailability calculations based on blood level data will result in overestimation, which cannot be resolved unless exact biliary excretion function is established.

Table 3. Least squares approximation of nitrofurantoin plasma level response from oral administration*

Dog	Treatment‡	b (μg/ml)	β_1 (min^{-1})	β_2 (min^{-1})	t_{lag} (min)	RSS† $(\mu g/ml)^2$
1	A	171·0	0·0119	0·0122	24·0	0·20
1	B	180·0	0·0112	0·0114	21·0	0·20
1	C	155·0	0·0140	0·0147	55·0	0·54
1	D	431·0	0·0191	0·0196	22·0	1·05
1	E	767·0	0·0197	0·0198	75·0	0·22
1	F	266·0	0·0255	0·0263	9·2	0·15
2	A	92·9	0·0182	0·0204	21·0	0·15
2	B	34·2	0·0136	0·0171	3·1	0·12
2	C	51·0	0·0121	0·0138	47·0	1·24
2	D	73·9	0·00933	0·0108	19·0	1·56
2	E	234·0	0·0172	0·0178	0·0	0·22
2	F	65·4	0·0241	0·0294	5·7	0·16
3	A	794·0	0·0116	0·0117	29·0	2·27
3	B	180·0	0·0215	0·0266	24·0	0·18
3	C	31·9	0·00791	0·00951	52·0	1·98
3	D	93·5	0·0162	0·0177	19·0	0·62
3	E	28·7	0·0101	0·0134	36·0	0·69
3	F	258·0	0·0357	0·0373	13·0	0·24
4	A	127·0	0·0118	0·0128	26·0	3·32
4	B	109·0	0·0123	0·0137	2·6	2·0
4	C	26·6	0·0122	0·0167	23·0	0·62
4	F	84·6	0·0157	0·0173	33·0	1·55

* $b[\exp(-\beta(t-t_{lag})_+)-\exp(-\beta_2(t-t_{lag})_+]$.
† RSS = Residual sum of squares.
‡ Key:
A 100 mg oral tablet (Furadantin), fasting.
B 100 mg oral tablet (Furadantin) with food.
C 100 mg oral tablet (Furadantin) with food +0·2 mg atropine given intramuscularly.
D 100 mg oral tablet (Purepac), fasting.
E 100 mg oral tablet (Cyantin), fasting.
F 100 mg oral solution (Ivadantin), fasting.

Oral tablet studies: effects of food and atropine

The effects of food and atropine were studied using only one commercial tablet dosage form. The plasma level profiles were fitted by a biexponential equation (5) and the computer-derived parameters are given in Table 3. The peak plasma levels ranged from 1·5 to 4·0 μg/ml and the time to reach peak concentration ranged from 0·6 to 3 h. The elimination half-lives ranged from 32 to 87 min and were significantly higher than obtained from intravenous or oral solution dosage forms (Table 5 at $p < 0·05$). There was no statistical difference in the half-lives obtained after administering nitrofurantoin solid dosage form

Table 4. Cumulative input function,* calculated by least squares poly-exponential deconvolution

Dog	Treatment†	u_0 (%)	u_1 (%)	u_2 (%)	v_1 (min^{-1})	v_2 (min^{-1})
1	A	67·2	−1178·0	1111·0	0·0119	0·0123
1	B	54·6	−1374·0	1319·0	0·0112	0·0114
1	C	66·5	−796·0	730·0	0·0140	0·0147
1	D	72·5	−1103·0	1031·0	0·0191	0·0196
1	E	38·1	−1810·0	1772·0	0·0197	0·0198
1	F	82·7	−417·0	334·0	0·0255	0·0263
2	A	60·6	−71·4	10·7	0·0182	0·0204
2	B	56·4	−95·0	38·6	0·0136	0·0171
2	C	56·0	−193·0	137·0	0·0121	0·0138
2	D	120·0	−477·0	357·0	0·00933	0·0108
2	E	48·4	−259·0	210·0	0·0172	0·0178
2	F	107·0	93·3	−200·0	0·0241	0·0294
3	A	79·7	−3496·0	3417·0	0·0116	0·0117
3	B	43·4	−35·2	−8·24	0·0215	0·0226
3	C	71·4	−275·0	203·0	0·00791	0·00951
3	D	72·3	−164·0	91·6	0·0010	0·0134
3	E	52·3	−171·0	118·0	0·0162	0·0177
3	F	68·0	900·0	−966·0	0·0357	0·03731
4	A	110·0	−507·0	397·0	0·0118	0·0128
4	B	110·0	−383·0	273·0	0·0123	0·0137
4	C	71·0	−95·5	24·5	0·0122	0·0167
4	F	117·0	−231·0	114·0	0·0157	0·0173

* Refer to equation (2).
† See Table 3 for key to the treatments.

either on fasting, with food or with atropine and food. However, the prolongation of half-lives compared to intravenous or oral solution dosage forms suggests continuous reabsorption according to the various biliary recirculation models.[11]

The absorption half-lives ranged from 30 to 72 min and these were significantly higher compared to oral solution form but there was no statistical difference of the treatments, fasting, food, or food with atropine (Table 5). Secondary plasma concentration humps were observed in several instances.

The percentage drug absorbed ranged from 38 to 120 per cent. Compared to the solution dosage form, absorption after food and atropine showed statistically higher absorption; however, there was no effect noted statistically between fasting and food, plus atropine treatment. This finding is contrary to a previous report,[12] where the percentage drug absorbed was shown to increase when the drug was given with food and it was attributed to delayed gastric emptying.

Table 5. Absorption and disposition characteristics of nitrofurantoin following administration of various dosage forms under different conditions

Treatments*	$t_{\frac{1}{2}}$ Elimination	$t_{\frac{1}{2}}$ Absorption	Percentage absorption
Intravenous	30·9 ± 5·61 (30·0)	~0	100†
F	29·8 ± 5·2 (27·4)	27·1 ± 4·6 (25·0)	93·7 ± 11·2 (89·5)
A	53·6 ± 5·2 (51·7)	50·8 ± 5·7 (48·4)	79·4 ± 10·9 (75·4)
B	50·3 ± 6·4 (47·3)	45·6 ± 6·5 (42·7)	66·1 ± 14·9 (58·7)
C	62·8 ± 8·5 (60·0)	52·9 ± 6·9 (50·6)	66·2 ± 3·6 (65·6)
D	59·7 ± 11·8 (53·9)	50·4 ± 8·3 (47·4)	88·3 ± 15·9 (83·4)
E	39·3 ± 2·2 (39·1)	37·7 ± 1·3 (37·6)	46·3 ± 4·2 (45·4)

* See Table 3 for key to the treatments.
† Assumed.
Values in parentheses represent harmonic means.

An apparent lack of influence of food and atropine on absorption can be explained on the basis of hydrochlorectic effects of nitrofurantoin, which may be dominant over other factors in influencing the amount of drug absorbed.

The relationship between the apparent disposition half-life and the blood levels is further clarified through the analysis of disposition half-life dependence on absorption half-life. Figure 2 shows striking linear relationship between absorption and elimination half-lives ($r > 0{\cdot}9$). This observation further elaborates on the role of biliary recycling on apparent disposition half-lives. Since the elimination half-life of nitrofurantoin is about 30 min in the absence of any significant biliary recycling such as shown for intravenous administration, the apparent disposition half-life when the absorption is prolonged is determined by the absorption phase. In addition, prolonged stay of the drug in the gastrointestinal tract will have enhanced hydrocholerectic effect. Thus the total area under the curve is increased due to recycling effect making it an inappropriate measure of bioavailability unless corrections for the factors described above have been made.

The nonlinear nature of nitrofurantoin disposition will be less apparent when total urinary recovery of nitrofurantoin is used as measure of its bioavailability. However, the highly variable nature of biliary recycling will result in different extent of drug excretion in the feces and thus the urine data represent only the

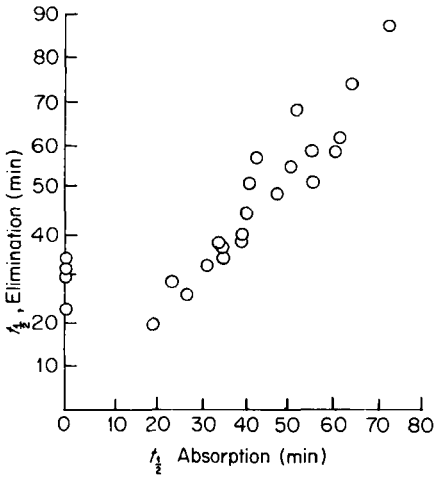

Figure 2. Correlation between absorption and elimination half-lives of nitrofurantoin

apparent bioavailability and cannot be used for the evaluation of dosage forms and to study the effect of treatments such as food on the bioavailability.

CONCLUSION

1. The plasma profiles of nitrofurantoin after intravenous administration can be fitted by a monoexponential equation resulting in an elimination half-life of 31 min. The consistency in the half-life values seems to indicate that during intravenous administration enterohepatic recycling is not predominant.

2. The plasma profiles after oral administration of drug either as solution or as a tablet can be adequately fitted by a biexponential equation with a lag-time. The elimination and absorption half-lives ranged from 32 to 89 min and 30 to 72 min independent of condition of drug administration. When nitrofurantoin is administered orally, it undergoes enterohepatic recycling, where the reabsorption of nitrofurantoin could occur either by continuous reabsorption or by discontinuous step function or process.

3. In the light of our findings, less justification exists for studies where an intact amount of nitrofurantoin excreted in urine is used to measure the bioavailability of nitrofurantoin, since biliary recycling will affect the extent of drug eliminated in the urine.

4. The bioavailability calculations of nitrofurantoin using blood level data are meaningful only if the rate and extent of enterohepatic recycling are known. A deconvolution to determine the rate and extent of enterohepatic recycling in our study as done for cimetidine[13] was not possible because of the apparent erratic nature of nitrofurantoin excretion into the intestine through the gallbladder and the significant hydrocholerectic effect of nitrofurantoin.

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