International Journal of Pharmaceutics, 57 (1989) 177–180
Elsevier

IJP 01978

Absorption of orally, intraduodenally, and intraileally administered nitrofurantoin in man

Daniel L. Wagner [1], John D. Nesbitt [1], John D. Conklin [1] and Francis J. Hailey [2]

[1] *Biopharmaceutics Section, Drug Safety Assessment Department, Norwich Eaton Pharmaceuticals, Inc., Norwich, NY (U.S.A.) and* [2] *Medical Affairs Division, Norwich Eaton Pharmaceuticals, Inc., Norwich, NY (U.S.A.)*

(Received 14 October 1987)
(Modified versions received 8 March 1989 and 9 August 1989)
(Accepted 22 August 1989)

Key words: Nitrofurantoin; Absorption; Dosage route; Pharmacokinetics; Plasma level; Urinary excretion

Nitrofurantoin in aqueous media was administered orally (PO), intraduodenally (ID), and intraileally (II) to a limited number of human volunteers. The results showed that the extent of absorption was similar when the drug was administered PO and ID. Relative to the PO and ID dosage routes, the drug was only about one-half as well absorbed when dosed II.

Nitrofurantoin is clinically effective in treating urinary tract infections (D'Arcy, 1985). The pharmacokinetics of nitrofurantoin in animals and humans has been reviewed (Conklin, 1978; Enzensberger and Stille, 1983). Although information is available indicating that nitrofurantoin is preferentially absorbed from the intestine in animals (Buzard et al., 1961; Veronese et al., 1974), only limited information is available for man (Parrott and Matheson, 1977; Voemel et al., 1969). Using a small number of subjects, the opportunity was taken to obtain preliminary corresponding information in man. The drug was administered orally, intraduodenally, and intraileally as an aqueous nitrofurantoin monohydrate suspension (NFM) and an aqueous nitrofurantoin sodium solution (NFNa).

Six healthy male Caucasian volunteers (23 to 39 years old, weight 60–90 kg) participated in the study. During the study, one subject voluntarily withdrew, and another failed to be properly intubated during one test period. Data are presented for the four subjects that completed the study.

The study was conducted at Medical & Technical Research Associates, Inc., Jamaica Plain, MA under the auspices of Norwich Eaton Pharmaceuticals, Inc. Informed consent was obtained from each volunteer. Complete physical examinations and clinical laboratory evaluations were performed on each subject prior to the study. No subjects exhibited overt symptoms or findings of disease (central nervous, cardiopulmonary, gastrointestinal, hepatic, renal, or hemopoietic systems) or clinical laboratory values which might indicate potential interference with drug absorption, metabolism, or excretion. On the day before drug administration, an intestinal tube (Cantor tube®, Becton Dickinson) was inserted through the nasal passage of fasted subjects scheduled for ID or II dosage. Just prior to drug administration, the tube was positioned, with the assistance of a fluoroscope, for drug delivery into the second part of the

Correspondence: D.L. Wagner, Norwich Eaton Pharmaceuticals, Inc., P.O. Box 191, Norwich, NY 13815-0191, U.S.A.

TABLE 1

Plasma nitrofurantoin AUCs and urine nitrofurantoin dose recoveries following single oral (PO), intraduodenal (ID) and intraileal (II) doses of 100 mg of nitrofurantoin monohydrate and nitrofurantoin sodium

Subject No.		Nitrofurantoin monohydrate			Nitrofurantoin sodium		
		PO	ID	II	PO	ID	II
		Plasma AUC 0–∞ h ($\mu g \cdot h \cdot ml^{-1}$)			Plasma AUC 0–∞ h ($\mu g \cdot h \cdot ml^{-1}$)		
1		3.8	3.1	2.1	4.7	6.4	2.1
2		3.5	2.8	1.2	4.1	3.2	1.1
3		3.0	2.1	1.1	3.2	3.7	2.8
4		3.0	2.7	1.6	2.3	2.4	1.7
	Mean	3.3	2.7	1.5	3.6	3.9	1.9
	±S.D.	±0.4	±0.4	±0.5	±1.1	±1.7	±0.7
	CV (%)	13.2	15.5	31.8	29.5	44.1	37.0
		Dose recovery 0–24 h (%)			Dose recovery 0–24 h (%)		
1		52.5	37.2	31.4	47.5	45.6	20.0
2		42.3	45.6	13.1	34.1	56.9	10.6
3		35.2	28.0	16.7	48.9	33.5	27.4
4		33.8	22.1	10.0	35.9	15.9	17.5
	Mean	41.0	33.2	17.8	41.6	38.0	18.9
	±S.D.	±8.6	±10.3	±9.5	±7.7	±17.5	±6.9
	CV (%)	20.9	31.1	53.2	18.5	46.2	36.7

duodenum or into the ileum, about 150 cm beyond the ligament of Treitz.

Fifty ml of NFM suspension or NFNa solution (100 mg nitrofurantoin) in water was prepared immediately prior to administration. The drug was administered to each fasted subject by one of the three dosage routes (PO, ID, or II). A rinse of 100 ml water was administered by the same route as drug dosage. Single drug doses were administered weekly during six 24-h test periods, according to a randomized, complete crossover design so that each subject received both dosage forms by each route.

Blood was collected (21 gauge needle) from a forearm vein by venipuncture using a heparinized evacuated container (Vacutainer®, Becton Dickin-

TABLE 2

Relative fractions of drug dose absorbed (F) based on plasma nitrofurantoin AUCs and urine nitrofurantoin dose recoveries for single oral (PO), intraduodenal (ID), and intraileal (II) doses of 100 mg of nitrofurantoin monohydrate and nitrofurantoin sodium

Subject No.		Plasma				Urine			
		Nitrofurantoin monohydrate $F\%$ [a]		Nitrofurantoin sodium $F\%$ [a]		Nitrofurantoin monohydrate $F\%$ [b]		Nitrofurantoin sodium $F\%$ [b]	
		ID/PO	II/PO	ID/PO	II/PO	ID/PO	II/PO	ID/PO	II/PO
1		81.6	55.3	136.2	44.7	70.9	59.8	96.0	42.1
2		80.0	34.3	78.0	26.8	107.8	31.0	166.9	31.1
3		70.0	36.7	115.6	87.5	79.5	47.4	68.5	56.0
4		90.0	53.3	104.3	73.9	65.4	29.6	44.3	48.7
	Mean	81.3	45.0	108.6	58.3	80.8	42.0	94.0	44.4
	±S.D.	±8.9	±12.1	±24.1	±28.0	±18.8	±14.4	±53.1	±10.5
	CV (%)	10.9	26.8	22.2	47.9	23.3	34.3	56.5	23.7

[a] Relative fraction of dose absorbed, based on AUC.

[b] Relative fraction of dose absorbed, based on dose recovery.

TABLE 3

Statistical results (paired t-test) for plasma nitrofurantoin AUCs and urine nitrofurantoin dose recoveries following single oral (PO), intraduodenal (ID), and intraileal (II) doses of 100 mg of nitrofurantoin monohydrate and nitrofurantoin sodium

	Nitrofurantoin monohydrate vs. nitrofurantoin sodium			Nitrofurantoin monohydrate		Nitrofurantoin sodium	
	Plasma AUC	Urine dose recovery		Plasma AUC	Urine dose recovery	Plasma AUC	Urine dose recovery
PO	NS	NS	PO vs. ID	S	NS	NS	NS
ID	NS	NS	PO vs. II	S	S	NS	S
II	NS	NS					

NS = not significantly different ($P > 0.05$).
S = significantly different ($P < 0.05$).

son) 0, 15, 30, 45, and 60 min and 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 10 h after drug administration. The specimens were centrifuged immediately to obtain plasma. Voided urine was collected just before drug administration and at 0–1, 1–2, 2–3, 3–4, 4–6, 6–8, 8–10, 10–12, 12–14, and 14–24 h intervals after drug dosage. Aliquots of plasma and urine were frozen (−20 °C) until nitrofurantoin analysis at Kansas City Analytical Services, Shawnee, KS. The specimens were assayed according to high performance liquid chromatography methods specific for nitrofurantoin (Mason and Conklin, 1987a, b).

Area under the plasma nitrofurantoin concentration-time profile (AUC) was calculated by trapezoidal rule. Urine nitrofurantoin dose recovery was calculated from mg of nitrofurantoin excreted and the mg of nitrofurantoin administered (determined from dosage form analysis). Fraction of dose absorbed (F) was calculated using plasma drug AUC or urine drug dose recovery data. The plasma drug AUCs and urine drug dose recoveries were evaluated statistically using a paired t-test.

Plasma nitrofurantoin AUCs and urine dose recoveries determined for each subject are presented in Table 1. Relative F values based on the plasma and urine data are shown in Table 2. The results of the statistical evaluations of the plasma and urine data are presented in Table 3. Although there was considerable intersubject variation in both the AUCs and dose recoveries, trends in the data were clearly evident. On the basis of both plasma and urine drug data, NFM and NFNa were absorbed to about the same extent when administered PO, ID, and II. NFM and NFNa were each absorbed to a similar extent when dosed PO and ID, but the relative absorption of both forms of nitrofurantoin was reduced by about 50% following II dosage. It is apparent that the preliminary information obtained for humans in this study is in agreement with information obtained for animals concerning gastrointestinal sites of nitrofurantoin absorption.

On the basis of this preliminary information, nitrofurantoin liquids are apparently well absorbed following drug dosage orally or intraduodenally, with about 50% less absorption efficiency when placed in the ileum. There is no substantial difference between the absorption of the monohydrate and the sodium salt forms of nitrofurantoin. These data should be taken into consideration when selecting animal models for nitrofurantoin absorption and also for the development of solid nitrofurantoin dosage forms.

Acknowledgements

The expertise of Miguel Zinny, M.D., gastroenterologist, and the technical assistance of Gail Holowacz and Jeanne White in data handling are gratefully acknowledged.

References

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.

Conklin, J.D., The pharmacokinetics of nitrofurantoin and its related bioavailability. *Antibiot. Chemother.*, 25 (1978) 233–252.

D'Arcy, P.F., Nitrofurantoin. *Drug. Intell. Clin. Pharm.*, 19 (1985) 540–547.

Enzensberger, R. and Stille, W., In *Nitrofurantoin. Eine Dokumentation.* W. Zuckschwerdt Verlag, Munich, 1983, pp. 1–107.

Mason, W.D. and Conklin, J.D., Analysis of nitrofurantoin in human plasma by high pressure liquid chromatography. *Anal. Lett.*, 20 (1987a) 617–626.

Mason, W.D. and Conklin, J.D., Analysis of nitrofurantoin in human urine by high pressure liquid chromatography. *Anal. Lett.*, 20 (1987b) 479–488.

Parrott, E.L. and Matheson, L.E., Rectal absorption of nitrofurantoin. *J. Pharm. Sci.*, 66 (1977) 955–958.

Voemel, W., Kienitz, M. and Sauer, W., Untersuchungen zur rectalen resorption von nitrofurantoin. *Arzneim. Forsch.*, 19 (1969) 333–336.

Veronese, M., Salvaterra, M., Barzaghi, D. and Setnikar, I., Urinary excretion in the rat of nifurpipone (NP) and of nitrofurantoin (NTF) administered by different routes. *Arzneim. Forsch.*, 24 (1974) 39–43.