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Relative bioavailability of four macrocrystalline nitrofurantoin capsules

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Summary

This report describes the results of a bioequivalence study in 22 healthy subjects, in which the rate and extent of recovery of nitrofurantoin in the urine were measured after administration of single 100 mg doses of 3 test products and of Macrodantin as the reference product. All 3 test products were found to release more nitrofurantoin at a greater rate than Macrodantin; therefore, they were not bioequivalent. In addition, the 3 test products did not provide a greater duration of effective concentrations in the urine and thus had no potential for greater effectiveness or reduced dosing intervals. Thus, use of the test products would increase potential for adverse effects, expressed as gastrointestinal intolerance, without increasing effectiveness.

Introduction

Nitrofurantoin is used extensively in humans for the treatment of urinary tract infections (Schroeder, 1985). A comprehensive review in 1978 (Conklin, 1978) presented the pharmacokinetics and related bioavailability of nitrofurantoin. This report states that nitrofurantoin is rapidly absorbed and eliminated from immediate-release dosage forms (suspensions and tablets) with about half of its systemic clearance through the kidney. Nitrofurantoin has a terminal half-life of about 1 h, and 40–60% of an oral dose is recovered in the urine.

Studies in the 1960's determined that the optimal crystal size to retard dissolution and subsequent absorption of nitrofurantoin is a macrocrystal (Paul et al., 1967; Hailey and Glascock, 1967). The goal of this macrocrystalline dosage form (Macrodantin) was to reduce the gastrointestinal intolerance associated with the immediate-release dosage forms, without compromising effectiveness (Hailey and Glascock, 1967). Over the years, Macrodantin has been used effectively to reduce gastrointestinal intolerance to the microcrystalline forms of nitrofurantoin and thus has extended the usefulness of this important antimicrobial agent.

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The World Health Organization has identified nitrofurantoin as a drug that, in conventional oral dosage forms, exhibits problems of bioavailability (Anonymous, 1986). Thus, the introduction of multiple products purported to be macrocrystalline, and therefore, possibly bioequivalent to the original product, requires that these new products be evaluated for bioavailability relative to the original. This study evaluates the bioavailability of three purportedly macrocrystalline nitrofurantoin products, currently available outside the United States, relative to that of Macrodantin, the originally marketed product.

Materials and Methods

Three internationally marketed brands of 100 mg nitrofurantoin capsules described as macrocrystalline (Uvamin Retard, Mepha Ltd., Switzerland; Nitrofurantoin Retard-Ratiopharm, Ratiopharm GmbH, F.R.G.; and Furaben, Laboratorio Abeefe S.A., Peru) and the reference product, 100 mg Macrodantin capsules (Norwich Eaton Pharmaceuticals Inc., U.S.A.) were evaluated in this study. All were assayed for potency, content uniformity, and in vitro dissolution rate before their administration to subjects.

Twenty-four healthy male Caucasians between the ages of 18 and 38 years, and weighing between 60 and 90 kg, participated as subjects after giving informed consent. The study, which was conducted under medical supervision, was designed with a complete 4-way crossover at 1-week intervals. Each dose was administered with 60 ml of deionized, distilled water after an overnight fast and 1 h after a standard breakfast. All urine was collected immediately before dosing and at 2-h intervals until 14 h after dosing. Urine voided between 14 and 24 h was pooled. The urinary volumes were recorded, each urine sample was divided into three 100-μl aliquots and a reserve tube of 4 ml, and then all the samples were frozen until analysis. All samples were assayed for nitrofurantoin content within 10 days of collection by a specific high-pressure liquid chromatographic method (Mason and Conklin, in press).

The amount of nitrofurantoin excreted in the urine during each 2 h interval was calculated and the rate of excretion for the interval was estimated by dividing the amount of nitrofurantoin excreted by the time. The maximal rate (R_{max}), time to R_{max} (T_{max}), total amount excreted in the urine over 24 h (DA), and the percentage of the dose recovered based on the actual amount of nitrofurantoin in the capsules ($DR\%$), were calculated for each dose given to each subject. In addition, a Wagner-Nelson approach for a one-compartment model with first-order elimination (Wagner, 1979) was used to compute profiles of the percent absorbed versus time (and the percent unabsorbed, as 100% minus the percent absorbed) for each dose. In this computation, the elimination rate constant was estimated from the slope of the logarithm of the excretion rate versus time plots for the terminal portion of each curve. Non-linear curve-fitting (Metzler and Weiner, 1985) of the percent unabsorbed versus time profiles, to both a first-order absorption model (Eqn. 1) and a zero-order absorption model (Eqn. 2), both with a lag time (t_L), was used to compare models and rates of absorption for the drugs.

$$\%\ \text{unabsorbed} = 100\% \times \exp[-k_a \times (t - t_L)] \quad (1)$$

$$\%\ \text{unabsorbed} = 100\% - (100\%/T_A) \times (t - t_L) \quad (2)$$

where T_A = absorption time for zero-order model. For those subjects who had sufficient data, non-linear curve-fitting (Metzler and Weiner, 1985) of the rate of appearance of nitrofurantoin in the urine (R) versus time to a zero-order absorption model (Eqn. 3) was also used.

$$R = (f \times F \times D/T_A) \times [\exp(-K_e \times t_1) - \exp(-K_e \times t_2)] \quad (3)$$

where $f \times F = DR\% \times 100$; f = fraction of clearance that is renal; F = bioavailable fraction of dose; D = actual dose administered; T_A = absorption time for zero-order model; K_e = elimination rate constant; $t_1 = 0$, when $t < (T_A +$

t_L); $t_1 = t - (T_A + t_L)$, when $t > (T_A + t_L)$; $t_2 = t - t_L$.

Both model-independent and the kinetic-model parameters were statistically evaluated by analysis of variance with the model being subjects, periods, and treatments (i.e. products). Multiple-range tests and paired *t*-tests were used to identify which treatments differed significantly ($P < 0.05$) when differences between treatments were found.

Results

Table 1 presents the in vitro dissolution results for the 4 products tested and the actual amount of nitrofurantoin in one capsule of each. At one hour, the 3 test products had released more nitrofurantoin than had the reference product, Macrodantin. This was also true for two of the products at the second hour.

Twenty-two subjects completed the study by receiving all 4 products and providing their complete, collected 24-h urine. Plots of the mean cumulative urinary nitrofurantoin excretion levels for each of the 4 products are presented in Fig. 1, and the corresponding rates of excretion are presented in Fig. 2. These figures show that the 3 test products released more nitrofurantoin, and faster, than did the reference product.

Table 2 summarizes the model-independent kinetic parameters by product and clearly shows significant differences in the means for both the maximal rate and the *DR*%, with the values for all three of the test products being higher than those for the reference product. The maximal rates showed that the 3 test products were excreted 34–49% faster than the Macrodantin was. The relative amounts recovered (*F*%) in the urine for the 3 test products ranged from 129% to 145% of the amount recovered for Macrodantin.

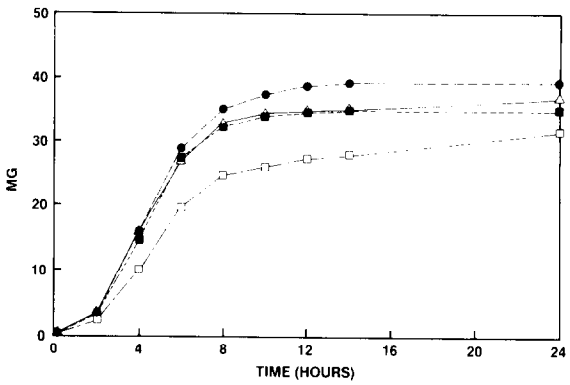

Fig. 1. Mean cumulative urinary excretion levels of nitrofurantoin after a single 100 mg dose of each of the 4 products. Macrodantin = □; Uvamin Retard = ●; Nitrofurantoin Retard-Ratiopharm = △; and Furaben = ■.

Fig. 3 presents the mean absorption–time profiles generated by the Wagner-Nelson calculations for all 4 products. All 4 profiles are the same shape and suggest the same type of absorption kinetics, although the absolute rates in mg/h are different because of the differences in the extent

TABLE 1

Description of the macrocrystalline nitrofurantoin capsules and drug doses administered — in vitro results

Drug product [a]	Actual dose of nitrofurantoin administered (1 capsule)	In vitro dissolution % released in			
		1 h	2 h	3 h	4 h
Macrodantin	102.9 mg	19	67	81	85
Uvamin Retard	101.4 mg	35	83	86	87
Nitrofurantoin Retard-Ratiopharm	103.6 mg	30	64	70	72
Furaben	103.4 mg	37	90	96	98

[a] Macrodantin, Norwich Eaton Pharmaceuticals Inc., U.S.A.
Uvamin Retard, Mepha Ltd., Switzerland.
Nitrofurantoin Retard-Ratiopharm, Ratiopharm GmbH, F.R.G.
Furaben, Laboratorio Abeefe S.A., Peru.

TABLE 2

Model-independent pharmacokinetics evaluated for 4 macrocrystalline nitrofurantoin products

Drug product [a]		R_{max} (mg/h) [b]	T_{max} (h) [b]	$DR\%$ [b]	$F\%$ [b]
Macrodantin	Mean [c]	5.55 A	4.7 A	24.45 A	100 A
	S.D.	1.93	1.7	6.21	–
	$CV\%$ [b]	34.8	36.2	25.40	–
Uvamin Retard	Mean [c]	8.26 B	3.7 B	34.11 B	145.30 B
	S.D.	1.71	1.2	7.22	42.63
	$CV\%$ [b]	20.7	32.4	21.17	29.34
Nitrofurantoin Retard-Ratiopharm	Mean [c]	7.46 B	3.7 B	30.35 C	129.18 C
	S.D.	2.93	1.6	8.30	42.32
	$CV\%$ [b]	39.3	43.2	27.35	32.76
Furaben	Mean [c]	7.60 B	4.2 AB	31.23 BC	130.91 BC
	S.D.	1.86	1.2	8.20	32.33
	$CV\%$ [b]	24.5	28.6	26.26	24.69

[a] Key to product identity is the same as in Table 1.
[b] R_{max} = maximal rate of excretion of nitrofurantoin
T_{max} = time to maximal rate of excretion
$DR\%$ = percentage of dose recovered, based on actual amount administered
$F\%$ – fraction of dose absorbed, relative to Macrodantin
$CV\%$ = coefficient of variation
[c] A common letter beside the means indicates no significant differences between the means ($P > 0.05$).

of absorption. Figs. 4 and 5 are plots of the percent unabsorbed versus time for a typical subject given Macrodantin. Based on the criteria of having lower sums of squares and higher correlation coefficients with random residuals, 68 of the 88 curves evaluated were best described by zero-order absorption, and 9 by first-order absorption. The remainder were indeterminate or had insufficient data to allow curve-fitting. The first-order and indeterminate curves were randomly distributed among the 4 products and were not indicative of different kinetics by product.

Table 3 summarizes the kinetic-model parameters both for the Wagner-Nelson percent unabsorbed–time plots, as they were fitted to the zero-order absorption of Eqn. 2, and for the rate of

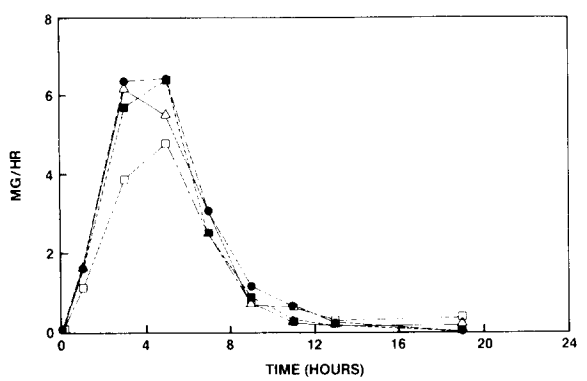

Fig. 2. Mean rates of urinary excretion of nitrofurantoin after a single 100 mg dose of each of the 4 products. Key to product identity is the same as that for Fig. 1.

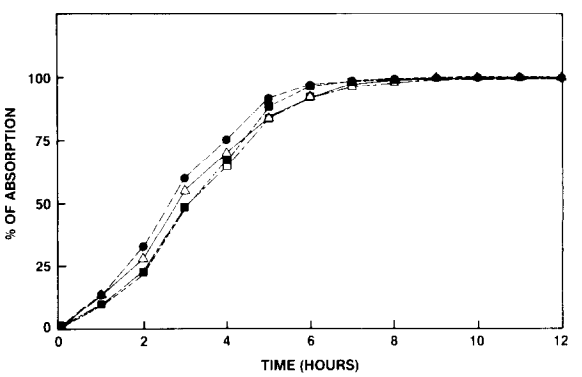

Fig. 3. Mean urinary nitrofurantoin absorption–time profiles generated by the Wagner-Nelson calculations for all 4 products. Key to product identity is the same as that for Fig. 1.

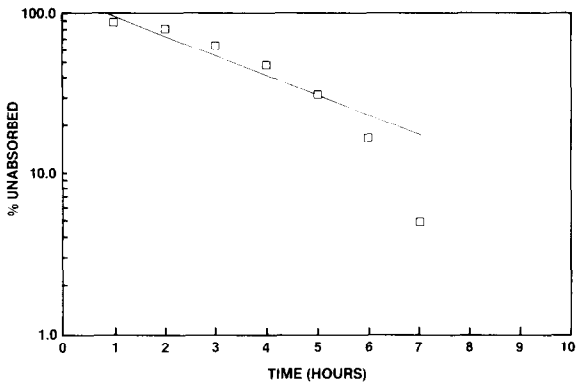

Fig. 4. Semilog plot of percent unabsorbed versus time profile (Wagner-Nelson) for a typical subject given a single 100 mg dose of Macrodantin.

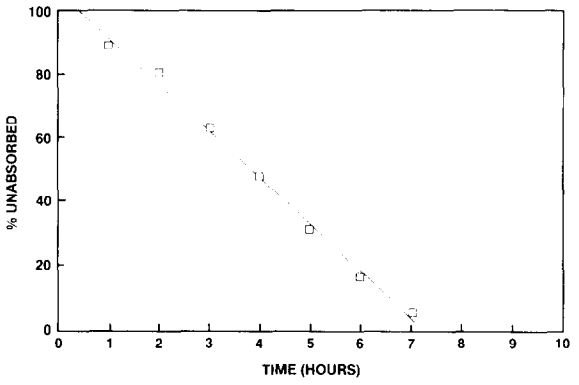

Fig. 5. Plot of the percent unabsorbed versus time profile (Wagner-Nelson) for a typical subject given a single 100 mg dose of Macrodantin.

excretion, as fitted to Eqn. 3. Sixty-eight sets of data were used in the Wagner-Nelson approach, and 10 subjects, or 40 sets of data, had sufficient data for curve-fitting the rate of excretion versus time. Both approaches gave essentially the same results: the time for absorption was about 5 h and the lag time about 0.75 h for all 4 products. The reference product had a slightly longer mean absorption time, but none of the differences were significant ($P > 0.05$). Also, the elimination rate constants estimated by both methods averaged about 0.75 h^{-1}, corresponding to an elimination half-life of about 55 min. These figures agree with previously reported values (Conklin, 1978; Hoener and Patterson, 1981).

Urinary nitrofurantoin concentrations of 32

TABLE 3

Summary of pharmacokinetics for the zero-order absorption model of nitrofurantoin, based on time of its appearance in urine, using both Wagner-Nelson and non-linear curve-fitting techniques

Test product [a]	Technique [b]	T_A (h) [c]	T_L (h) [c]	K_e (1/h) [c]
Macrodantin	W-N	5.15 (2.02)	0.67 (0.34)	0.78 (0.35)
	NCF	5.37 (1.45)	0.66 (0.41)	0.73 (0.57)
Uvamin Retard	W-N	4.95 (1.37)	0.73 (0.32)	0.73 (0.46)
	NCF	4.51 (1.17)	0.78 (0.28)	0.64 (0.52)
Nitrofurantoin Retard-Ratiopharm	W-N	4.69 (1.57)	0.72 (0.36)	0.79 (0.27)
	NCF	4.27 (1.43)	0.77 (0.18)	0.69 (0.17)
Furaben	W-N	4.54 (1.43)	0.81 (0.38)	0.86 (0.31)
	NCF	4.32 (0.78)	0.89 (0.68)	0.73 (0.26)

Results are means; standard deviations are in parentheses. These results were determined by non-linear curve-fitting of the Wagner-Nelson percent-unabsorbed-time data by Eqn. 2 (see text) for 68 data sets and, for the rate of appearance in the urine, by Eqn. 3 for 40 data sets. None of the differences by product are significant ($P > 0.05$).

[a] Key to product identity is the same as in Table 1.

[b] W-N = Wagner-Nelson
NCF = non-linear curve-fitting

[c] T_A = time for absorption
T_L = lag time until start of absorption
K_e = elimination rate constant

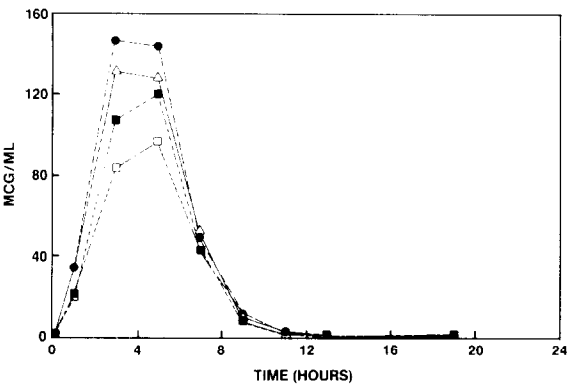

Fig. 6. Plot of mean urinary nitrofurantoin concentration–time profiles after a single 100 mg dose of each of the 4 products. Key to product identity is the same as that for Fig. 1.

μg/ml or greater have generally been considered bactericidal (Turck et al., 1967). More recently, however, clinical data have shown that nitrofurantoin has bactericidal effect at urinary concentrations as low as 20 μg/ml (Data on file, Norwich Eaton Pharmaceuticals Inc.). In this study, the duration of bactericidal urinary nitrofurantoin concentrations of Macrodantin and the three test products was about 8 h, with no significant differences ($P > 0.05$) between the 4 products (see Fig. 6).

Discussion

The rate and extent to which nitrofurantoin appears in the urine following administration of a 100 mg capsule of each of the test products are greater than those for Macrodantin, the reference capsule. Pharmacokinetic modeling techniques indicate that the absorption kinetics for all 4 products are best described by a zero-order model and that the time for absorption for each product is about 5 h. Thus, the differences in the rates of excretion and absorption are due to the extent of release and absorption, and the 3 test products release more nitrofurantoin.

This is confirmed by the *DR*% values observed. The 3 test products gave recoveries of 129–145% of that for Macrodantin. If one assumes that the fraction of clearance that is renal (f) is constant for a given subject, then the differences in *DR*% and the rate of excretion are due to the greater bioavailable fraction (F) for the 3 test products. Hoener and Patterson (1981) found f to be 0.47 (S.D. 0.13) in 6 subjects, after an intravenous dose. Assuming this value for f in our subjects resulted in mean bioavailable fractions of 0.52, 0.73, 0.65, and 0.66, respectively, for Macrodantin, Uvamin Retard, Nitrofurantoin Retard-Ratiopharm, and Furaben. As shown in Table 3, multiplying by the actual doses and dividing by the absorption times (T_A) for the Wagner-Nelson approach gave the estimated rates, at which nitrofurantoin entered the general circulation, as 10.38, 14.95, 14.36, and 15.03 mg/h, respectively.

Although the extent of release for the 3 test products was greater and produced more rapid absorption and excretion than for Macrodantin, the time during which the concentrations in the urine remained at or above 20 μg/ml did not differ significantly ($P > 0.05$). Thus, the test products offer no advantages of therapeutic efficacy over Macrodantin, and patients may be exposed to a greater potential for symptoms of gastrointestinal intolerance such as anorexia, nausea, or vomiting. In normal use, dosing 4 times daily is used for Macrodantin, and its duration of effective concentrations of about 8 h is more than adequate for antimicrobial activity. Since Macrodantin is released and absorbed more slowly, it can be considered a safer product.

The results of this study also confirm the reasons why nitrofurantoin is included in the World Health Organization's list of drugs that exhibit problems of bioavailability. The 3 test products dissolved to a greater extent than Macrodantin did during the first hour of in vitro dissolution testing; this observation agrees with the more rapid absorption and excretion rates in the subjects. Although coincident dissolution profiles may not guarantee in vivo bioequivalence, differences in these profiles may point to potential problems.

In summary, the 3 test products evaluated in this study are not bioequivalent to Macrodantin, the reference macrocrystalline nitrofurantoin product, and their use would expose the patient to a greater risk of gastrointestinal intolerance, without increased effectiveness.

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