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BIOAVAILABILITY IN MAN OF NALIDIXIC ACID TABLETS

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ABSTRACT

An *in vivo* absorption study was carried out in volunteers to compare the bioavailability of two brands of nalidixic acid tablets against a marketed paediatric suspension serving as a reference standard. Absorption was assessed by a urinary excretion method in which drug and major metabolite were assayed fluorimetrically. The excretion data were statistically treated. Results of the analysis of variance indicated a significant difference in rate, but not in extent of absorption, among the preparations tested. Poor disintegration quality of one of the tablet brands was found responsible for its delayed dissolution and, consequently, slow absorption.

INTRODUCTION

The present study is one of a series of investigations aiming at assessment of the bioavailability of some locally manufactured drug products. In this respect, the *in vivo* absorption of different brands of tetracycline capsules and griseofulvin tablets, manufactured in Egypt, has been investigated (1,2). Anticipated

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benifits of this line of research include ensuring the interchangeability of multisource products and initiating modifications, when justified, in formulations and manufacturing procedures of local brands to improve drug bioavailability.

Nalidixic acid is currently used in chemotherapy of urinary tract infections (3-5). While the literature supplies ample data on the pharmacokinetics of this drug (6-10), information relating to the influence of formulation factors on the absorption of nalidixic acid is scarce. The poor solubility in water of this naphthyridine drug together with the high doses needed to achieve therapeutic concentrations in urine suggest that misformulation could result in subeffective products. The recent inclusion of a dissolution test for nalidixic acid tablets in the USP XX - NF XV (11) is compatible with these speculations.

In the present study, the bioavailability in man of two brands of nalidixic acid tablets, obtainable in Egypt, was assessed. A marketed oral suspension served as standard for the absorption study.

METHODS

In-Vivo Absorption Study- Five apparently healthy volunteers participated in this study. Nalidixic acid (500 mg) was administered around 8 a.m., on an empty stomach, with 100 ml of warm tea without milk and 20 g

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of dry biscuits to avoid nausea and gastric irritation. Volunteers abstained from food for four hours after dosing. Urine was collected at 2,4,6,8,12 and 24 hours. Volume and pH of each sample were recorded. The following treatments were administered randomly at weekly intervals:

Treatment A- One 500 mg nalidixic acid tablets manufactured in Egypt during 1977.

Treatment B- One 500 mg Negram[1] tablet, batch no. IND364

Treatment C- Ten ml (equivalent to 500 mg of nalidixic acid) of Negram[1] Paediatric Suspension, batch no. 2LE274

Analysis of Urine- proceeded fluorimetrically as suggested by McChesney, et al, (6) for the determination of total nalidixic and hydroxynalidixic acids (free and conjugated) in urine. Standards for adjusting the fluorimeter to 100 percent emission were prepared by spiking aliquots of diluted blank urine with 10-40 ug of nalidixic acid[2] and running them through the analytical procedure along with the urine samples. All measurements were made on a Perkin Elmer 204 fluorescence spectrophotometer at excitation and emission wave lengths of 294 and 355 nm respectively.

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[1] Manufactured in England for Winthrop Products inc., N.Y., U.S.A.

[2] Sterling-Winthrop Research Institute, Rensselaer, N.Y.

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Tablets and Suspension Content- was determined following BP 1973 (12) instructions, using a Unicam SP 500 spectrophotometer.

Tablets Disintegration Time- was determined by both BP 1973 (12) and NF XIV (13) methods.

Tablets Dissolution Rate Test- was carried out according to USP XX-NF XV method using apparatus 2 at 50 rpm (11).

RESULTS AND DISCUSSION

Nalidixic acid and its major metabolite, hydroxynalidixic acid, are excreted in urine partly free but mainly as glucuronides (10). The method of assay adopted in the present *in vivo* study, collectively determined all four naphthyridine species excreted in urine. Such an approach, whereby total drug and metabolites are monitored in urine is a recognized method in bioavailability determination (14).

Cumulative urinary excretion data of total naphthyridines, obtained after administering treatments A-C are given in Table 1. A previous report indicated complete drug recovery within 24 hours (8). The inflated recovery values (Table 1, 24 h column), were due to the higher fluorescence, on a weight basis, of hydroxynalidixic acid compared to nalidixic acid (6). The untreated average data (Table 1), indicated higher recovery values for the suspension form compared to the two tablet brands. Average urinary excretion rate profiles (Fig. 1), rated tablets of treatment A, slowest in absorption rate.

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TABLE 1
Cumulative Urinary Excretion Data Following the Administration of 500 mg of Nalidixic Acid in Treatments A-C.

Treatment	Subject	Total Naphthyridine Excreted[a], mg					
		2	4	6	8	12	24 hours
A	AH	81.7	193.1	265.9	341.3	399.9	439.3
	NK	86.2	220.1	315.3	395.5	437.7	464.6
	MZ	83.2	267.5	407.7	497.5	572.7	620.3
	AM	84.4	235.3	326.8	394.3	447.1	574.4
	MB	85.1	218.2	398.2	539.3	571.6	633.2
	Average	84.1	226.8	342.8	433.6	485.8	546.4
	SE[b]	0.8	12.2	26.7	36.6	36.1	40.0
B	AH	29.2	277.8	361.3	402.1	464.7	506.3
	NK	100.3	310.1	431.7	464.7	521.8	581.2
	MZ	42.3	292.2	374.1	418.5	489.3	542.3
	AM	99.4	315.2	300.7	449.9	494.1	541.2
	MB	167.4	333.7	427.7	473.3	511.0	550.0
	Average	87.7	305.8	398.9	441.7	496.2	544.2
	SE[b]	24.6	9.6	14.0	13.6	9.8	11.9
C	AH	100.3	262.3	370.1	409.3	444.2	486.8
	NK	98.0	267.7	383.6	419.6	458.0	493.0
	MZ	73.5	305.8	531.6	672.4	706.5	753.4
	AM	173.3	370.4	469.0	542.4	583.3	615.7
	MB	196.0	374.6	523.0	569.0	602.6	662.4
	Average	121.0	316.2	455.5	522.5	558.9	602.3
	SE[b]	21.3	24.2	33.9	49.2	48.8	50.9

[a] Calculated as nalidixic acid

[b] Standard error of the mean

Results of tablets and suspension assay indicated a drug content exceeding 95% in each case. This ruled out chemical inequivalency among the preparations tested. Similarly, insignificant week-to-week intrasubject fluctuations in urinary pH suggested a negligible effect of urine pH on excretion data. Thus, interbrand differences in excretion data were indicative of differences in bioavailability.

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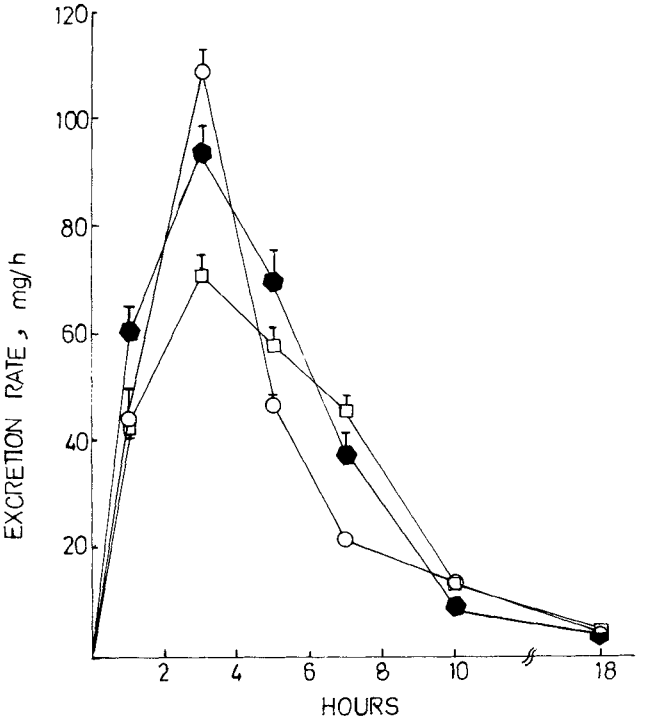

FIGURE 1

Excretion rate profiles following the administration of 500 mg of nalidixic acid in the form of tablets, □ -Treatment A, ○ -Treatment B; and in the form of suspension, ● -Treatment C. Each point is the mean of five volunteers. Bars denote the standard error of the mean.

Excretion data were statistically analysed. Peak excretion rate and total amount of drug ultimately recovered in urine were selected as indices of rate and extent of drug absorption. ANOVA results indicated an insignificant difference in extent of absorption among the products tested (Table 2). However, a statistically

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TABLE 2
Analysis of Variance of the 24 h Cumulative Excretion Data Obtained Following The Administration of 500 mg of Nalidixic Acid in Treatments A-C.

Source	df	SS	MS	F	Significance
Between Brands	2	10842.0	5421.0	0.705	NS[a]
Between Subjects	4	55353.9	13838.5	1.800	NS
Error	8	61484.5	7685.6		
Total	14	127680.4			

[a]Not significant

significant difference in rate of absorption was observed (Table 3).

Determination of disintegration time of both brands of tablets showed failure of tablets of treatment A to pass the 15 minutes BP 1973 test (12), specified by the BPC 1973 (15) for nalidixic acid tablets. The same tablets (treatment A), however, passed the 30 minutes disintegration time limit of the NFXIV (13). Such a delayed disintegration would be rate limiting to both dissolution and absorption. Disintegration of tablets of treatment B, was complete within 2 minutes.

During this study, a dissolution test for nalidixic acid tablets appeared in the USPXX-NFXV (11). Treatment A tablets, when tested, were found unable to meet the dissolution rate limit specified (11). Only 25% of the tablet content dissolved within 30 minutes. Rapid disintegration of tablets of treatment B, permitted them to pass the same dissolution test. More than 80% of the drug was liberated

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TABLE 3
Analysis of Variance of the 3 h Excretion Rate Data Obtained Following the Administration of 500 mg of Nalidixic Acid in Treatment A-C.

Source	df	SS	MS	F	Significance
Between Brands	2	3605.0	1799.1	8.38	$P < 0.05$
Between Subjects	4	2203.5	550.9	2.56	NS
Error	8	1716.9	214.6		
Total	14	7525.4			

into solution in the same time period. The partially alcoholic dissolution medium did not appear to affect the disintegration properties of tablets of either treatment A or B.

For nalidixic acid and other drugs administered on a multiple dosage regimen basis, the extent of absorption is considered a more crucial biopharmaceutical parameter than the rate of absorption. Comparision of excretion date of treatment A with those of C, using the student t-test, indicated a significantly lower rate and extent of absorption of the tablets compared to the suspension (Table 4). Delayed disintegration of treatment A tablets, therefore, comparatively impaired both rate and extent of their bioavailability. The importance of prompt disintegration of tablets as a means of promoting dissolution, and consequently absorption, of drugs should not be underestimated.

The data obtained in the present study have been made available to the local pharmaceutical firm produ-

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TABLE 4
Student t-test Applied to Urinary Excretion Data Following the Administration of 500 mg in Treatments A and C.

Data Analysed	t	Significance
3 h Excretion Rate	5.30	$P < 0.05$
24 h Cumulative Excretion	2.84	$P < 0.05$

cing the tablets of treatment A. A study of possible batch-to-batch variation in disintegration and dissolution of the same tablets is underway.

In conclusion, the results of the present study support the recent specification of a dissolution rate test for nalidixic acid tablets (11). Based on the *in vivo* and *in vitro* data obtained, the dissolution test proved more effective in detecting a potentially low bioavailability preparation than the 30 minutes disintegration time limit (13).

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REFERENCES

1. L.M. Mortada, Z.A. ElGholmy, M.W. Gouda, N.Khalafallah and S.A. Khalil, Proc. XIV Conf. Pharm.Sci., Cairo, Egypt, Dec. 1975.
2. N.Khalafallah, Z.A. ElGholmy and S.A. Khalil, Pharmazie, 35, 482 (1980).

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3. G.Y. Lesher, E.J. Froelich, M.D. Gruett, J.H.Bailey and R.P. Brundage, J.Med.Chem., 5, 1063 (1962).

4. I.V. Lishman, J.Swinney, Brit.J.Urol., 35, 116 (1963)

5. T.A. Stamev, N.Y. Nemoy and M.Higgins, Invest. Urol., 6, 582 (1969).

6. E.W. McChesney, E.J. Froelich, G.Y. Lesher, A.V.R. Crain and D. Rosi, Toxicol. Appl. Pharmacol., 6, 292 (1964).

7. W.E. Moore, G.A. Portmann, H. Stander and E.W. McChesney, J.Pharm.Sci., 54, 36 (1965).

8. G.A. Portmann, E.W. McChesney, H.Stander and W.E. Moore, ibid., 55, 59 (1966).

9. Ibid., 55, 72 (1966).

10. E.W. McChesney, G.A. Portmann and R.F. Koss, ibid., 56, 594 (1967).

11. The United States Pharmacopeia, twentieth revision, The National Formulary, fifteenth edition, 1980, United States Pharmacopeial Convention, inc., Rockville, Md., p. 539.

12. British Pharmacopoeia 1973, Her Majesty's Stationary Office, London, p A 131.

13. National Formulary, fourteenth edition, 1975, Am. Pharm. Ass., Washington, p. 978 & 477.

14. J.G. Wagner "Biopharmaceutics and Relevant Pharmacokinetics", Drug Intelligence Publications, Hamilton,ill., 1971, p 185.

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15. British Pharmaceutical Codex, 1973, The Pharmaceutical Society of Great Britain, p 831.

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