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CONTROL OF RELEASE AND BIOLOGICAL AVAILABILITY OF DRUGS – INVESTIGATIONS INTO THE RENAL ELIMINATION OF NITROFURANTOIN

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SUMMARY

The present study was concerned with the reasons for the bioavailability problems of slow release forms of nitrofurantoin. The particular aim of the study was to obtain more information about the period of absorption of this chemotherapeutic agent from the gastrointestinal tract. When the degree of renal elimination of nitrofurantoin from dosage forms showing different onsets of release was measured, it was shown that a delay in release of merely a few hours leads to a statistically significant reduction in bioavailability of active ingredient. The investigations, carried out in 4 subjects, showed that after administration of coated tablets where release was delayed for up to 5 h, only 8.3% of the dose was excreted in the urine, whereas with rapidly disintegrating tablets, 34.5% of the dose underwent renal elimination. The studies thus indicate that with dosage forms of nitrofurantoin which are subject to passage through the gastrointestinal tract, only that part of the active ingredient which is released from the preparation within the first few hours of administration is optimally absorbed and eliminated in the urine.

INTRODUCTION

A few years ago, the Food and Drug Administration (FDA) in the United States named 50 problem drugs for which demonstration of the biological availability of their dosage forms in man was deemed necessary (New News, 1975). For oral preparations of these problem drugs there exists a very close relationship between the rate of release and the biological availability of the active ingredient. Drug forms which permit only a slow release of active ingredient show a reduced bioavailability. However, the limited rate of dissolution of a drug is generally not sufficient to completely account for all bioavailability problems. Without the influence of other physiological and pharmacokinetic factors, administration of such oral preparations as those showing a slow release of active ingredient would merely be expected to result in a somewhat flatter serum or urine drug level vs time curve, with the total availability of the drug remaining roughly the same as that of

more rapidly released dosage forms. The present investigations have used the example of the chemotherapeutic agent, nitrofurantoin, to study the reasons for the bioavailability problems of slow release dosage forms. In the case of nitrofurantoin, previous investigations in man have shown that, within the normal therapeutic dose-range, the pharmacokinetics of this drug are not dose-dependent (Gröning, 1978). The aim of the current studies was to gain more information concerning the period of absorption of nitrofurantoin from the gastrointestinal tract. Such information is particularly needed for the drug development of oral sustained release or 'depot' dosage forms which are subject to passage through the gastrointestinal tract, since only by knowing when absorption occurs can appropriate measures be devised to delay release until the optimal time.

MATERIALS AND METHODS

Manufacture of enteric-coated dosage forms

Tablet press. Betema hand-operated press with compression tool for tablets. Punch diameter 10 mm, flat-faced, facetted (Betema, Berlin).

Film-making apparatus. Film frame for film widths of 60 mm and film thicknesses of up to 240 μm (Erichsen, Hemer-Sundwig/Westphalia).

Base. Polytetrafluoroethylene foil.

Lacquer. Eudragit L 90: Eudragit S 90 (Röhm Pharma, Weiterstadt).

Plasticiser. Dibutylphthalate 99% (Merck, Darmstadt).

Potato starch (Ph. Eur.) Mainland, Frankfurt/M.). Potato starch was dried in a drying oven for 2 h at 38°C before use. Coated tablets were prepared by placing 150 mg potato starch in the mould of the tabletting machine and gently pressing this down with the upper die. After placing a commercial tablet of 50 mg nitrofurantoin in the middle of the mould and further slight pressure, another 150 mg potato starch was added to the mould and the tablet compressed.

Composition of the coating solution: film former (Eudr. ®L 90/S 90) = 5.0 g; dibutylphthalate = 0.5 g; and isopropanol/acetone (1 + 1) to 50.0 g.

The coating solutions were prepared by warming the ingredients together. To make the

DOSAGE FORM: ENTERIC COATED TABLET	DRUG: NITROFURANTOIN
	DOSE: 50 mg
	⌀ : 10 mm
	ROUND, FLAT FACED, FACETTED
① CORE: commercial nitrofurantoin tablet, 50 mg	③ OUTER COATING: Eudragit® L, S 5.0
	Dibutylphthalate 5.0
② INNER COATING: potato starch 300 mg	VEHICLE: Isopropanol 25.0
	Acetone 25.0

Fig. 1. Construction of an enteric-coated tablet.

TABLE 1

AGE AND BODY WEIGHT OF SUBJECTS

Subject	Age (years)	Body weight (kg)
I (♂)	35	86
II (♂)	32	79
III (♀)	32	64
IV (♂)	18	64

film, some 4 g of the coating solution were poured into the trough which was then run over the base to produce a homogeneous wet film initially some 120 μm thick.

Before the film had completely dried, a roughly square piece some 9 cm^2 was detached. The film was manually wrapped round the starch-coated tablet and closed round one of the flat sides of the tablet by pressing the edges together. Only one layer was placed round the tablet at a time. With repeated coverings, the closure sites were on alternate sides. The construction of the tablets used is schematically represented in Fig. 1.

Clinical studies

Four healthy subjects aged 18–35 years and weighing 64–86 kg took part on the in vivo studies (Table 1). Three of the subjects (nos. I, II and IV) were males.

The clinical studies were carried out at weekly intervals in the administration sequence shown in Table 2. The subjects were fasted overnight and at 08.00 h were given a standard breakfast (2 slices of toast with butter and jam, 1 boiled egg, coffee). At 09.00 h, the dosage form was swallowed with 200 ml water. The next light meal was allowed at 13.00 h at the earliest and the next drink not before 10.00 h. Urine samples were collected every 30 or 60 min and the content of nitrofurantoin measured by polarography.

TABLE 2

ADMINISTRATION SEQUENCE OF THE IN VIVO STUDIES

Administration sequence	Subject I	Subject III
(1)	Coated tablet of 50 mg nitrofurantoin 3 × 12 μm Eudragit S	Coated tablet of 50 mg nitrofurantoin 5 × 12 μm Eudragit L
(2)	Tablet of 50 mg nitrofurantoin	Tablet of 50 mg nitrofurantoin
(3)	Coated tablet of 50 mg nitrofurantoin 3 × 8 μm Eudragit L	Coated tablet of 50 mg nitrofurantoin 3 × 12 μm Eudragit L
	Subject II	Subject IV
(1)	Tablet of 50 mg nitrofurantoin	Tablet of 50 mg nitrofurantoin
(2)	Coated tablet of 50 mg nitrofurantoin 3 × 12 μm Eudragit L	Coated tablet of 50 mg nitrofurantoin 3 × 12 μm Eudragit L

RESULTS AND DISCUSSION

The aim of the present study was to obtain more information concerning the period of absorption of nitrofurantoin from the gastrointestinal tract by the oral administration of dosage forms with differing onsets of release. With this intention enteric-coated tablets, from which the active ingredient is released after a delay of several hours, were compared with the corresponding uncoated tablets. The extent of renal elimination of nitrofurantoin after the various dosage forms was used to assess their biological availability.

The enteric-coated dosage forms were prepared by coating commercial nitrofurantoin tablets (content 50 mg) with potato starch and then covering them with a coating resistant to gastric juice (Fig. 1). The starch coating was to ensure that when the film coating was penetrated by gastrointestinal juice, the surrounding coating would dissolve very quickly on an 'all-or-nothing' principle. The starch coating also helped to prevent the film coating having any effect on the tablet itself. The thickness of the layer of enteric coating required to produce an adequate delay in release in each patient was first established in preliminary investigations.

Four subjects participated in the clinical studies and the results are summarized in Table 3.

The mean renal excretion of 34.8% of the administered dose obtained for the uncoated tablet gives a biological availability similar to that obtained earlier with other German commercial preparations of this drug under corresponding conditions (Gröning, 1978). The comparable result of 8.3% for the enteric-coated tablets, from which release is delayed for a maximum of 4–5 h shows that these tablets have a markedly reduced biological availability – only about one-quarter of that of the uncoated tablet. The difference in bioavailability is statistically significant ($P < 0.001$) when tested using the Student's t-test.

In Fig. 2 the excretion profiles of the various dosage forms are compared in each subject. In 2 of the 4 subjects further studies of the dependence of absorption of nitrofurantoin on the time of release of active ingredient were carried out in which the delay in release was lessened by modification of the film coating. The results, shown in Fig. 3 indicate that administration of an enteric-coated tablet of nitrofurantoin in which release

TABLE 3

RENAL EXCRETION OF NITROFURANTOIN (% OF ADMINISTERED DOSE) FROM ENTERIC-COATED (KEY, SEE FIG. 2) AND UNCOATED TABLETS

Dosage form	Tablet of 50 mg nitrofurantoin	Tablet of 50 mg nitrofurantoin, enteric-coated
Subject I	37.2	10.8
Subject II	24.7	2.9
Subject III	45.2	9.8
Subject IV	31.0	9.7
Mean	34.5	8.3

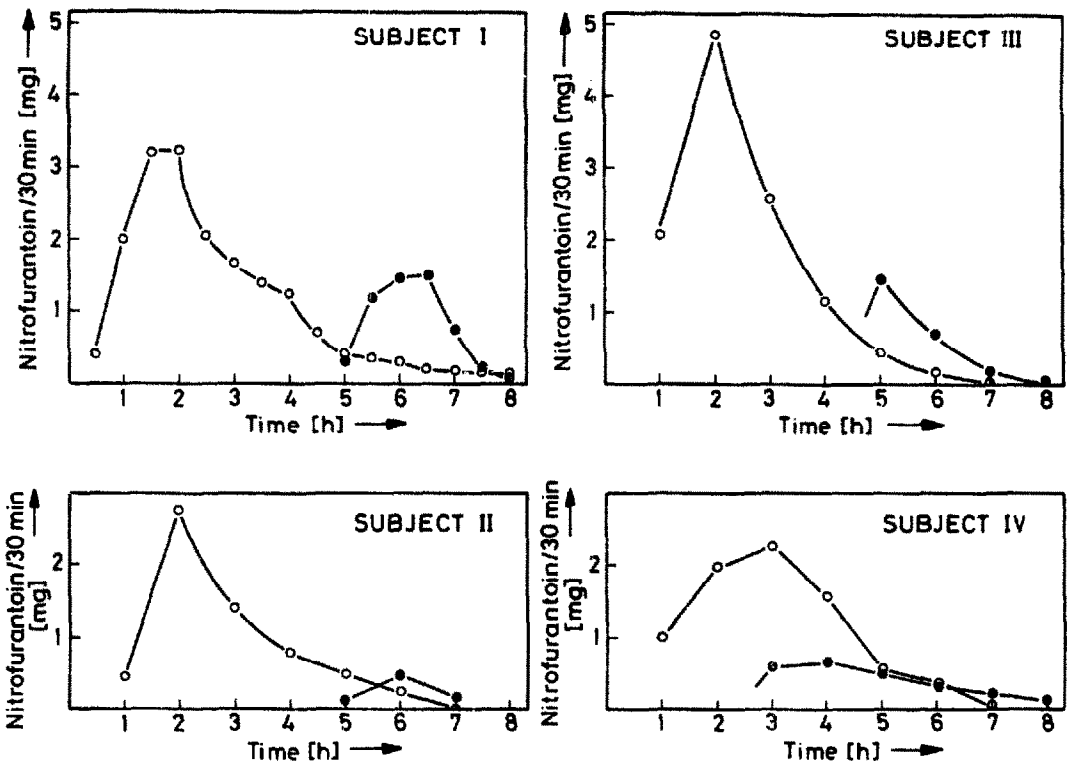

Fig. 2. Renal excretion of nitrofurantoin after oral administration of uncoated tablets and enteric-coated dosage forms. o——o, tablets of 50 mg nitrofurantoin; •——•, enteric-coated tablets of 50 mg nitrofurantoin. Subject I = 3 X 12 μm Eudragit S; Subject II = 5 X 12 μm Eudragit L; Subject III = 3 X 12 μm Eudragit L; and Subject IV = 3 X 12 μm Eudragit L.

is only delayed for some 2 h, results in only a slight decrease in renal excretion of the drug compared to an uncoated tablet.

The results of the present study thus show that nitrofurantoin is only optimally available from the gastrointestinal tract over a limited period. The use of enteric-coated dosage forms results in a reduction in the renal elimination of nitrofurantoin and the magnitude of this reduction depends on the delay in dissolution of the film coating. In fact preliminary investigations revealed that with an even longer delay in release of nitrofurantoin, no urinary excretion can be demonstrated at all. It is only these latter results that confirm those of another author, who showed that no renal elimination occurred after administration on an enteric-coated nitrofurantoin tablet (Fussek, 1968). Although no information is available concerning the precise site of release of nitrofurantoin from enteric-coated dosage forms, other workers who studied the passage time of a capsule of corresponding size showed that disintegration of comparable enteric-coated preparations occurs in the small intestine (Eckert et al., 1976).

A point of difficulty in evaluating the results of the current investigations is the use of solid dosage forms. Using solid dosage forms the results represent the sum total of all factors affecting absorption in the lower parts of the gastrointestinal tract, such as the

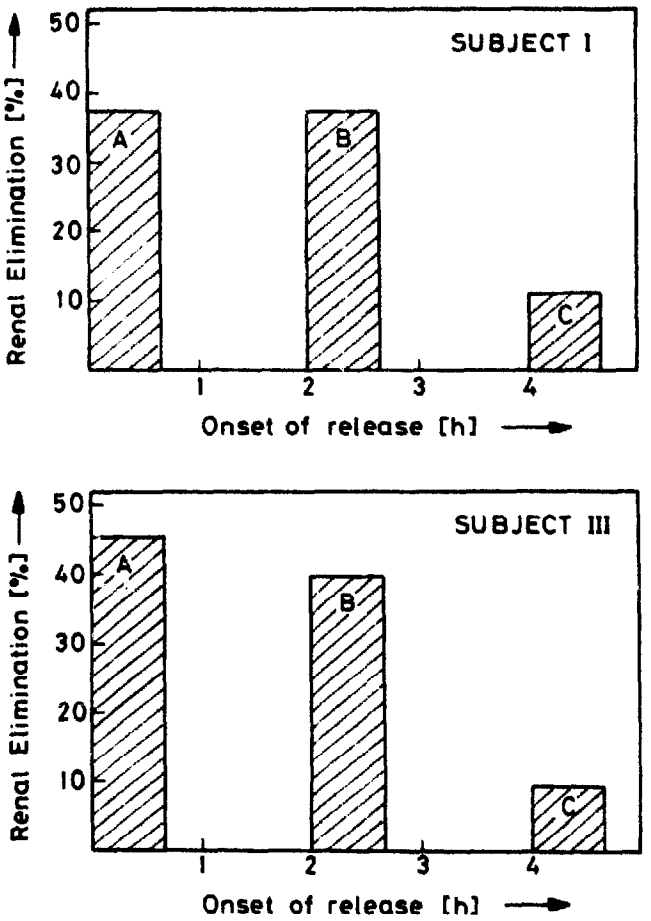

Fig. 3. Influence of renal elimination of nitrofurantoin by the time of onset of release from the dosage form containing 50 mg nitrofurantoin *. A: uncoated tablet: onset of release in the urine collection interval 0–60 min. B: enteric-coated tablet: onset of release in the urine collecting interval 120–180 min. (Subject I: 3 X 8 μm Eudr. L; Subject III: 3 X 12 μm Eudr. L.) C: enteric-coated tablet: onset of release in the urine collecting interval 240–300 min. (Subject I: 3 X 12 μm Eudr. S; Subject III: 5 X 12 μm Eudr. L.)

* The total amount of unmetabolized nitrofurantoin excreted in the urine over several hours is expressed in terms of the % of the administered dose, in the collection interval during which renal excretion begins.

limited absorptive capacity, stability and conditions for dissolution. It would be highly desirable to investigate absorption studies of dissolved drugs in man in various regions of the gastrointestinal tract by using a sampling tube.

The limited period of absorption of nitrofurantoin explains the problems which can arise with slowly releasing dosage forms of the drug. Forms, which are subject to passage through the gastrointestinal tract have, 3 or 4 h after administration, reached areas where the absorption of nitrofurantoin is markedly reduced.

Somewhat more favourable conditions are met by dosage forms which disintegrate in the stomach and some of whose particles are slowly transported further down the tract, e.g. with food. Such dosage forms generally show no abrupt loss in absorption. However, even here only that part of the active ingredient is optimally absorbed which is present, in dissolved form, in the upper part of the small intestine. This probably explains the reduced biological availability of various commercial preparations (McGilveray et al., 1971; Mattock et al., 1972; McGilveray et al., 1973; Meyer et al., 1974).

Although not confirmed experimentally in the same way as the current studies with nitrofurantoin, it is highly probable from the mathematical evaluation of plasma levels, that many other drugs are subject to a similarly limited period of absorption in the gastrointestinal tract (von Hattingberg, 1977; Süverkrüp, 1979). In the case of nitrofurantoin, however, evaluation of the period of absorption must also take into account the comparatively limited lipophilic nature of the drug and its low permeation ability. Other drugs, e.g. salicylic acid or acetylsalicylic acid, are also absorbed over a comparatively longer period.

The results of the studies with nitrofurantoin show that it is particularly important for drug development of sustained release or 'depot' dosage forms that the time course of absorption of the drug is known. For the majority of drugs such information is currently lacking.

REFERENCES

Eckert, Th., Cordes, G. and Ollenschläger, G., Zur Wirkstoff-Freigabe bei magensaftresistent überzogenen Gelatinekapseln in vitro und in vivo. 5. Mitteilung: Vergleichende Untersuchungen an Filmüberzügen aus Celluloseacetatphthalat (CAP) und Hydroxypropylmethylcellulosephthalat (HP-50). Pharm. Ind., 38 (1976) 836–841.

Fussek, H., Klinische Erfahrungen mit Nitrofurantoin-Präparaten. Wiener med. Wschr., 118 (1968) 668–671.

Gröning, R., Untersuchungen zur biologischen Verfügbarkeit von Nitrofurantoin I. Renale Ausscheidung nach Applikation handelsüblicher Tabletten und Retardkapseln beim Menschen. Dtsch. Apoth. Ztg., 118 (1978) 1354–1357.

Gröning, R., Untersuchungen zur biologischen Verfügbarkeit von Nitrofurantoin II. Renale Ausscheidung nach Applikation von Lösungen beim Menschen. Dtsch. Apoth. Ztg., 118 (1978) 1747–1750.

von Hattingberg, H.M., Pharmakokinetik von Lincomycin und Clindamycin. Infection, 5 (1977) S29–S36.

Hew News, U.S. Department of Health, Education and Welfare, 75-23 (1975) 1–11.

Mattok, G.L., Hossie, R.D. and McGilveray, I.J., In vivo : in vitro studies of nitrofurantoin tablets. Can. J. Pharm. Sci., 7 (1972) 84–87.

McGilveray, I.J., Mattok, G.L. and Hossie, R.D., A study of bioavailabilities and dissolution rates of commercial tablets of nitrofurantoin. J. Pharm. Pharmacol., 23 (1971) 246S.

McGilveray, I.J., Mattok, G.L. and Hossie, R.D., The comparison of the bioavailabilities of commercial nitrofurantoin tablets. Rev. Can. Biol., 32 (1973) 99–106.

Meyer, M.C., Slywka, G.W.A., Dann, R.E. and Whyatt, P.L., Bioavailability of 14 nitrofurantoin products. J. Pharm. Sci., 63 (1974) 1963–1968.

Süverkrüp, R., Discontinuous absorption processes in pharmacokinetic models. J. Pharm. Sci., 68 (1979) 1395–1400.