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Effect of antacids on oral absorption of rifampicin

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Summary

A study has been carried out on the effect of concomitant administration of aluminium hydroxide gel (15 ml), magnesium trisilicate (2 g) and sodium bicarbonate (2 g) on the bioavailability of rifampicin in healthy male volunteers. The antibiotic bioavailability, as measured by a urinary excretion method over a period of 24 h, was significantly reduced by the 3 antacids following the sequence: magnesium trisilicate > aluminium hydroxide > sodium bicarbonate. Doubling the dose of either magnesium trisilicate or aluminium hydroxide gel produced no further reduction. The results obtained are interpreted in the light of the effect of gastric pH elevation on the solubility and dissolution rate of rifampicin, chelation of the drug with aluminium ions and binding by magnesium trisilicate.

Introduction

Rifampicin is a first line drug in the chemotherapy of tuberculosis. The drug is commonly administered in a single daily dose of 600 mg on an empty stomach to effect optimum absorption (Furesz et al., 1967; Siegler et al., 1974). This may result in gastrointestinal disorders and the concomitant administration of antacids is not uncommon. A number of reports point out drug interactions with rifampicin (Acocella, 1978; Chowdary and Ramana Murthy, 1982b; McAllister et al., 1983) but no studies appear to have been made of possible interactions with antacids and consequent effect on the bioavailability of the drug.

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Rifampicin was reported to form complexes with polyvalent cations (Paraschiva, 1973; Gandhi et al., 1978; Chowdary and Ramana Murthy, 1982a). The interaction has been made use of in the colorimetric assay of rifampicin (Gandhi et al., 1978). Hence, the possible interaction of rifampicin with antacids containing polyvalent cations cannot be ruled out. Interactions of this type were shown to have varying effects on drug absorption. For instance, the reduced absorption of tetracyclines in the presence of aluminium, calcium and magnesium ions containing antacids (Kunin and Finland, 1961; Hurwitz, 1977) and the enhanced bioavailability of bis-hydroxy-coumarin (Ambre and Fischer, 1973; Bighley and Spivey, 1977) in the presence of magnesium hydroxide are well documented.

The objective of the present study has been to examine the influence of aluminium hydroxide, magnesium trisilicate and sodium bicarbonate on the bioavailability of orally-administered rifampicin. Sodium bicarbonate has been included in the study to test the effect of gastric pH elevation on rifampicin bioavailability in the absence of chelating cations.

Materials and Methods

Measurement of urinary excretion

Five healthy men, aged 34–43 years (mean 39 years) and weighing 65–82 kg (mean 74 kg) volunteered for the study. After an overnight fast, a blank urine sample was collected and the subject swallowed two 300 mg capsules of rifampicin [1] according to one of the following treatments:

Treatment A — 200 ml of water;
Treatment B — 15 ml of Aluminium Hydroxide Gel B.P. followed by 200 ml of water;
Treatment B*— 30 ml of Aluminium Hydroxide Gel B.P. followed by 200 ml of water;
Treatment C — 2 g of magnesium trisilicate [2] suspended in 200 ml of water;
Treatment C*— 4 g of magnesium trisilicate suspended in 200 ml of water;
Treatment D — 2 g of sodium bicarbonate [3] dissolved in 200 ml of water.

Treatments were given at weekly intervals in a randomized cross-over sequence. Four subjects only received Treatments C* and D. Subjects abstained from food for 4 h after administration and were asked to ingest 200 ml of water hourly to stimulate diuresis. Urine was collected at hourly intervals for 8 h and pooled samples were collected within the intervals 8–12 h, 12–18 h and 18–24 h. The pH values and volumes of urine were recorded and samples were frozen until analyzed within 2 days.

[1] Rimactane 300 capsules, batch no. 097B, SWISSPHARMA, Cairo, Egypt, under license from Ciba-Geigy Ltd., Basle, Switzerland.
[2] E. Merck, Darmstadt, F.R.G.
[3] B.D.H., Poole, U.K.

The amounts of rifampicin in urine samples were assayed spectrophotometrically according to the method described below. The method used is a modification of that proposed by Sunahara and Nagakawa (1972): In a 50 ml separator, 6 ml of Sørensen phosphate buffer, pH 5 (1/15 M) was added to 2 ml urine. The diluted urine sample was extracted once with 10 ml of chloroform (A.R.) by manual shaking for 3 min. The chloroformic layer was separated and centrifuged. The amount of rifampicin in the chloroformic phase was estimated by measuring the absorbance at 478 nm using a Unicam SP 1800 Spectrophotometer. At this wavelength, blank readings were negligible. The absorbance readings obtained correspond to the intact rifampicin and desacetylrifampicin (total rifampicin) since the latter is the only metabolite extractable with chloroform (Kolos and Eidus, 1972).

The suitability of the proposed method was tested by replicate assays of a blank urine sample spiked with known amounts of rifampicin (5–60 μg/ml). The mean percentage recovery of 10 determinations ($\bar{m} \pm$ S.D.) was 99.75 ± 1.51.

Effect of pH on the solubility of rifampicin

The effect of pH on the apparent equilibrium solubility of rifampicin was examined at 37 ± 0.2°C over the pH range 2.5–8.2 using 1/15 M phosphate buffer. After shaking for 3 h, the amount of rifampicin in solution was assayed spectrophotometrically at 337 nm after dilution with 0.1 N HCl. Longer equilibrium times were avoided due to instability of the drug.

Effect of pH on the dissolution rate of rifampicin

The dissolution rate of rifampicin capsules was tested using the U.S.P. Apparatus (paddle method). One capsule was used, the dissolution medium being either 500 ml 0.1 N HCl or 500 ml distilled water adjusted to pH 6.

Binding of rifampicin by magnesium trisilicate and hydrated silica gel

The possible binding of rifampicin by magnesium trisilicate at pH 5 was examined. This pH value was selected since the administration of a dose of magnesium trisilicate elevates the gastric pH to values between 4 and 5. Magnesium trisilicate (0.5 g) was digested with 50 ml of 0.08 N HCl at 37°C for 1 h. Under these conditions, magnesium trisilicate was partially decomposed with the formation of a hydrated silica gel and the medium had a pH value of 5. Different amounts of rifampicin were equilibrated with the antacid suspensions for 1 h at 37 ± 0.2°C. The supernatant was assayed for the 'unbound' rifampicin spectrophotometrically.

Results and Discussion

Urinary excretion data of rifampicin were found to reflect serum levels (Siegler et al., 1974; Brechbühler et al., 1978) and were, therefore, considered valid as a parameter for the assessment of rifampicin bioavailability. In the present study, urinary excretion rates (U.E.R.) and cumulative amounts excreted (C.A.E.) were used to assess the effect of antacids on the rate and extent of rifampicin absorption.

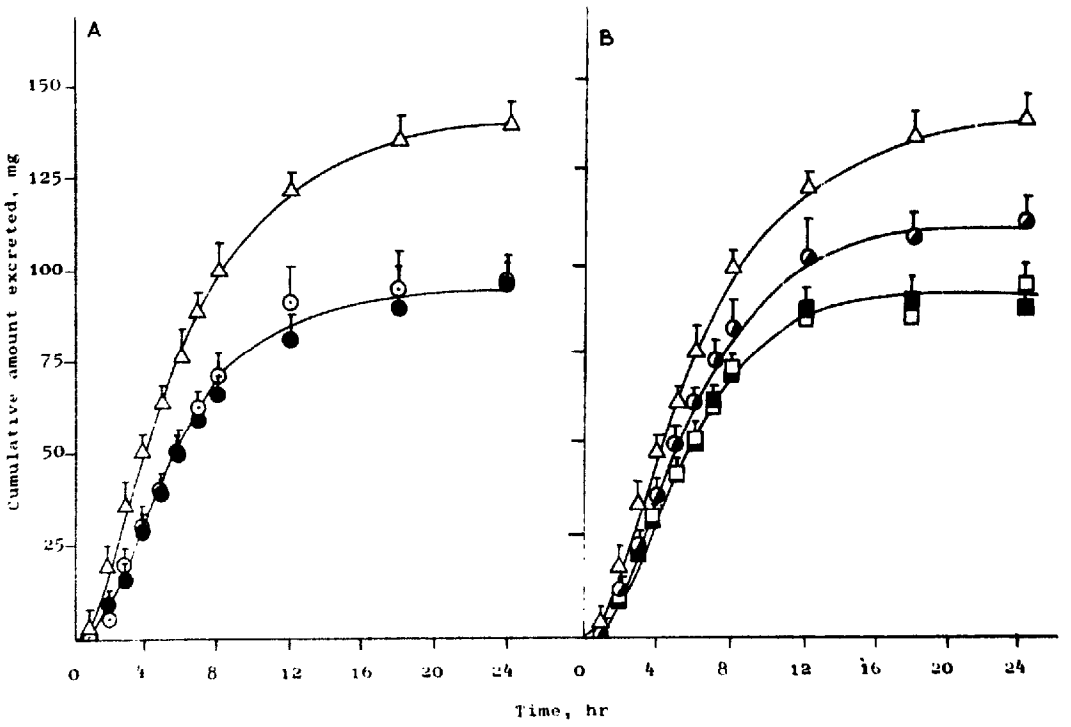

Fig. 1. A: effect of aluminium hydroxide gel on the cumulative amount (mg) of total rifampicin excreted in urine. Results from 5 subjects shown as mean ± S.E.M. △, control; ⊙, 15 ml aluminium hydroxide gel; ●, 30 ml aluminium hydroxide gel. B: effect of sodium bicarbonate and magnesium trisilicate on the cumulative amount (mg) of total rifampicin excreted in urine. △, control; ◕, 2 g sodium bicarbonate; □, 2 g mag. trisilicate; ■, 4 g mag. trisilicate.

Fig. 1A and B show that the concomitant administration of either aluminium hydroxide gel (Treatment B), magnesium trisilicate (Treatment C) or sodium bicarbonate (Treatment D) reduced the mean C.A.E. in 24 h. Doubling the dose of either aluminium hydroxide gel (Treatment B*) or magnesium trisilicate (Treatment C*) produced no further reduction. All the subjects showed almost complete urinary

TABLE I

URINARY EXCRETION DATA FOR THE ADMINISTRATION OF 600 mg RIFAMPICIN IN TREATMENTS A–D

Treatment	% dose excreted in 24 h ± S.E.M.	Mean % reduction in 24 h C.A.E. **	Mean % reduction in P.E.R. **
A	23.5 ± 0.9		
B	16.7 ± 1.3	29.0 $P < 0.025$	28.2 $P < 0.01$
B*	16.1 ± 1.8	31.3 $P < 0.025$	34.4 $P < 0.01$
C	15.0 ± 0.6	36.3 $P < 0.001$	35.1 $P < 0.01$
C*	16.0 ± 0.5	31.7 $P < 0.001$	29.2 $P < 0.01$
D	18.6 ± 1.4	20.7 $P < 0.05$	20.1 $P < 0.10$

** Relative to treatment A.

The statistical significance was assessed using Student's *t*-test. CAE = cumulative amounts excreted; PER = peak excretion rate.

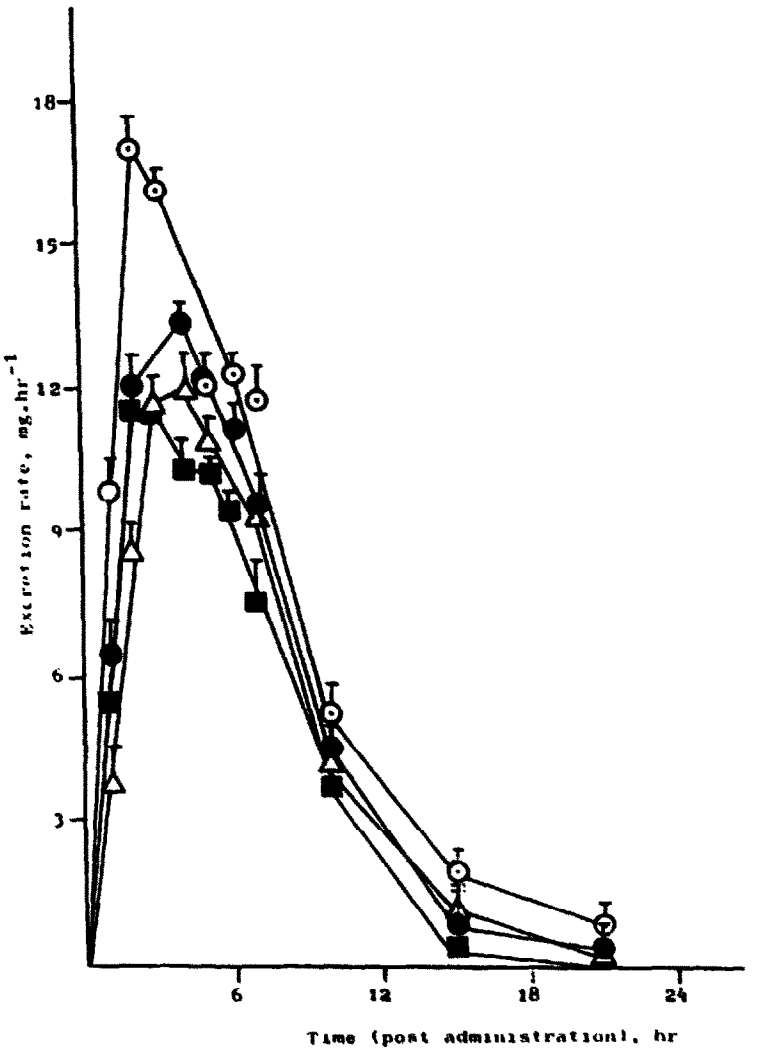

Fig. 2. Urinary excretion rates of total rifampicin following Treatments A (⊙), B (△), C (■) and D † (●). Data from 5 subjects shown as mean ± S.E.M.
† n = 4.

excretion of rifampicin in 24 h following Treatments A–D (Fig. 1A and B). This is in accordance with previously reported data (Brechbühler et al., 1978). The percent dose excreted and the mean percent reduction in C.A.E. are presented in Table 1. Analysis of variance (ANOVA) of the 24 h C.A.E. following Treatments A–D indicated a statistically significant difference in the extent of rifampicin absorption as well as significant inter-subject variation. Nevertheless, the relative rank order of the C.A.E. of the different subjects remained unchanged after treatments A–D.

Reduced urinary excretion rates occurred following the ingestion of the antacids under study (Fig. 2). The extent of reduction was statistically significant (Table 1).

The urinary pH of the volunteers remained almost unchanged following antacid administration, hence, the observed reduction in rifampicin bioavailability cannot be

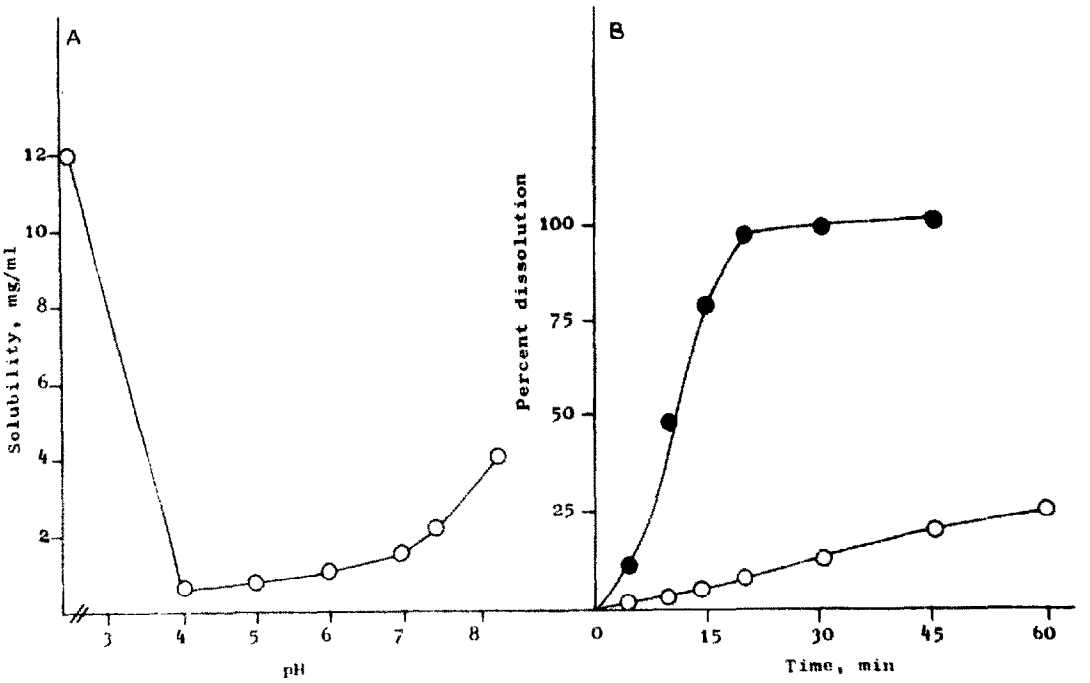

Fig. 3. A: effect of pH on the apparent equilibrium solubility of rifampicin. B: effect of pH on the dissolution rate of rifampicin capsules. ●, pH 1.2; ○, pH 6.0.

attributed to the effect of antacids on renal elimination. Moreover, the cumulative amount of drug excreted is considered to be independent of changes in tissue distribution or renal clearance, provided that the urine collection period is sufficient for most of the drug to be eliminated (Wagner, 1969). The effects of antacids on rifampicin bioavailability can, therefore, be attributed to interference with the antibiotic absorption.

Antacids affect the absorption of drugs by a number of mechanisms. These include gastric pH elevation, alteration of gastric motility, adsorption by the antacid particles and chelation by polyvalent cations of the antacids (Hurwitz, 1977).

A rise in the gastric pH would influence the state of dissociation and solubility of rifampicin (pK_a 1.7 and 7.9). The two factors significantly affect the absorption of ionic drugs. As would be expected, rifampicin was found to exhibit minimum solubility over the pH range 4–6 and an increase was found at relatively low and high pH values (Fig. 3A). Also, dissolution rate data indicated complete dissolution of rifampicin from capsules in 20 min at pH 1.2, whilst at pH 6.0 only 26% of the drug dissolved in 60 min (Fig. 3B). Since rifampicin dissolves optimally at low pH, elevation of gastric pH by an antacid would reduce the dissolution rate of the drug and adversely affect its absorption process. This is supported by previously reported data (Binda et al., 1971) where 50% reduction in rifampicin absorption occurred in patients with alkaline gastric pH.

Relative to sodium bicarbonate, a greater reduction in the bioavailability of rifampicin occurred when co-administered with either aluminium hydroxide gel or

TABLE 2

IN VITRO BINDING OF RIFAMPICIN BY MAGNESIUM TRISILICATE AT pH 5

Rifampicin (mg/50 ml)	% bound
5	19.9
10	20.2
15	16.4
20	16.6

magnesium trisilicate (Table 1). This implies that the latter two antacids interfered with rifampicin absorption via mechanism(s) other than gastric pH elevation. The chelation of rifampicin by aluminium ions has been reported (Paraschiva, 1973; Chowdary and Ramana Murthy, 1982a) and may account for the observed reduction in rifampicin bioavailability upon simultaneous administration of aluminium hydroxide gel. Aluminium ions containing antacids are known to reduce the bioavailability of a variety of drugs by alkalinizing the gastric contents and forming less absorbable chelates (Neuvonen, 1976; McElnay and D'Arcy, 1980). Also, aluminium ions are known to delay drug absorption due to slowed gastric emptying (Hurwitz, 1974).

Binding of drugs by the antacid particles is generally more pronounced in the case of magnesium trisilicate (Khalil, 1974; Naggar and Khalil, 1979). Both the antacid and its by-product after neutralization (the hydrated silica gel) possess adsorbent properties. In the present study, rifampicin was found to be bound to the extent of 16–20% by the partially neutralized magnesium trisilicate at pH 5 (Table 2). Hence, gastric pH elevation and binding of rifampicin by magnesium trisilicate would explain the relatively greater reduction in the antibiotic bioavailability observed in vivo (Table 1).

In summary, the bioavailability of rifampicin was significantly reduced when simultaneously administered with antacids. Reduced availability of the drug due to gastric pH elevation, chelation with aluminium ions and binding by magnesium trisilicate appeared to be implicated in the impaired oral absorption of rifampicin. Although the clinical significance of the rifampicin–antacid interaction has not been assessed, it might be prudent to avoid simultaneous administration of rifampicin with antacids.

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