J. Pharm. Pharmac., 1974, **26**, 961–967 *Received April* 29, 1974

The uptake of digoxin and digitoxin by some antacids

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The adsorption of digoxin and digitoxin by some antacids has been investigated. Magnesium trisilicate showed the highest adsorptive effect, the extent of adsorption being up to 99% for the two glycosides. The calculated values of monolayer adsorption were 0·93 and 1·36 mg g^{-1} for digoxin and digitoxin respectively. At 37° only partial elution of adsorbed glycosides occurred in 0·2N HCl due to re-adsorption on the hydrated silica gel formed. Antacid preparations containing magnesium trisilicate adsorbed digoxin from a paediatric elixir to the extent of about 95%. Dissolution of digoxin tablets was similarly affected since almost complete suppression of dissolution occurred in the presence of 0·5 g magnesium trisilicate per 0·25 mg digoxin tablet. The effect of antacids, when concurrently administered with oral digoxin, on the bioavailability of the drug, is discussed.

The *in vitro* adsorption of drugs by antacids has been the subject of a number of studies. Among the antacids tested, magnesium trisilicate appeared to possess the highest adsorptive capacity. This was shown by Chulski & Forist (1958), Blaug & Gross (1965), El-Nakeeb, Aggag & Yousef (1969), Khalil & Moustafa (1973) and El-Masry & Khalil (1974). During a study on the effect of some antacid preparations on the dissolution of digoxin tablets, it was found that the dissolution was completely suppressed in the presence of preparations containing magnesium trisilicate. In view of the attention recently focussed on the problem of digoxin bioavailability (Fraser, Leach & others, 1973; Shaw, Raymond & others, 1973) it was of interest to examine: (a) the possible uptake of digoxin and digitoxin by some antacids; and (b) the elution of the adsorbed glycosides in different elution media. The effect of some antacid preparations on the uptake of digoxin from a paediatric elixir and the dissolution of digoxin tablets has also been studied. The implications of the data obtained on the bioavailability of digoxin are discussed.

MATERIALS AND METHODS

Materials

Magnesium trisilicate (Evans Medical Ltd.) of mean volume-surface diameter 11·2 μm was used. Digoxin powder B.P. was a gift from Burroughs Wellcome & Co. Digitoxin (BDH), product No. 28147 was used. Lanoxin paediatric elixir, 0·05 mg ml^{-1} (Burroughs Wellcome & Co., Batch No. 0436 O) and digoxin tablets, 0·25 mg (Lanoxin Batch No. 2042 X) were purchased. Aluminium hydroxide gel, B.P. (Aludrox, Wyeth, Batch No. C IG42) was used. All antacid powders used were of B.P. quality (BDH).

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Methods

Adsorption experiments. These were carried out at 37 ± 0·1°. Due to the limited solubility of both digoxin and digitoxin in water (the determined equilibrium solubility values at 37 ± 0·1° were 1·69 and 0·48 mg % for digoxin and digitoxin, respectively), it was necessary to maintain the concentrations below the equilibrium solubility values to avoid precipitation. The following procedure was adopted.

Each glycoside was dissolved in ethanol to give a stock solution of 50 mg %. A duplicated series of 150 ml glass stoppered conical flasks, containing the antacid suspended in water, were prepared. In all the flasks, the volume of the aqueous antacid suspension was adjusted so that after the addition of the 0·5 ml aliquot(s) of the glycoside solution, the final volume was 100 ml. To each flask was added an aliquot (0·5 ml) containing 0·25 mg of the glycoside. The flasks were equilibrated for 30 min at 37 ± 0·1°. The contents of two flasks were centrifuged at 4000 rev min^{-1} for 3 min and the supernatants were assayed for the glycoside content. This gave the first point in Fig. 2 (i.e. at an initial glycoside concentration of 0·25 mg %). A second aliquot (0·5 ml) of the glycoside solution was added to the remainder of the flasks and the contents again were equilibrated for 30 min. At that stage, the total concentration of the added glycoside was 0·5 mg %. Two flasks were assayed as above and the results obtained gave the second point in Fig. 2. Further additions of the 0·5 ml aliquots were made and the analyses completed as before. In this way the adsorption curve, shown in Fig. 2, was completed. Using the above procedure, it was possible to add a total of up to 1·75 mg % of either glycoside to prepare the adsorption plot shown in Fig. 2 for magnesium trisilicate. The 'free', unadsorbed glycoside concentrations found at 1·75 mg % (total glycoside concentration) were 0·80 and 0·38 mg % for digoxin and digitoxin, respectively. These values are less than the determined solubility values for the two glycosides.

To study the effect on adsorption by magnesium trisilicate of hydrochloric acid, strengths of 0·01–0·2N were used. The antacid was digested at 37 ± 0·1° in the medium for 1 h before the glycoside solution was added.

Dissolution of magnesium trisilicate. This was determined from the amounts of magnesium released in the medium, as previously reported (El-Masry & Khalil, 1974). Analyses of the glycosides in the supernatant, obtained after centrifugation at 4000 rev min^{-1} for 3 min were as described below.

Determination of digoxin and digitoxin. The following procedure, based on the European Pharmacopoeia (1969) method for digoxin and digitoxin, was used. An aliquot of the supernatant was extracted with 4 × 10 ml of chloroform and after evaporation ethanol (0·5 ml) was added and again evaporated. After cooling, the residue was dissolved in ethanol (5 ml) and then freshly prepared alkaline sodium picrate solution (3 ml) was added. The colour intensity produced was measured at 495 nm after 16 min and then at 2 min intervals the highest reading was taken. Runs using standard solutions of either glycoside were concurrently made and compared with a blank. During the assay procedure the solutions were maintained at 22 ± 2° and protected from direct light.

Extraction rate. Extraction of the glycosides adsorbed on magnesium trisilicate was made at 37 ± 0·1° by digesting the residue (1 g), left after centrifugation, in 100 ml

of water, or 0·05N or 0·2N HCl. The glass stoppered flasks were shaken and at specified time intervals aliquots were centrifuged and the concentration of the extracted glycoside was determined. An average of three replicate runs was taken.

Adsorption of digoxin from the paediatric elixir

Aliquots (10 ml) of the liquid antacid preparations were made up to 100 ml with the diluted elixir (diluted 1:10 with water). The glass stoppered flasks were shaken at 37 ± 0·1° in an oscillating water bath and samples were centrifuged at specified time intervals. The digoxin content in the supernatant was determined as described previously. Three replicates were made and the results averaged.

Dissolution testing of digoxin tablets

The apparatus used was a rotating basket assembly based on the apparatus described in NF XIII (1970) under Method I water at pH 5·4 was used as the dissolution medium. The dissolution rate of 8 tablets in 800 ml of the medium, contained in a 1 litre vessel was made at a speed of 120 ± 5 rev min^{-1}. The stirring shaft of the rotating basket assembly was placed 2 cm above the bottom of the vessel. The dissolution experiments were at 37 ± 0·2°. In testing the effect of antacids on dissolution, 5 ml of the antacid suspension for each digoxin tablet was added to the dissolution medium. Samples were withdrawn at 5, 15, 30, 45, 60 min and then at 30 min intervals to 180 min. Fresh aliquots of the dissolution medium were added each time to maintain constant volume. The digoxin content was determined in the samples withdrawn, after centrifugation, following the procedure described earlier. Three replicate runs were made and the results averaged. Single tablet dissolution was checked by placing one tablet in 100 ml of water maintained at 37 ± 0·2°. The glass-stoppered flasks were shaken in a Gallenkamp shaking reaction incubator at 25 ± 2 strokes min^{-1}. One flask was prepared for each time interval at which sampling was to occur. The amount of digoxin dissolved was determined after filtering an aliquot through sintered glass filter (grade 4). Six replicates were made simultaneously for each time interval over a period of 1 h.

RESULTS

Determination of digoxin and digitoxin. With the method adopted, the data obtained obeyed Beer's law over the concentration ranges used for the two glycosides. The coefficients of variation of 10 of the replicates of 0·5 mg each of glycoside were ±1·61 and 1·30% for digoxin and digitoxin, respectively. Compared with direct estimation, extraction with chloroform gave 97·8% recovery (average of 6 replicates ±3·1%) for digoxin and 99·1% (average of 6 replicates ±2·6%) for digitoxin.

Adsorption experiments. Fig. 1 shows the adsorption of digoxin and digitoxin at 37° on five antacids. For both drugs, magnesium trisilicate exhibited the highest adsorptive effect. At an initial concentration of 0·25 mg %, both glycosides were completely adsorbed by 1 g of magnesium trisilicate. Other antacids showed relatively weaker adsorptive effects; the extent of adsorption did not exceed 25%. Adsorption by magnesium trisilicate was fast since about 85% adsorption occurred within 5 min and equilibrium was attained after 30 min. Fig. 2 shows the adsorption plots of the two glycosides at various initial concentrations. At initial concentrations higher than 0·5 mg % more digitoxin was adsorbed than digoxin. The adsorption data

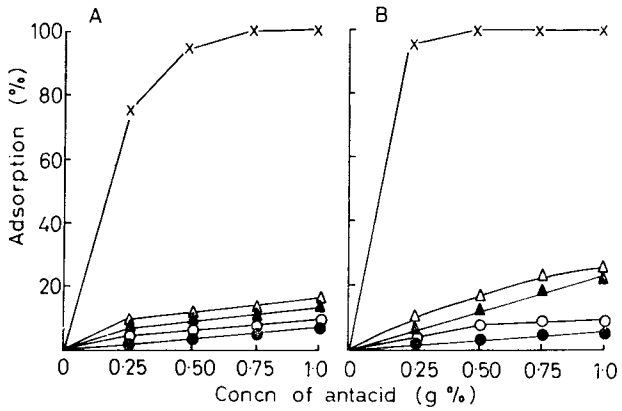

FIG. 1. Adsorption of (A) digoxin and (B) digitoxin by some antacids at 37 ± 0·1°. (×) magnesium trisilicate; (△) aluminium hydroxide gel B.P.*; (▲) light magnesium oxide; (○) light magnesium carbonate; (●) calcium carbonate. Initial concentration of the glycoside: 0·25 mg %.
* Aludrox was used in the concentration range of 2·5 to 10% v/v.

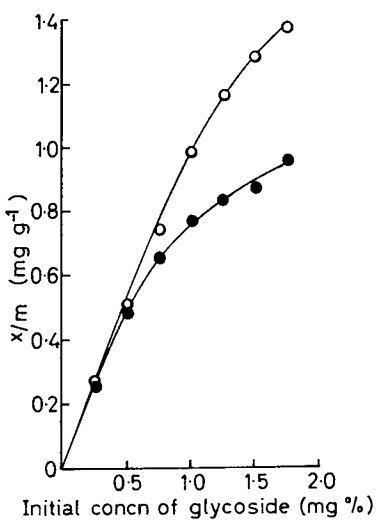

FIG. 2. Adsorption of digoxin (●); and digitoxin (○) by 1% w/v magnesium trisilicate at 37 ± 0·1°.

fitted a Langmuir plot for both glycosides and the values of monolayer adsorption (calculated from 1/slope of the Langmuir plot) were 0·93 and 1·36 for digoxin and digitoxin, respectively. Table 1 shows the effect of hydrochloric acid concentration on both dissolution of magnesium trisilicate and adsorption of the two glycosides. The extent of adsorption by 1% w/v magnesium trisilicate was dependent on the level of hydrochloric acid in the medium. This also affected the percentage dissolution of the antacid (Table 1). In systems where dissolution of the antacid was about 94%, both glycosides were adsorbed to the extent of about 52 and 66%. Since a hydrated silica gel is one of the products in acid media, its adsorptive effect was tested. The residue remaining after the B.P. acid adsorption test for magnesium trisilicate (but using 1 g) was separated by centrifugation. In the presence of 0·25 mg % of either

Table 1. *Effect of hydrochloric acid content on the adsorption of digoxin and digitoxin by 1% w/v magnesium trisilicate at 37 ± 0·1°.* (Initial concentration of each glycoside: 0·25 mg %.)

Adsorption medium	Dissolution of magnesium of trisilicate (%)*	pH†	Adsorption (%) Digoxin	Digitoxin
Water (pH 5·5)	0·6	9·6	98·9	99·6
0·01N HCl (pH 2·1) ..	9·3	7·2	92·1	99·3
0·05N HCl (pH 1·5) ..	40·8	6·9	87·0	91·7
0·10N HCl (pH 1·2) ..	81·1	6·1	68·3	83·4
0·20N HCl (pH 0·3) ..	93·9	1·4	52·1	66·2

* Calculated from the amounts of magnesium released after 1 h (El-Masry & Khalil, 1974).

† Measured after equilibration for 1 h before addition of the glycoside solution.

glycoside, the hydrated silica gel adsorbed 37·2 and 45·7% of digoxin and digitoxin, respectively, after 1 h at 37 ± 0·1°.

Extraction rate. The results of the extraction experiments are shown in Fig. 3. The rate of extraction of digitoxin was slower than that of digoxin, and depended on the medium used. In water (pH 5·5) not more than 13% of either glycoside was extracted within 3 h. Slightly higher amounts were obtained in 0·5N HCl (pH 1·5). In the presence of 0·2N HCl, where about 94% dissolution of the antacid occurred, extraction amounted to 65·1 and 47·3% for digoxin and digitoxin, respectively (Fig. 3).

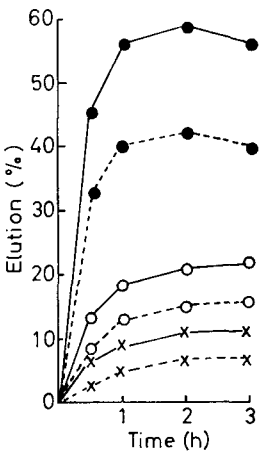

FIG. 3. Elution rates at 37 ± 0·1° of digoxin (——) and digitoxin (– – –) adsorbed on magnesium trisilicate. Elution media: (×) Water; (○) 0·05N HCl; (●) 0·2N HCl. The adsorption run was made using 1% w/v magnesium trisilicate and 0·25 mg % of either glycoside.

Adsorption of digoxin from the paediatric elixir

Figure 4A shows the rate of uptake of digoxin from Lanoxin paediatric elixir by some antacid preparations. Aluminium hydroxide gel (Aludrox) produced a slight reduction (about 15%) of the digoxin content in solution. Both magnesium trisilicate mixture, B.P.C. and a suspension* containing 6·2% aluminium hydroxide

* Gelusil, W. R. Warner & Co. Ltd., Hants. (Batch No. 705038).

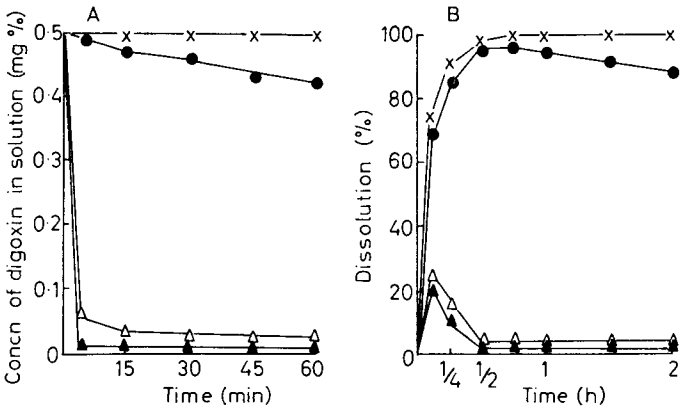

FIG. 4A. Adsorption of digoxin from Lanoxin paediatric elixir at 37 ± 0·1° by (●) aluminium hydroxide gel B.P. (10% v/v); (△) magnesium trisilicate mixture, B.P.C. (10% v/v); (▲) Gelusil suspension (10% v/v). (×) Lanoxin elixir diluted 1:10 with water.
B. Effect of some antacid preparations on the dissolution rate of Lanoxin tablets at 37 ± 0·1°. (×) dissolution in water; (●) in 10% v/v aluminium hydroxide gel; (△) in 10% v/v magnesium trisilicate mixture, B.P.C., (▲) in 10% v/v Gelusil suspension.

dried gel and 12·4% magnesium trisilicate produced a marked reduction in digoxin content. After 1 h, not more than 5% of the labelled digoxin content was found in the supernatant.

Dissolution testing of digoxin tablets

The batch of Lanoxin tablets used complied with the content uniformity test as described in B.P. Results of single tablet dissolution revealed that, with the exception of the 5 min sample, dissolution at various time intervals was uniform in the six replicates. The coefficient of variation did not exceed 2·7%. For the 5 min sample the coefficient of variation was 6·3%. Figure 4B shows the effect of three antacid preparations on the dissolution of digoxin tablets. The dissolution profile was affected in a manner similar to that found for the paediatric elixir. Whilst aluminium hydroxide gel produced a maximum suppression of about 13%, both the B.P.C. mixture and Gelusil suspension produced almost complete suppression of the dissolution.

DISCUSSION

The results suggest that among the antacids tested, magnesium trisilicate exhibited the highest adsorptive effect. The relatively weak adsorptive capacity of calcium carbonate, magnesium oxide, magnesium carbonate and aluminium hydroxide gel is of minor significance since these antacids would dissolve in the gastric juice *in vivo*. The calculated values of monolayer adsorption for digoxin and digitoxin on magnesium trisilicate are lower than those reported for streptomycin (El-Nakeeb & others, 1969) and atropine and hysocine (El-Masry & Khalil, 1974). The extents of adsorption of the two glycosides, however, are significant in view of the relatively low dosages of these drugs. The presence or absence of the hydroxyl group at C-12 appears to be responsible for the observed variation in the extent of adsorption of the two glycosides. According to Patrick & Eberman (1925), for a given solvent the more soluble solutes are generally less strongly adsorbed than the less soluble

solutes. Owing to the presence of the hydroxyl group at C-12, digoxin is relatively more soluble in water than digitoxin since the equilibrium solubility values determined at 37° were 1·69 and 0·48 mg%, respectively. Digoxin would therefore be expected to be less adsorbed than digitoxin. Because of the dissolution of magnesium trisilicate in acid media, the adsorption of the two glycosides was dependent on the level of the hydrochloric acid in the medium (Table 1). Adsorption was noted, however, even when the percentage dissolution of the antacid was about 94. This was due to the adsorptive effect of the hydrated silica gel formed.

Extraction of the glycosides adsorbed by magnesium trisilicate depended on the extent of dissolution of the antacid. Again, extraction was incomplete due to the re-adsorption of glycoside on the hydrated silica gel formed in acid media.

As would be anticipated, the presence of antacid preparations containing magnesium trisilicate decreased the availability of digoxin from both the elixir and tablets (Fig. 4). The disappearance of digoxin from solution after 30 min is synchronous with its adsorption on the antacid. From the foregoing discussion and in the light of the established correlation between *in vitro* dissolution and digoxin bioavailability (Fraser & others, 1973; Shaw & others, 1973) it is concluded that the concurrent administration of oral digoxin with magnesium trisilicate-containing antacids may impair digoxin bioavailability. The application of any of the suggested *in vitro* dissolution parameters which reflect bioavailability (e.g. amount of digoxin dissolved after 30 min or the reciprocal of the time of 50% dissolution) to the present data suggest that a significant loss of digoxin bioavailability may occur.

Acknowledgements. The author thanks Dr. S. El-Masry for the valuable suggestions and Mr. B. C. Pilcher of Burroughs Wellcome & Co. for the gift of digoxin powder B.P.

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