fusion layer control since diffusion away from the matrix is rate controlling. This behavior results when K is large, *i.e.*, $\beta^2K^2 \gg \alpha C_s t$, and Eq. 2*a* simplifies to:

$$\text{rate} = \frac{D_a C_a}{h_a} \qquad \text{(Eq. 7)}$$

The dashed lines in Fig. 1 indicate that period for which the diffusion layer contribution to the overall release is substantial (*i.e.*, until the time when $\alpha C_s t = \beta^2K^2$), while the continuous lines represent that period when the release is primarily under matrix control. The crossover of the curves results because the transition of diffusion layer to matrix control occurs at different times. Comparison of the 5 and 15% loading doses indicates that release rates are independent of drug concentration at longer chain lengths. However, the shorter chain lengths do exhibit a dependence on concentration which follows Eq. 6 at long times. Also, at the higher concentration, diffusion layer control is operative for a longer time (Fig. 1).

Figure 2 shows the applicability of Eq. 2*a* from a different viewpoint. Here, rate is plotted as a function of the number of carbons *(n)* in the alkyl chain. The dashed line is the rate calculated from Eq. 7 and is directly proportional to C_a. The continuous line is the rate calculated from Eq. 6 and is proportional to $(C_s)^{1/2}$ at a given time. The expected rate given by Eq. 2*a* is represented by the dotted line, and the shaded area is the transition region.

Based upon the model discussed here, factors such as particle size or polymorphic forms of the drug which may influence C_s and/or C_a would be expected to alter the release profile. A forthcoming publication[5] will experimentally test the applicability of these equations.

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Received May 17, 1974.
Accepted for publication July 8, 1974.

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Bioavailability of Digoxin in Presence of Antacids

Keyphrases □ Digoxin—bioavailability in presence of antacids □ Antacids—effect on bioavailability of digoxin □ Bioavailability—digoxin, effect of concurrent antacid administration

To the Editor:

Considerable attention has recently been focused on the problem of bioavailability of digoxin (1–5), and several factors have been reported as responsible for the observed therapeutic effect (6–8). This communication reports the effect of some antacids on the dissolution of digoxin tablets[1] in an attempt to predict the bioavailability of the drug.

Recently, a number of reports (4, 5, 8) confirmed the existence of a close correlation between *in vitro* dissolution and the plasma digoxin level. Shaw *et al.* (4), using seven brands of digoxin tablets, found a good correlation between the percentage of dissolution at 30 min and the plasma digoxin level. Fraser *et al.* (5) reported that both the amount of digoxin dissolved in 1 hr and the reciprocal of the time for 50% dissolution ($1/t_{50\%}$) agreed well with the bioavailability data as computed from the mean area under the serum concentration–time curve. Therefore, dissolution experiments were carried out in the present work to reflect bioavailability.

The dissolution apparatus and procedure adopted were as reported previously (4). The liquid antacid preparation was incorporated in the dissolution medium (water), and an aliquot of 5 ml per digoxin tablet was used. Dissolution tests were performed at 37 ±

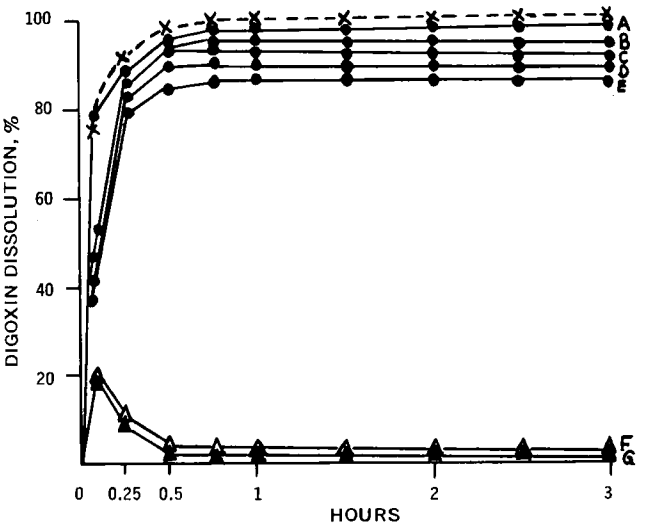

Figure 1—*Effect of some liquid antacid preparations on the dissolution rate of digoxin tablets at 37 ± 0.2° (average of four replicates). Key: – – –, dissolution in the absence of antacids; and ——, dissolution in the presence of antacids. For key to antacid preparations, see Table I.*

[1] Lanoxin tablets (0.25 mg), Batch 2042 X, Burroughs Wellcome & Co., Kent, England.

Table I—Effect of Some Antacid Preparations on Dissolution of Digoxin Tablets at 37 ± 0.2°

Antacid Product[a]	Composition (per 10 ml)			Dissolution Data		
				Percent Digoxin Dissolved after		
	Aluminium Hydroxide	Magnesium Hydroxide	Magnesium Trisilicate	0.5 hr	1 hr	$1/t_{50\%}$
A	9.8 ml (as gel)	0.170 g	—	95.1	97.8	0.250
B	0.43 g (as dried gel)	0.160 g	—	91.8	93.1	0.250
C	10 ml (as gel)	—	—	89.8	92.1	0.167
D	9.5 ml (as gel)	0.200 g	—	85.7	91.8	0.167
E	0.44 g (as dried gel)	0.195 g	—	86.3	89.6	0.143
F	—	—	0.50 g	9.8	1.4	<0.001
G	0.62 g (as dried gel)	—	1.24 g	7.9	0.0	<0.001

[a] A = Dijex suspension (Batch No. 7 V), Boots, Nottingham, England; B = Simeco suspension (Batch No. 3720076), Wyeth Lab., Inc., Philadelphia, Pa. (this preparation also contains activated dimethicone); C = Aludrox gel (Batch No. C. IG42), J. Wyeth & Brothers Ltd., Hants, England; D = Polycrol Forte gel (Batch No. 71/2), Nicholas Lab. Ltd., Slough, England; E = Maalox suspension (Batch No. 98508), W. H. Rorer, Inc., Fort Washington, Pa.; F = magnesium trisilicate mixture BPC (this preparation also contains sodium bicarbonate and light magnesium carbonate, the latter having no adsorptive effect on digoxin); and G = Gelusil suspension (Batch No. 705038), W. R. Warners & Co., Ltd., Hampshire, England.

0.2°, and samples were withdrawn periodically over 3 hr. Fresh aliquots of the dissolution medium were added each time to maintain constant volume. The digoxin content in the centrifuged sample was determined by a modification of the European Pharmacopoeia method (9). The surpernate, obtained after centrifugation of the sample, was extracted with chloroform (4 × 10 ml); after evaporation, the residue was dissolved in alcohol and the alkaline sodium picrate solution was added. The color intensity was measured at 490 nm using a spectrophotometer[2] and was compared with a blank. Digoxin powder[3] BP was used as the standard.

Table I shows the compositions of the antacids used, the percentages dissolution of digoxin after 0.5 and 1 hr, and the values of $1/t_{50\%}$. Figure 1 shows the effect of the antacid preparations on dissolution profile over 3 hr. Dissolution of the tablets in the "plain" dissolution medium is shown for comparison. In the presence of antacid preparations containing no magnesium trisilicate, only a relatively slight reduction in dissolution occurred. The presence of magnesium trisilicate in both Products F and G appeared to be responsible for the observed drastic suppression of dissolution. After 1 hr, less than 5% of the labeled digoxin was found in solution (Fig. 1). Values of $1/t_{50\%}$ were, therefore, infinitesimal since the 50% dissolution was not attained even after 12 hr. In the plain dissolution medium, the tablets gave 99.2% dissolution after 1 hr and the time for 50% dissolution was less than 5 min.

The disappearance of digoxin from solution in the presence of magnesium trisilicate-containing antacids may be attributable to the adsorption of the drug on magnesium trisilicate. Preliminary results showed that digoxin was adsorbed on magnesium trisilicate, the value of monolayer adsorption being 0.93 mg/g. Other ingredients of the antacid preparations tested gave negligible adsorption. Magnesium trisilicate has been reported to adsorb a number of drugs including steroids (10–13).

Attempts were made to elute the digoxin adsorbed by both Products F and G. Various elution media were used, with pH values between 1.2 and 8.0. (Hydrochloric acid was used to adjust the pH.) At 37 ± 0.2°, elution of the adsorbed digoxin was insignificant since a maximum of 15% was eluted after 6 hr. In the light of the confirmed correlation between digoxin dissolution and bioavailability, the concurrent administration of oral digoxin and antacids containing magnesium trisilicate may impair the bioavailability of the drug. Investigations are underway in this laboratory to study, in more detail, the *in vitro* adsorption and *in vivo* implications.

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Received May 7, 1974.
Accepted for publication July 15, 1974.
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Preparation and Curarimimetic Activity of (+)-Isotubocurarine

Keyphrases □ (+)-Isotubocurarine—preparation and curarimimetic activity □ Curarimimetic activity—(+)-isotubocurarine □ Neuromuscular blocking activity—stereochemical requirements, preparation and curarimimetic activity of (+)-isotubocurarine

To the Editor:

We have been interested in the stereochemical requirements for nondepolarizing neuromuscular junction blockade of the voluntary nervous system for some time. King (1), who initially determined the structure of (+)-tubocurarine as I*a* and later isolated and tested (−)-tubocurarine (2), reported a 20–60 times lower activity on the rat diaphragm–phrenic nerve preparation for the latter enantiomer. The rather marked difference in activity and the scarcity of research directed toward this facet of neuromuscular junction blocking agents have been noted (3). Recently, we submitted several reports (4–6) bearing on the problem.

Our present interest was prompted by a report (7) indicating that the structure of (+)-tubocurarine was I*b* instead of I*a*. These investigators found that not only was (+)-tubocurarine represented by I*b* but that (+)-chondrocurarine must have the formula I*a*. The finding that I*b* was a monotertiary, monoquaternary species has been disquieting in view of the generally accepted belief that a bisquaternary form was necessary for potent blocking activity. Although no ready explanation for the potency of I*b* has been forthcoming, Waser (8), noting the easy protonation of the tertiary nitrogen, appears to imply that the resultant dicationic species is somewhat comparable to I*a*.

Since our interest has been directed toward relating the influence of an asymmetric carbon of specific configuration adjacent to the quaternary moiety to neuromuscular junction blocking potency, we felt it would be of interest to prepare what we term "(+)-isotubocurarine" (I*c*). Compound I*c* would have the reverse order of quaternization to that in I*b* and would provide an isomeric tubocurarine in which the only structural change would be that the quaternary moiety would be adjacent to a center with the *S*- rather than the *R*-configuration as in I*b*. Obtaining the relative potencies of I*b* and I*c* would help to answer the question as to whether Waser's implied explanation for the activity of I*b* has substance. If it has merit, there should be only a minor potency difference, dependent on pKa differences, between the two rather similar tertiary nitrogens of I*b* and I*c* derived from (+)-tubocurine [now known to be (+)-chondrocurine (7)]. But if a significant potency difference were found, it could indicate that there is importance to the configuration of the carbon atom adjacent to the quaternary head.

(+)-Isotubocurarine was obtained from (+)-tubocurine, which had been prepared by the demethylation procedure of Shamma *et al.* (9) involving the dequaternization of I*b* with sodium thiophenoxide. The ditertiary base had a melting point of 235–237° and an $[\alpha]_D^{20}$ of +220° (c 1.0, 0.1 *N* HCl). Shamma *et al.* (9) reported a melting point of 222.5–223.5°, and an $[\alpha]_D$ of +221° (c 1.15, 0.1 *N* HCl) for (+)-tubocurine, although (+)-chondrocurine is reported (10) to have a melting point of 232–234° and an $[\alpha]_D^{24}$ of +200° (c 0.5, 0.1 *N* HCl), the two compounds being identical. A direct comparison by mixed melting point, TLC, and spectral (IR and UV) methods showed complete agreement[1]. The discrepancy in melting point is presently not explicable since the sample supplied to us, in our apparatus, gave a melting point of 227–231°. Since analytical data (C, H, N) on our (+)-tubocurine were also in accord with the assigned formula, we believed our compound to be suitable for further experiments.

(+)-Tubocurine, in a large volume of acetone, was treated with 0.5 *M* equivalent of a dilute acetone solution of methyl iodide in increments over approximately 0.5 hr. The reaction mixture, evaporated to dryness, was dissolved in a minimum amount of methanol and crystallization of a large portion of the excess (+)-tubocurine was induced. The mother liquor was evaporated under reduced pressure to provide a yellowish-white powder.

TLC examination of this powder on silica gel, using a mixture of 10% aqueous ammonia–methanol–ethyl acetate–isopropyl alcohol (2:2:1:1), showed four spots with R_f values of 0.83, 0.43, 0.26, and 0.05. Of these, the spots with R_f values of 0.83, 0.43, and 0.05 were shown to correspond to authentic (+)-tubocurine,(+)-tubocurarine chloride neutralized with sodium bicarbonate, and the expected bisquaternary base, respectively. On this basis, the spot with R_f value 0.26 was concluded to represent the isomeric tubocurarine (I*c*). Judging from the intensity of the spot at R_f 0.26 compared to that at R_f 0.43, the former was in the major amount.

A methanolic solution of the mixture subjected to TLC analysis was then passed through an ion-exchange resin[2] (chloride cycle). No iodide ion was detected in the effluent, which was evaporated to give a residue. This residue was dissolved in methanol and distributed on a small portion of alumina which was then air dried. The dried residue was placed on top of a column of grade V neutral alumina and eluted with ethyl acetate to provide the residual amounts of (+)-tubocurine in the early fractions. Continued elution with a mixture of ethyl acetate–methanol, followed

[1] The comparisons were made possible through the cooperation of Dr. M. Shamma, Pennsylvania State University.
[2] Amberlite IRA 410.