phenothiazine concentration should change with time in the presence of oxygen according to:

$$P = aP_0 \frac{k_1}{k_1 - k_2} (e^{-k_2 t} - e^{-k_1 t}) \quad \text{(Eq. 1)}$$

where P is the phenothiazine concentration, aP_0 is the initial concentration of I, k_1 is the rate constant for I degradation, and k_2 is the rate constant for phenothiazine degradation. At the various pH values, the phenothiazine concentrations were calculated using the values for k_1 given in Table I and the value of 19.7×10^{-3} hr^{-1} for k_2 (1). The calculated curves were in good agreement with the observed ones; a typical example is given in Fig. 2. The small differences were probably due to the experimental conditions being not exactly the same as in the previous studies.

In the absence of oxygen, the phenothiazine concentration can be calculated from the equation:

$$P = aP_0(1 - e^{-k_1 t}) \quad \text{(Eq. 2)}$$

With the evaluated k_1 values, the phenothiazine concentration was calculated as a function of time. Values in good agreement with the experimental ones were obtained (Fig. 2).

From these findings, it can be concluded that the first step in the degradation of I is its hydrolytic cleavage, giving II, which is degraded further by oxidation. This increase in stability of the phenothiazine ring system is probably caused by two factors: the steric effect of the introduction of a side chain at the nitrogen atom (1) and the electron-withdrawing properties of the acetyl group, which decrease the electron density in the ring system.

Interpretation of the data obtained for the formation of III and IV is difficult. Their formation proceeds *via* a number of consecutive reactions (2), their concentrations are rather small so they cannot be measured accurately, and they are unstable at the pH values used. There is, however, no reason to assume that their formation proceeds *via* pathways different from the ones elucidated previously.

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Drug Absorption from *In Situ* Rat Small Intestine during Metoclopramide Administration

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Abstract □ The effect of metoclopramide on the absorption of drugs in solution in the small intestinal lumen of rats *in situ* was studied. Metoclopramide in doses up to 50 mg/kg sc did not significantly modify the disappearance of isoniazid and quinidine from the small intestinal lumen. At the end of the absorption experiments, quinidine in the whole blood of the experimental animals was increased after metoclopramide. The blood level did not correlate to the drug disappearance from the intestinal lumen. The results probably differ from those obtained when drugs are given orally to subjects treated with metoclopramide.

Keyphrases □ Metoclopramide—effect on absorption of other drugs, *in situ* rat small intestine preparation □ Absorption—drugs from *in situ* rat small intestine, effect of metoclopramide administration □ Isoniazid—absorption from rat small intestinal lumen, effect of metoclopramide administration □ Quinidine—absorption from rat small intestinal lumen, effect of metoclopramide administration

Metoclopramide modifies the absorption of orally administered drugs (1, 2). Its effects are mainly due to changes in gastric emptying, resulting in an accelerated, but not necessarily totally increased, absorption when measured by urinary drug excretion (1). Decreased intestinal drug absorption, probably due to rapid GI transit, also was reported (3).

EXPERIMENTAL

To study whether metoclopramide has effects on the absorption of drugs already in solution in the small intestinal lumen, experiments were carried out in urethan-anesthetized (1–1.5 g/kg im) rats using an *in situ* absorption technique (4, 5) whereby the drug disappearance from a buffer (pH 6.0) in the small intestinal lumen can be measured. Depending on the weight of the rats (200–250 g), 10–15 ml of warm (37°) buffer was introduced into the intestinal lumen through a polyethylene cannula in the proximal duodenum.

Samples were taken from this "intestinal fluid," expelled at 10-min intervals, either through the other cannula in the distal ileum or through the proximal cannula in the duodenum. At the end of the 40-min experiment, whole blood was drawn by heart puncture and the whole small intestine was removed as a sample.

Metoclopramide[1], 50 mg/kg sc, was administered to the anesthetized rats 30 min before the absorption experiment; isoniazid (neutral drug) and quinidine sulfate (basic drug) were used as the test drugs. Smaller doses of metoclopramide (5–10 mg/kg) also were used.

Isoniazid was assayed spectrophotometrically (6), and quinidine was assayed fluorometrically (7).

RESULTS AND DISCUSSION

Figure 1 shows the disappearance of quinidine from the small intestinal lumen in control and metoclopramide-treated (50 mg/kg) rats. A similar plot was made for isoniazid. The absorption half-lives of isoniazid and quinidine, measured from the semilogarithmic plot of drug concentration in the intestinal lumen (intestinal fluid) *versus* time, are presented in Table I.

No statistically significant differences in absorption half-lives could be demonstrated, although the quinidine absorption half-life seemed to be somewhat longer after metoclopramide than in controls. However, in spite of an unchanged absorption half-life, the blood level of quinidine, but not of isoniazid, at the end of the 40-min experiment was statistically significantly increased by metoclopramide, 50 mg/kg (Table I). After 5–10 mg of metoclopramide/kg, the blood quinidine level (0.62 ± 0.03 μg/ml, two experiments) seemed to be also higher than in controls, but blood isoniazid level was the same as in controls.

With solids, a decreased intestinal motility allows more time for the drugs to be dissolved, tending to increase absorption and vice versa (8).

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Table I—Isoniazid and Quinidine Absorption Half-Lives *In Situ* and Their Levels in the Whole Blood and Intestinal Wall at the End of the Experiments [a]

Drugs and Treatment	Absorption Half-Life, min	Correlation Coefficient	Drug Levels at 40 min	
			Whole Blood, μg/ml	Intestinal Wall, μg/g
Isoniazid, 100 μg/ml				
Metoclopramide, 50 mg/kg (6)	17	0.96	3.6 ± 1.1 / 5.9 ± 0.8	1.8 ± 0.8 / 2.4 ± 1.1
Control (7)	17	0.98	2.8 ± 1.1 / 6.7 ± 1.1	0.7 ± 0.7 / 3.9 ± 0.4
Quinidine sulfate, 100 μg/ml				
Metoclopramide, 50 mg/kg (6)	32	0.91	0.63 ± 0.05[b]	19.0 ± 2.8
Control (8)	24	0.84	0.26 ± 0.02	20.4 ± 2.1

[a] Means ± *SE*. Number of experiments is in parentheses. Isoniazid in the whole blood and intestinal wall refers to unacetylated isoniazid divided by total isoniazid hydrazides. [b] $p < 0.001$.

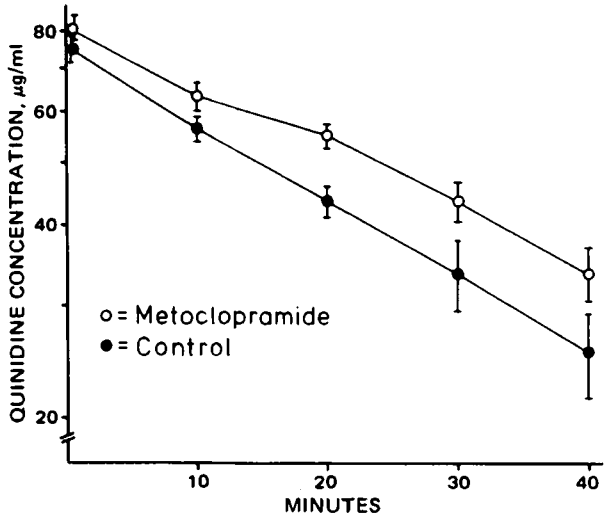

Figure 1—*Disappearance of quinidine sulfate from the rat small intestine* in situ *in control rats (n = 8) and rats treated with metoclopramide (n = 6), 50 mg/kg sc, 30 min before the start of the absorption experiment (means ± SE).*

In humans, metoclopramide reduces the transit time of fluid in the intestinal lumen and may induce an increased water and electrolyte secretion into the intestinal lumen (9), an effect that might be expected to decrease drug absorption. The reduced transit time of fluid both in humans and in animals seems to be associated with a reduction in the diameter of the small intestinal lumen (1). In spite of a relatively large dose (50 mg/kg) of metoclopramide, it did not clearly affect absorption half-lives in the present experiments. This result is understandable since the drugs were in solution in the intestinal lumen and in a better absorbable state than solid drugs.

The increased blood quinidine concentration at the end of the experiment did not correlate with the slightly decreased or unchanged drug disappearance from the intestinal lumen. Because the drugs in blood were measured only at the end of the experiments, these concentrations cannot be regarded as important indexes of drug absorption. The reason for the increased blood quinidine level cannot be found with this experimental setup. The present results indicate that, at least with metoclopramide, the *in situ* rat small intestine is not the best technique of studying its effect on drug absorption; the results do not seem to reflect the eventual absorption changes when drugs are administered orally.

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