Sustained Propranolol Delivery and Increased Oral Bioavailability in Dogs Given a Propranolol Laurate Salt

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INTRODUCTION

A sustained-release, once-a-day dosage form of propranolol has been shown to be as effective for angina therapy as immediate-release propranolol q.i.d. (1). There is a therapeutic advantage of maintaining sustained β-receptor blockade. In addition, there may be increased patient compliance with once-a-day formulations. However, one drawback of oral sustained-release propranolol is that in several studies systemic bioavailability was lower than with immediate-release propranolol, which is only 30–40% in humans (2). The reduction in bioavailability is probably related to a dependence of first-pass metabolism (which follows Michaelis–Menten kinetics) on the input rate (3). An alternative explanation, suggesting the possibility of incomplete absorption from the gastrointestinal tract, was also recently proposed, based on the observation that metabolite levels were similar after immediate- and sustained-release formulations (4). It was suggested that the sustained-release formulation might be eliminated before releasing all of its drug load, based on a comparison of the release rate of propranolol from the formulation and typical gastrointestinal transit times in fasted individuals.

A fatty acid salt of propranolol was considered here as an alternative to polymeric formulations sustaining the release of propranolol HCl. This approach utilizes the possibility of lowering the aqueous solubility and dissolution rate of the drug to sustain its release. More interesting, though, is the possibility that the fatty acid component of the formulation could increase oral propranolol bioavailability. That a fatty acid salt might accomplish this is suggested by various studies showing that the oral bioavailabilities of various other drugs were increased when they were formulated with lipid components in solutions, dispersions, or emulsions (5,6). Lipid vehicles have been most often proposed for water-insoluble compounds, poorly absorbed, water-soluble compounds, or compounds degraded in the stomach or intestinal lumen contents. We are unaware of another instance in which a fatty acid salt of a well-absorbed drug, subject to first-pass metabolism, has been proposed and evaluated.

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MATERIALS AND METHODS

Materials. Propranolol HCl (Sigma Chemical Company) was used to prepare calibration standards, to prepare propranolol laurate, and to prepare the intravenous (i.v.) and oral immediate-release doses. The sustained-release propranolol HCl product tested was Inderal LA (Wyeth-Ayerst). Propranolol laurate was prepared as follows. Sodium laurate (1 m*M*) was dissolved in hot water. A 1.20 m*M* propranolol HCl solution was added dropwise with stirring and while remaining heated. The mixture was cooled to room temperature and the precipitate was filtered and dried (m.p. 80–81°C). HPLC analysis for propranolol indicated equimolar amounts of propranolol and lauric acid. Elemental analysis calculated for $C_{28}H_{45}NO_4$: C, 73.16%; H, 9.87%; N, 3.05%. Found C, 73.28%; H, 9.89%; N, 3.03%.

Bioavailability Study. Three female beagle dogs (Marshall Farms) were administered four treatments of propranolol in a crossover design experiment. A washout period of at least 2 weeks separated experiments. The treatments were i.v. propranolol HCl, oral immediate-release propranolol HCl, oral sustained-release propranolol HCl, and oral propranolol laurate. For i.v. dosing, propranolol was dissolved in water for a 1 mg/kg (0.5 ml/kg) dose, which was injected via the cephalic vein. The immediate-release oral dose was 40 mg propranolol HCl packed into a hard gelatin capsule. The sustained-release oral dose was 80 mg propranolol HCl and was the marketed preparation. The propranolol laurate dose was 124.5 mg, which is equivalent to 80 mg propranolol HCl. This was packed into a hard gelatin capsule. All oral doses were followed by a small volume of water. Dogs were fasted overnight before each part of the study and were allowed water ad libitum.

Blood (5 ml) was collected by jugular venipuncture into evacuated tubes containing Na_2EDTA as an anticoagulant. Plasma was separated and frozen until analyzed. Plasma propranolol concentrations were determined by HPLC using fluorimetric detection, after solvent extraction, as described by Lo *et al.* (7).

C_{max} and t_{max} represent the observed maximum plasma propranolol concentrations after oral dosing and the time of that occurrence. The trapezoidal method was used to calculate the area under the plasma concentration vs time curve, AUC_{0-t}, where t is the time of the last sample. The residual AUC, if the last sample had a detectable propranolol concentration, was calculated as C_t/k. The value of k used was from the terminal slope of the decay of plasma propranolol concentrations after i.v. or oral immediate-release propranolol doses. The i.v. k value was used to extrapolate to infinity after the sustained-release oral doses. Bioavailability (F) was calculated as the ratio of individual dose-corrected $AUC_{0-\infty}$ values (oral/i.v.) and is expressed as the percentage of the dose.

Statistical comparisons of F values were done using analysis of variance and Duncan's multiple-range test.

RESULTS

Plasma propranolol concentration vs time profiles after oral dosing with immediate-release and sustained-release formulations of propranolol HCl and after propranolol lau-

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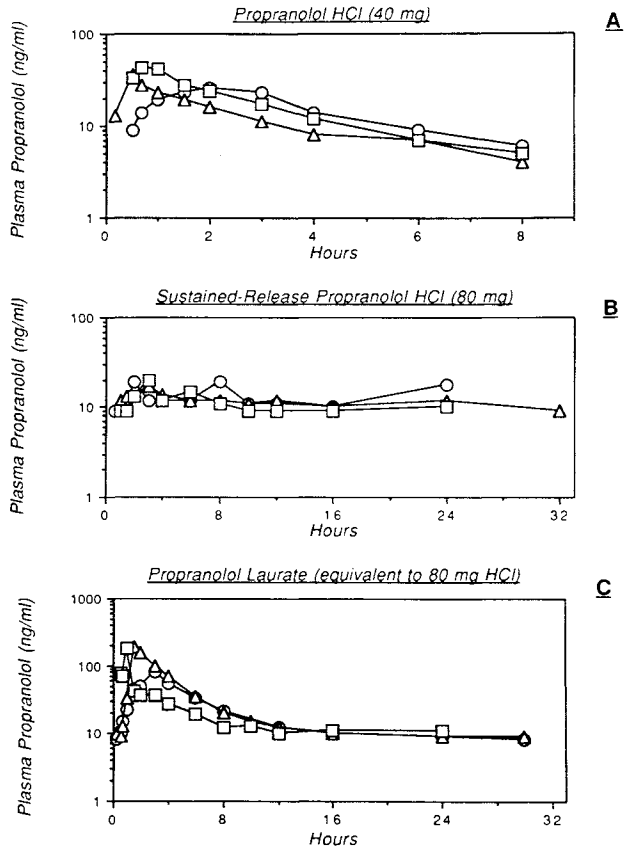

Fig. 1. Individual plasma propranolol concentrations in dogs administered immediate-release propranolol HCl (A), sustained-release propranolol HCl (B), and propranolol laurate (C). The symbol used for a particular dog is the same in A, B, and C. Note that the scales are different.

rate are shown in Fig. 1. The terminal half-life value after immediate-release propranolol HCl was 2.6 hr ± 0.1 hr. The marketed sustained-release formulation of propranolol HCl provided consistent plasma propranolol concentrations over the 1- to 24-hr period. As shown in Table I, bioavailabilities after dosing with the immediate-release and sustained-release dosages were not significantly different.

Plasma propranolol concentration profiles after oral propranolol laurate appeared to be comprised of a combination of immediate-release and sustained-release components. The average t_{max} was similar to that after immediate-release propranolol. C_{max} was more than fourfold greater than after the immediate-release formulation, despite only a twofold greater dose. Systemic bioavailability was significantly greater than either the immediate-release or the sustained-release formulations of propranolol HCl.

Propranolol absorption kinetics after the sustained-release propranolol HCl or propranolol laurate doses were further evaluated using the Wagner–Nelson method. Plots of the cumulative fraction of the bioavailable dose absorbed vs time are given in Fig. 2. The absorption rate with the marketed sustained-release dosage form was fairly constant and absorption continued for 24 hr. In contrast, after propranolol laurate, 40–60% of the bioavailable dose was absorbed in the initial 2–4 hr after dosing, and the remaining fraction of the bioavailable dose was absorbed slowly until approximately 24 hr after dosing. *In vitro* dissolution studies showed fairly rapid propranolol release from propranolol laurate in 0.1 *N* HCl, but release was much more prolonged in water or pH 7.4 buffer compared to propranolol HCl. Therefore, propranolol laurate dissolution rate could limit the absorption rate of propranolol.

DISCUSSION

Oral bioavailability of propranolol is related primarily to the extent of its first-pass metabolism. Hepatic metabolism is saturable, and bioavailability is dependent on the concentration and rate of delivery to the liver (3). Consequently, increasing the dose can increase oral bioavailability; and decreasing the rate of delivery, as with sustained-release formulations, can decrease bioavailability (2). The extent of first-pass metabolism is also dependent on hepatic blood flow. When blood flow increases in response to a stimulus, such as a meal, bioavailability increases (8,9).

Oral bioavailability averaged 7.2% in dogs administered the immediate-release 40-mg propranolol HCl doses. This is similar to values reported by others for propranolol bioavailability in fasted dogs (10–12). Several clinical studies have reported that bioavailability is lower with this marketed sustained-release formulation than with immediate-release formulations because of concentration-dependent first-pass metabolism (as reviewed in Ref. 2). However, we found no significant difference between the immediate-release and the sustained-release dosage forms in propranolol bioavailability. This would imply that metabolism was not saturated after these doses.

The increase in bioavailability after propranolol laurate administration is intriguing. One possible explanation for greater bioavailability with propranolol laurate is that the rapid initial delivery of high concentrations to the liver saturated first-pass metabolism, since plasma concentrations peaked rapidly. Although this may have been a contributing factor, the similar bioavailabilities after the immediate-release and sustained-release formulations indicated no saturation. Another possibility is that splanchinc and hepatic

Table I. Propranolol Bioavailability Parameters After Various Oral Formulations in Dogs (Mean ± SE)

	40 mg propranolol HCl, immediate release	80 mg propranolol HCl, sustained release	80 mg (HCl equivalents) propranolol laurate
C_{max} (ng/ml)	34.8 ± 4.0	18.7 ± 0.7	151 ± 28
t_{max} (hr)	1.1 ± 0.4	4.7 ± 1.4	1.8 ± 0.5
F (%)	7.2 ± 0.3	9.4 ± 1.0	17.9 ± 2.5*

* Significantly ($P < 0.05$) different from the other groups. C_{max} and t_{max} values were not compared statistically.

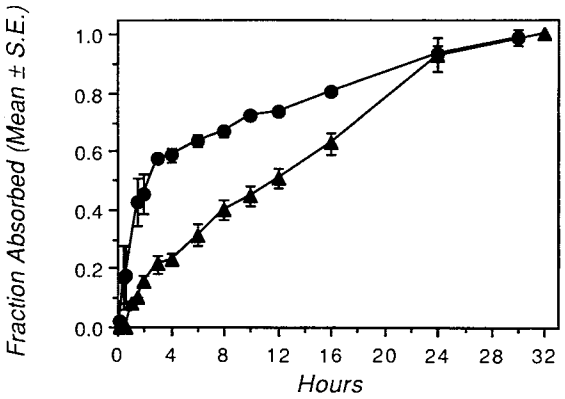

Fig. 2. Comparison of Wagner–Nelson absorption profiles (fraction of the bioavailable dose absorbed vs time) for sustained-release propranolol HCl (▲) and propranolol laurate (●) formulations.

blood flow increased in response to propranolol laurate or dissociated lauric acid. However, the amount of lauric acid was insignificant relative to the 35–60 g of fat ingested by the subjects in the study by Svensson *et al.* (9), which showed a food effect on blood flow. Furthermore, the effect of food on propranolol bioavailability was shown to be proportional to the protein content of the meal (13).

Increased propranolol bioavailability could also be related to other effects of the coadministered lauric acid. Lipid vehicles, including fatty acids, have been shown to increase the intestinal absorption or oral bioavailability of other drugs by various mechanisms. An oleic acid vehicle increased the oral bioavailability of cinnarizine, a poorly water-soluble weak base, in dogs (14). Increased dissolution rate appeared to contribute to this effect. Fatty acids or fatty acid esters have also been shown to increase the intestinal absorption of poorly absorbed, water-soluble drugs, including cefoxitin (15), fosfomycin (16), and carboxyfluorescein (17). In these studies the lipid vehicles probably increased intestinal membrane permeability (5,6). It has also been suggested that short-chain fatty acids can increase the pH at the mucosal surface and increase net water absorption and, by these mechanisms, increase membrane permeation of weak bases (18). However, propranolol is normally well absorbed through the intestinal membrane. Increased intestinal permeation, regardless of the mechanism, would not be expected to influence bioavailability, as with these poorly absorbed compounds. In fact, in a previous study in rats propranolol oral bioavailability was not significantly affected by administration in triglyceride or fatty acid emulsions, with bioavailabilities similar to that after an aqueous solution (19).

Therefore, we must consider how first-pass metabolism of propranolol could have been reduced. An association of propranolol and lauric acid in solution, or micellar solubilization of propranolol and lauric acid, would seem possible. An ion pairing association of propranolol and lauric acid has been described, and that association was suggested to be responsible for increasing the partition coefficient and skin permeation of propranolol (20). This could have contributed to increased oral bioavailability if that associated or encapsulated form remained intact after absorption. Then there could have been absorption via the lymphatics or less efficient extraction by the liver. This remains to be tested.

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