Effects of cholestyramine and colestipol on the plasma concentrations of propranolol

D. M. HIBBARD, J. R. PETERS & D. B. HUNNINGHAKE*

Departments of Medicine and Pharmacology, University of Minnesota, Minneapolis, Minnesota 55455, USA

1 The effect of equivalent hypolipidaemic doses of cholestyramine (8 g) or colestipol (10 g) on the plasma concentrations of propranolol and 4'-hydroxypropranolol was studied in 12 normal volunteers following the oral administration of 120 mg of normal release propranolol tablets.

2 When two doses of either cholestyramine or colestipol were administered prior to the propranolol, the peak plasma concentrations and area under the curve for both propranolol and the metabolite 4'-hydroxypropranolol were reduced significantly ($P < 0.05$).

3 We conclude that the drug interaction between cholestyramine or colestipol and propranolol leads to significant reductions in plasma concentrations of propranolol and 4'-hydroxypropranolol which may cause a clinically diminished effect for a given dosage. Therefore, patients should be observed when either of these resins are added to or deleted from a therapeutic regimen.

Keywords cholestyramine colestipol propranolol

Introduction

Cholestyramine and colestipol are nonabsorbable anionic exchange resins that are primarily utilized for lowering total and LDL cholesterol in patients with Type II hyperlipoproteinaemia (Hunninghake & Probstfield, 1977). Although they may have other effects, including an effect on LDL receptors, the resins bind bile acids in the gastrointestinal tract and decrease their enterohepatic circulation. Since the resins are not absorbed from the gastrointestinal tract and form insoluble complexes with the bile acids, the faecal excretion of bile acids is increased. The resins are also capable of binding a wide variety of anionic drugs in the gastrointestinal tract and altering the absorption of these drugs (Hunninghake, 1980).

Propranolol, a non-selective β -adrenergic

receptor antagonist, is almost completely absorbed following oral administration. There is an avid hepatic extraction which limits the systemic availability of propranolol because of presystemic (first-pass) elimination which is a dose dependent process (Routledge & Shand, 1979). Propranolol is eliminated almost entirely by metabolism with the formation of a number of metabolites including 4'-hydroxypropranolol, which also has β -adrenergic receptor blocking effects (Paterson *et al.*, 1970). Administration of food and a number of drugs have been reported to affect the rate and/or total absorption of propranolol (Melander *et al.*, 1977; Wood & Feely, 1983).

Either of the two resins are sometimes administered concomitantly with propranolol for the treatment and/or prevention of various types of cardiovascular disease. Prior reports of significant drug interactions involving absorptive mechanisms for these two classes of drugs led to this investigation (Hunninghake, 1980; Wood & Feely, 1983). The purpose of the study

* Address for reprint requests: Donald B. Hunninghake, M.D., University of Minnesota, Department of Pharmacology, 3-260 Millard Hall, 435 Delaware Street, S.E. Minneapolis, MN 55455, U.S.A.

was to determine whether cholestyramine or colestipol altered the plasma concentrations of propranolol or its active metabolite, 4'-hydroxypropranolol.

Methods

Subjects and study design

Twelve healthy male volunteers, aged 19–48 years, participated in the study. After the protocol was explained, all gave written, informed consent before entering the study. Weight and height ranged from 70.5–106.8 kg and 169–203 cm, respectively. All subjects were given routine admission physical examinations and the results of haematological tests, serum and urine chemistries were found to be normal. No medication was taken either during or for at least 1 week prior to the study.

Each subject was studied on three occasions, with each visit being separated by at least 2 weeks. The subjects remained in the semi-recumbent position during the study and had been fasting except for water for 8 h prior to administration of propranolol. A low fat meal was provided 4.5 and 10.0 h after administration of propranolol. Six of the subjects received, in random order, equivalent hypolipidaemic doses of 10 g colestipol (Colestid, Upjohn), 8 g cholestyramine (Questran, Mead Johnson), or water, 2 min prior to receiving 120 mg racemic propranolol HCl orally. The second group of six subjects received an additional dose of the resins 12 h prior to the ingestion of propranolol. The same lot number of drugs was used throughout the study. Measurements of blood pressure and pulse were made and blood samples were collected for the measurement of plasma concentrations of propranolol and 4'-hydroxypropranolol at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 h following dosage.

Blood sampling

An indwelling butterfly cannula (Abbott Hospital Supply) was inserted in a forearm vein and blood samples were drawn into plastic syringes. The cannula was kept patent with normal saline. The blood samples were transferred immediately to a Vacutainer tube containing powdered EDTA, mixed and centrifuged. Plasma was transferred to glass vials. This method of blood sampling was compared to an all-glass

system and separate venepuncture (Cotham & Shand, 1975), and no significant differences in plasma concentrations of propranolol and 4'-hydroxypropranolol were found. The 4'-hydroxypropranolol was extracted immediately and analysed the same day. The remaining plasma was stored at -20°C and was analysed for propranolol within 4 weeks. Haematocrit was measured prior to the start of each visit.

Analytical methods

Racemic propranolol, 4'-hydroxypropranolol, and pronethalol, used as the internal standard, were supplied by Ayerst Laboratories, Quebec, Canada. Organic solvents were chromatographic grade and were obtained from MCB, E-Merck, Darmstadt, West Germany. Chemicals were reagent grade from Aldrich Chemical Co., Milwaukee, Wisconsin.

Propranolol was extracted according to the method of Gyselinck *et al.* (1980). After addition of the internal standard, the plasma was made alkaline, extracted with chloroform/butanol mixture, and the organic solvent was evaporated under the stream of nitrogen. The residue was dissolved in dilute acetic acid and re-extracted with 2-butanone. An aliquot of the aqueous layer was then injected into the chromatograph.

4'-hydroxypropranolol was extracted according to the method of Schneck *et al.* (1979). Antioxidants and the internal standard were added to plasma before making the mixture alkaline and 4'-hydroxypropranolol was extracted into ether. The organic solvent was evaporated under a vacuum rather than a stream of nitrogen. The residue was dissolved in water/ethylene glycol/glacial acetic acid and re-extracted with 2-butanone. An aliquot of the aqueous layer was then injected into the chromatograph.

Plasma concentrations of propranolol and 4'-hydroxypropranolol were measured by h.p.l.c. A Varian MCH-10 10 μm reversed phase column (250 mm $\times$ 4 mm ID), a precolumn packed with SC Vydac (50 mm $\times$ 4 mm ID) and a Varian Fluorochrom detector and deuterium light were used. Band filters (Corning) were used for the following: 280 nm for propranolol and 4'-hydroxypropranolol excitation; 360 nm and 410 nm for the emission of propranolol and 4'-hydroxypropranolol, respectively.

All results were analysed on the CLINFO computer system using paired *t*-tests and one way analyses of variance.

Figure 1 Mean plasma propranolol concentration time profiles during the five treatment periods.

Results

The mean plasma propranolol concentrations for the various treatment groups and time periods are shown in Figure 1. Significant differences were noted between treatment groups within the first 6 h only. A summary of the important kinetic parameters is included in Table 1. The two dose treatments with either colestipol or cholestyramine lowered both the total area under the curve (AUC) and the peak plasma concentrations of propranolol significantly ($P < 0.05$). There were no significant differences between the effects of these two treatments. The peak plasma concentration of propranolol was also lowered by a single dose of cholestyramine ($P < 0.05$). However, single dose colestipol administration was associated with both a significant increase in total AUC ($P < 0.05$) and peak plasma concentration of propranolol ($P < 0.01$).

The mean plasma 4'-OH-propranolol concentrations for the various treatment groups and time periods are illustrated in Figure 2 and a summary of the important kinetic parameters is included in Table 1. The results paralleled those seen with the parent drug. The two dosage regimens of both resins were associated

with decreases in the peak plasma concentration and AUC of 4'-OH-propranolol ($P < 0.05$). The single dose of colestipol increased the peak plasma concentration of 4'-OH-propranolol ($P < 0.05$).

The observed differences in plasma drug and metabolite concentrations were not due to a change in red blood cell mass of the subjects as there was no significant differences between the haematocrits during the treatment periods. Thus, mean haematocrits during the control, colestipol, and cholestyramine treatment periods were 43.8, 43.4, and 43.4%, respectively. There were no significant differences in systolic or diastolic pressures or pulse between any treatment group or for any dosage regimen. For example, the mean pulse rates for the first 8 h of each treatment period with control, colestipol and cholestyramine were 53.4, 52.8 and 52.6, respectively. The corresponding mean systolic blood pressures were 104.5, 106.8 and 105.2.

Discussion

The plasma concentration of propranolol was

Table 1 Effects of colestipol and cholestyramine on peak plasma concentrations, time to peak and area under the curve of propranolol and 4'-hydroxypropranolol

	Dose	Propranolol		Cholestyramine		4'-hydroxypropranolol	
		Control	Colestipol Mean ($\pm$ s.e. mean)	Control	Colestipol Mean ($\pm$ s.e. mean)	Control	Colestipol Mean ($\pm$ s.e. mean)
Peak plasma concentration (ng/ml)	1	102.6 (12.3) ^{a,b}	133.0 (14.7) ^{a,c}				
	2	104.1 (12.8) ^{a,b}	67.0 (16.6) ^{a,c}				
Time to peak (h)	1	1.0 (0.13) [*]	1.0 (0.11) ^{*,c}	11.2 (1.7) ^a	14.2 (2.0) ^{*,a,c}	8.7 (1.0) ^{*,c}	8.7 (1.0) ^{*,c}
	2	2.0 (0.21)	1.5 (0.53)	9.6 (1.0) ^{a,b}	5.2 (0.5) ^a	4.6 (0.7) ^b	4.6 (0.7) ^b
AUC [†] (ng ml ⁻¹ h)	1	732.0 (136.3) ^a	869.7 (102.0) ^{*,a,c}	1.5 (0.11) ^{a,b}	1.0 (0.15) ^{*,a,c}	2.5 (0.20) ^{b,c}	2.5 (0.20) ^{b,c}
	2	751.8 (77.0) ^{a,b}	522.6 (62.5) ^{a,b}	2.0 (0.30)	2.0 (0.36)	4.0 (0.59)	4.0 (0.59)
				41.2 (9.1)	49.1 (13.2) ^{*,c}	34.1 (3.6) ^{*,c}	34.1 (3.6) ^{*,c}
				37.2 (3.4) ^{a,b}	21.3 (2.1) ^a	20.5 (1.8) ^b	20.5 (1.8) ^b

* $P < 0.05$ for difference between 1 dose and 2 dose regimen within each treatment group** $P < 0.01$ for difference between 1 dose and 2 dose regimen within each treatment group^a $P < 0.05$ for difference between control and colestipol^b $P < 0.05$ for difference between control and cholestyramine^c $P < 0.05$ for difference between colestipol and cholestyramine[†] Total AUC for propranolol; 8 h AUC for 4'-hydroxypropranolol

decreased following administration of two doses of either cholestyramine or colestipol. Plasma concentrations of 4'-hydroxypropranolol were also decreased. The two dose regimen of resin administration was associated with a 43% decrease in propranolol AUC following cholestyramine and a 27% decrease following colestipol. This difference between the two resins was not significant, but is in agreement with the results of other studies which generally indicated a greater effect with cholestyramine (Hunninghake, 1980).

This study demonstrated that a significant interaction can occur between each of the two resins and propranolol *in vivo*. The most plausible explanation for the decrease in plasma levels of propranolol and 4'-hydroxypropranolol is altered absorption. Neither resin is absorbed from the gastrointestinal tract and only one or two doses of the resins were administered to healthy volunteers. One would not expect alterations of hepatic metabolism or plasma protein binding under the conditions of this experiment although any effects of the resins on plasma levels of α_1 -acid glycoprotein, a major binding site to propranolol, were not investigated. However, the binding of propranolol to the resins in the gastrointestinal tract is of considerable importance.

Propranolol has been demonstrated to bind to a number of polar lipids *in vitro* (Lüllman *et al.*, 1979). Hydrophobic bonding was demonstrated to be the major mechanism in complex formation. The charge of the monovalent cationic propranolol, which possesses a high degree of lipophilicity was of minor importance. Another cationic drug, quinidine sulphate, was minimally and reversibly bound *in vitro* to cholestyramine in the absence of bile acids at a pH 7.5 (Gallo *et al.*, 1965). This pH was chosen to approximate the pH of the ileum which typically has a pH of 6–8. In our study, the significant reductions of propranolol and 4'-hydroxypropranolol plasma concentrations occurred during a two dosage schedule. Presumably the resins are distributed throughout much of the small intestine by 12 h. It was not possible in this study to determine if propranolol binds to the resins alone, if bile acids facilitate the binding to the resins, or if the binding is pH dependent. Further studies will need to be performed to explain the exact mechanism of the interaction between propranolol and these resins.

The study also did not consider the issue of whether separating the time of administration of the resin and propranolol influences the effect. Since a single dose of colestipol administered in close proximity to propranolol resulted

Figure 2 Mean plasma 4'-hydroxypropranolol concentration time profiles during the five treatment periods.

in both an increased rate of absorption and plasma concentrations of propranolol, it is unlikely that separating the time of administration of colestipol and propranolol will diminish the interaction. The optimum time for administering cholestyramine and propranolol will have to be evaluated in additional studies. It is generally recommended that the time of administration of the resins be separated from that of other drugs, but this does not uniformly negate the effect of the resins on the absorption of other drugs (Hunninghake & King, 1978; Caldwell & Greenberger, 1971).

A number of previous reports indicate that the absorption of propranolol can be altered by both diet and drugs. Food increased the systemic availability (Melander *et al.*, 1977) while the effects of ethanol have been reported to decrease the absorption of propranolol (Grabowski *et al.*, 1980). Aluminium hydroxide decreased the bioavailability (Dobbs *et al.*, 1977), while metoclopramide, a drug which affects gastric emptying, did not affect the absorption of propranolol (Charles *et al.*, 1981). Cholestyramine and colestipol can now be added to the list of drugs which appear to alter the absorption of propranolol.

A variety of interactions involving the resins and other drugs have been reported. These include clinically significant interactions involving a diverse group of drugs such as hydrochlorothiazide, digitoxin, levothyroxine and warfarin (Hunninghake, 1980). The magnitude of the decrease in plasma concentrations of propranolol seen in this study suggests that this is also a clinically important interaction. While plasma concentrations of propranolol and its metabolites are not generally used to monitor therapy, biological measurements such as blood pressure and heart rate may be useful clinical adjuncts in determining the appropriate dose of propranolol. One would not expect significant differences in blood pressure and resting pulse in this study, but this does not negate the possibility that adjustments in the dosage of propranolol may have to be made whenever a resin is either added to or deleted from the therapeutic regimen of a patient who is receiving propranolol chronically.

This work was supported in part by NHLBI Contract NO1 HV-2915-L and grant RR-400 from the General Clinical Research Center Program of the Division of Research Resources, NIH.

References

- Caldwell, J. H. & Greenberger, N. J. (1971). Interruption of the entero-hepatic circulation of digitoxin by cholestyramine. Protection against lethal digitoxin intoxication. *J. clin. Invest.*, **50**, 2626-2637.
- Charles, B. G., Renshaw, P. J., Kay, J. J. & Ravenscroft, P. J. (1981). Effect of metoclopramide on the bioavailability of long-acting propranolol. *Br. J. clin. Pharmacol.*, **11**, 517-518.
- Cotham, R. H. & Shand, D. (1975). Spuriously low plasma propranolol concentrations resulting from blood collection methods. *Clin. Pharmacol. Ther.*, **18**, 535-538.
- Dobbs, J., Skoutakis, V. A., Acchiardo, S. R. & Dobbs, B. R. (1977). Effects of aluminium hydroxide on the absorption of propranolol. *Curr. Ther. Res.*, **21**, 887-892.
- Gallo, D. G., Bailey, K. R. & Sheffner, A. L. (1965). The interaction between cholestyramine and drugs. *J. exp. Biol. Med.*, **120**, 60-65.
- Grabowski, B. S., Cady, W. J., Young, W. W. & Emery, J. F. (1980). Effects of acute alcohol administration on propranolol absorption. *Int. J. clin. Pharmacol. Ther. Tox.*, **18**, 317-319.
- Gyselinck, P., Remon, J. P., Van Severen, R. & Braekman, P. (1980). An improved extraction procedure for the liquid chromatographic determination of propranolol and 4'-hydroxypropranolol in plasma. *Br. J. clin. Pharmacol.*, **10**, 406-408.
- Hunninghake, D. B. (1980). Drug interactions involving hypolipidemic drugs. In *Cardiovascular and respiratory disease therapy*, ed. Petrie, J. C., pp 79-105. Amsterdam: Elsevier/North Holland.
- Hunninghake, D. B. & King, S. (1978). Effect of cholestyramine and colestipol on the absorption of methyl dopa and hydrochlorothiazide. *Pharmacologist*, **20**, 220.
- Hunninghake, D. B. & Probstfield, J. L. (1977). Drug treatment of hyperlipoproteinemia. In *Hyperlipidemia: Diagnosis and therapy*, eds Rifkind, B. M. & Levy, R. I., pp 327-362. New York: Grune and Stratton.
- Lüllman, H. & Wehling, M. (1979). The binding of drugs to different polar lipids *in vitro*. *Biochem. Pharmacol.*, **28**, 3409-3415.
- Melander, A., Danielson, K., Schersten, B. & Walin, E. (1977). Enhancement of the bioavailability of propranolol and metoprolol by food. *Clin. Pharmacol. Ther.*, **22**, 108-112.
- Paterson, J. W., Connolly, M. E. & Dollery, C. T. (1970). The pharmacodynamics and metabolism of propranolol in man. *Pharmacologia Clin.*, **2**, 127-133.
- Routledge, P. A. & Shand, D. G. (1979). Clinical pharmacokinetics of propranolol. *Clin. Pharmacokin.*, **4**, 73-90.
- Schneck, D. W., Pritchard, J. F. & Hayes, A. H. (1979). Measurement of propranolol, 4'-hydroxypropranolol and propranolol glycol in human plasma. *Res. Comm. Chem. Path. Pharmacol.*, **24**, 3-12.
- Wood, A. J. J. & Feely, J. (1983). Pharmacokinetic drug interactions with propranolol. *Clin. Pharmacokin.*, **8**, 253-262.

(Received January 30, 1984,
accepted May 20, 1984)