International Journal of Pharmaceutics, 37 (1987) 127–134
Elsevier

IJP 01248

Intestinal absorption of a β-adrenergic blocking agent nadolol. Enhancement of in situ and in vivo absorption of nadolol in rats

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(Received 3 June 1986)
(Modified version received 10 October 1986)
(Accepted 29 December 1986)

Key words: Nadolol; Sodium cholate; Enhanced absorption; Fatty acid; Glyceride; Anion exchange resin; Binding capacity

Summary

Sodium cholate and its taurine and glycine conjugates are known to inhibit the intestinal absorption of nadolol in rats. The effect of certain lipids and anion exchange resins on the bile salt-mediated inhibition of the intestinal absorption of nadolol was studied in rats. The in situ intestinal absorption of nadolol from the jejunum loop was pronouncedly enhanced by lipids and anion exchange resins in the presence of twice the molar quantity of sodium cholate. The absorption of nadolol after oral administration (20 mg/kg) was also improved by lipids and resins. The percentage absorption of oral nadolol was moderately increased to about 40% of the dose with the oral ingestion of lipids (mono- and triglycerides, 500 mg/kg), 2.2-fold excess compared to control (18%). Anion exchange resins (DEAE Sephadex, QAE Sephadex and Dowex 1 × 2, 400 mg/kg) exhibited the marked enhancing effect on oral nadolol, about 60% of the dose being absorbed, which was 3.3–3.5 times higher than that in control rats. The effect of anion exchange resins on nadolol absorption was roughly estimated to be consistent with binding capacity for sodium cholate. These results indicate the interaction of nadolol and trihydroxy bile salts in the intestinal lumen, and support the proposed mechanism underlying the inhibited absorption of nadolol by the stable micellar formation with trihydroxy bile salts.

Introduction

Nadolol (*cis*-5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-2,3-naphthalenediol), a non-selective β-adrenergic blocking agent (Lee et al., 1975), is effective in the treatment of hypertension (Frithz, 1978), angina pectoris (Ferberg et al., 1978) and cardiac arrhythmias (Evans et al., 1976). The drug is primarily excreted unchanged, and has a long elimination half-life of 12–20 h in man (Dreyfuss et al., 1977; Yamaguchi et al., 1983). However, the oral absorption of nadolol is incomplete (20–30% in man, Dreyfuss et al., 1977, and 15–20% in rats, Dreyfuss et al., 1978; Yamaguchi et al., 1986a), in contrast to other β-blocking agents, such as propranolol and alprenolol, which are completely absorbed.

We have shown that the intestinal absorption of nadolol in rats inhibited both in situ and in vivo by trihydroxy bile salts (sodium cholate and its taurine and glycine conjugates), but not by dihydroxy bile salts (sodium chenodeoxycholate and sodium deoxycholate) (Yamaguchi et al., 1986a). However, the absorption of other β-adren-

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ergic blocking agents was not altered by trihydroxy bile salts. Such a specific inhibitory effect on nadolol absorption can be interpreted in terms of the loss of thermodynamic activity of nadolol due to stable micellar complex formation with sodium cholate, resulting in a decreased uptake of nadolol into the intestinal membrane (Yamaguchi et al., 1986b). Other β-blocking agents also form the micellar complex with sodium cholate, but their micelles are 10 times less stable than nadolol micelle (Yamaguchi et al., 1986b). Accordingly, the stability of micellar complex may be an important factor for the inhibited intestinal absorption of nadolol. The stability of the formed complex of β-blocking agents with sodium cholate depends upon the steric effect of the arrangement of both hydrophobic and hydrophilic parts of the drug molecule. Our previous report showed that the hydrophilic *cis*-2,3-diol of nadolol may play an important role in stabilizing the formed micellar complex with sodium cholate (Yamaguchi et al., 1986c).

The purpose of this paper was to examine whether the trihydroxy bile salt-mediated inhibition of the intestinal absorption of nadolol in rats can be restored by decreasing the micellar formation in the intestinal lumen.

Materials and Methods

Materials

Nadolol is a gift from Squibb Institute (NJ, U.S.A.). Sodium cholate and its taurine and glycine conjugates were purchased from Nakarai (Kyoto, Japan). Fatty acids (palmitic acid, palmitoleic acid, stearic acid, oleic acid and linoleic acid, all used as sodium salts) were obtained from Nakarai, glycerides (mono- and tristearin, mono- and triolein) from Sigma (MO, U.S.A.), cholesterol from Wako (Osaka, Japan) and lecithin (distearoyl-L-α-phosphatidylcholine) from Sigma. The following anion exchange resins of fine grade were obtained from commercial sources: Dowex 1 × 2, 1 × 8 and 2 × 8 (Dow Chemical, MI, U.S.A.), Cellex T and QAE (Bio Rad, CA, U.S.A.), DE-32 (Whatman, Kent, U.K.) and QAE and DEAE Sephadex (Pharmacia, Uppsala, Sweden). All other chemicals were of analytical-reagent grade.

In situ experiments on absorption from rat jejunum loop

The intestinal absorption of nadolol (0.01 mmol) from the jejunum loop was studied in the presence of sodium cholate (0.02 mmol) and following test materials; fatty acids, glycerides, cholesterol and lecithin (0.02 and 0.05 mmol), and anion exchange resins (100–400 mg/kg). Male Wistar rats weighing about 200 g were used after fasting overnight. The procedures for the jejunum loop preparation were described in the previous paper (Yamaguchi et al., 1986a). Briefly, the rat was anesthetized with sodium pentobarbital (40 mg/kg, i.p.). The intestine was exteriorized through a central mid-line incision, and the bile duct was ligated. A loop of about 10 cm long was prepared from the upper part of jejunum by ligature of both ends. Nadolol, sodium cholate and test materials, all adjusted to pH 6.5, were injected separately into the loop. The total volume of injection was 0.5 ml in all experiments. Four hours after the injection, the contents in the loop were drained off with water, followed by 0.01 N hydrochloric acid solution, and adjusted to 50 ml. The absorption of nadolol from each loop was determined by subtracting the remaining amount from the amount administered.

In vivo experiments on nadolol absorption

Male Wistar rats weighing about 250 g were used after fasting overnight. Nadolol (20 mg/kg) was administered orally (2 ml/kg) by using an oral syringe, just after the oral ingestion of glycerides (100–500 mg/kg) or anion exchange resins (100–400 mg/kg). Heparinized blood specimens (about 0.5 ml) were drawn from each of the rats by cardiac puncture at 1, 2, 3, 4, 6 and 8 h after dosing, and the plasma samples were kept frozen until analysis. The fraction of the dose of nadolol absorbed was calculated from the area under the plasma concentration–time curve (AUC) divided by that after intravenous dosing (Yamaguchi et al., 1986a). The AUC was determined according to the trapezoidal rule, and the area to infinity was added as calculated by C_8/β, where C_8 is the plasma concentration at 8 h after dosing, and β is the apparent plasma elimination rate constant of the log-linear part of the plasma concentration–time curve.

Binding of bile salt to anion exchange resin

The bile salt binding capacity of the anion exchange resin was determined by adding 50 mg of the resin to 5 ml of the bile salt solution (10 mg/ml, sodium cholate and its taurine and glycine conjugates) in pH 6.5 isotonic buffer. The mixture was vigorously shaken for 20 min at 37 °C, and centrifuged. The amount of bile salt in the supernatant fluid was measured by the method of Singer and Fitschen (1961), and compared with the original solution. The binding capacity was expressed as mequiv. cholate/g resin. Nadolol was not absorbed by any of the resins examined.

Analytical methods

The nadolol content in the jejunum loop was measured by direct injection of sample solution into the high-performance liquid chromatography (HPLC; Yamaguchi et al., 1986a). HPLC was carried out using a Waters ALC/GPC 204 liquid chromatograph equipped with an ultraviolet detector (280 nm). The stainless steel column (30 cm × 4 mm i.d.) packed with μBondapak C18 (10 μm, Waters, MA, U.S.A.) was used with a mobile phase of methanol–M/15 potassium dihydrogen phosphate (1 : 1) at a flow rate of 1 ml/min. The minimum detectable concentration of nadolol was about 0.5 μg/ml

Plasma levels of nadolol after oral administration were determined by gas chromatography (GC) equipped with a nitrogen-selective detector as described previously (Yamaguchi et al., 1982). The procedure for sample preparation is briefly described as follows. To plasma sample (0.2 ml) were added the internal standard solution and 5 N sodium hydroxide solution. The cyclohexylidene derivative of nadolol, synthesized from nadolol and 1,1-dimethoxycyclohexane (m.p. 225–228 °C, Yamaguchi et al., 1983), was used as an internal standard. The mixture was shaken with ether, and centrifuged. The organic layer was transferred into another tube, and evaporated to dryness under a gentle stream of air at 40 °C. The residue was dissolved in *n*-butylboronic acid solution (1 mg/ml in ethyl acetate containing 5% of dimethyl sulfoxide), and an aliquot of the solution was injected into GC. GC was carried out using a HP 5840A gas chromatograph (Hewlett Packard, PA, U.S.A.), A silanized glass column (120 cm × 2 mm i.d.) packed with 3% SP-400 on Gas Chrom Q (80–100 mesh) was operated at 260 °C. The minimum detectable concentration of nadolol was 1 ng/ml plasma.

Statistical analysis

Absorption data were compared for statistical significance by using Student's *t*-test. A probability level of $P < 0.05$ was considered statistically significant.

Results

Effect of lipids on inhibited nadolol absorption

Effect of fatty acids, glycerides, cholesterol and lecithin on the in situ intestinal absorption of nadolol (0.01 mmol) was investigated in rats. The results are shown in Table 1. The percentage absorption of nadolol from jejunum loop with and without twice the molar quantity of sodium cholate were 46.1 and 71.5% of the dose, respectively, indicating the inhibited absorption of nadolol by sodium cholate. Fatty acids and glycerides re-

TABLE 1

Effect of lipids on in situ intestinal absorption of nadolol in rats with jejunum loop

Materials	Absorption in 4 h (% of dose) [a]		
	Without sodium cholate	With sodium cholate molar ratio (lipid/nadolol)	
		2	5
Control	71.5 ± 1.7	46.1 ± 3.8	
Palmitic acid	68.3 ± 3.2 (5) [b]	59.0 ± 3.7 *	59.7 ± 2.2 **
Palmitoleic acid	72.5 ± 2.7 (5)	57.0 ± 3.4 *	56.4 ± 2.7 *
Stearic acid	69.2 ± 3.6 (5)	63.7 ± 3.6 *	67.5 ± 2.6 **
Oleic acid	71.8 ± 4.1 (5)	63.6 ± 4.1 *	68.9 ± 4.9 **
Linoleic acid	69.5 ± 4.4 (5)	52.7 ± 2.0	57.2 ± 2.2 *
Monostearin	68.7 ± 3.4 (2)	60.4 ± 3.8 *	–
Tristearin	70.3 ± 1.7 (2)	59.9 ± 1.8 *	–
Monoolein	72.1 ± 2.9 (2)	73.0 ± 2.5 **	–
Triolein	73.2 ± 5.1 (2)	69.3 ± 4.3 **	–
Cholesterol	54.6 ± 2.6 (5) **	49.2 ± 2.8	48.8 ± 3.8
Lecithin	52.6 ± 1.7 (5) **	50.8 ± 5.5	47.9 ± 2.7

[a] Results are expressed as the mean ± S.E. of 4–5 rats.
[b] Parentheses represent the molar ratio of lipid to nadolol.
* $P < 0.05$, ** $P < 0.01$, compared to control.

stored the inhibited absorption of nadolol, suggesting that they form the micellar complex competitively with nadolol in the intestinal lumen. Some lipids, such as oleic acid and monoolein, markedly increased the absorption of nadolol to about 70% of the dose, which was equal to that in the absence of sodium cholate. However, the percentage absorption of nadolol was not affected by the addition of cholesterol and lecithin. In the absence of sodium cholate, fatty acids and glycerides showed no effect on nadolol absorption (68–73%), but cholesterol and lecithin significantly reduced the absorption to 54.6% and 52.6%, respectively (Table 1).

Effect of glycerides (100–500 mg/kg) on the oral absorption of nadolol (20 mg/kg) was studied in rats (Fig. 1). Plasma levels of nadolol in control rats were maximal 2 h after dosing with a level of 463 ng/ml, and the percentage absorption was estimated to be 18.0% of the dose (Yamaguchi et al., 1986a). In contrast, plasma levels of nadolol in glyceride-treated rats (500 mg/kg) were significantly higher than those in control rats, as shown in Fig. 1. The effects of four glycerides tested were equal on the oral absorption of nadolol, and the percentage absorption of nadolol was enhanced to about 40% of the dose, 2.2-fold excess in control rats. However, no enhanced absorption was observed (16–22%) in rats at doses of 100 and 250 mg/kg of glycerides.

Effect of anion exchange resins on inhibited nadolol absorption

The second approach is the use of anion exchange resins which may bind to bile salts and inhibit the micellar formation of nadolol with sodium cholate. Eight commercially available resins were examined for this purpose. Table 2 shows the binding capacity of these resins at pH 6.5 for sodium cholate and its taurine and glycine conjugates. The resins showed a wide range of binding capacity for sodium cholate (0.1–1.6 mequiv./g resin). The binding capacity was almost equal in each resin for sodium cholate and its taurine and glycine conjugates. The capacity seemed to depend upon the basic polymeric structure of resin, in the order of dextran, polystyrene and cellulose, and to be independent of the func-

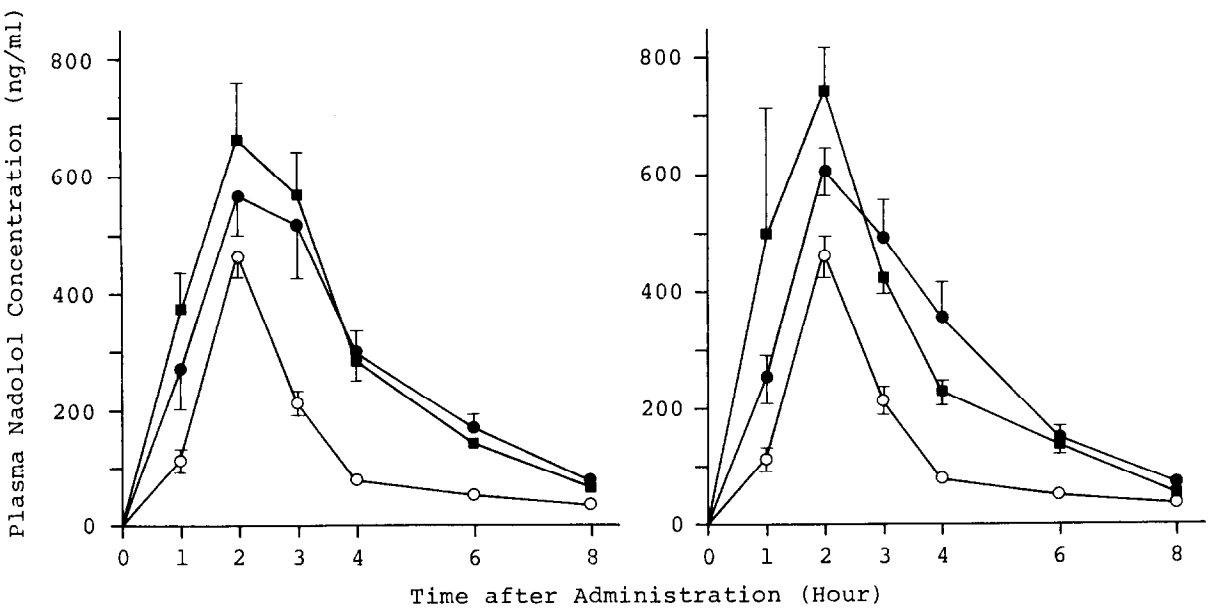

Fig. 1. Effect of glycerides on plasma levels of nadolol in rats. Left: monostearin (●), monoolein (■), and control (○). Right: tristearin (●), triolein (■), and control (○). Nadolol (20 mg/kg) was orally administered just after the oral ingestion of glycerides (500 mg/kg). Each point represents the mean ± S.E. of 5 rats.

tional group of resin. A marked difference was observed between Dowex 1 × 2 and Dowex 1 × 8. The latter, the cross-linked type of the former, had little binding capacity. There was no binding between nadolol and resins examined (< 0.05 mequiv./g resin).

Effect of anion exchange resins was evaluated on the 4 h absorption of nadolol from the ligated loop of rat jejunum in the presence of twice the molar quantity of sodium cholate. The results are presented in Table 3. DEAE Sephadex and QAE Sephadex showed the pronounced effect on nadolol absorption even at a low dose (100 mg/kg). Dowex 1 × 2 abolished the inhibitory effect of sodium cholate at a dose of 200 mg/kg, but no effect was observed by the addition of Dowex 1 × 8, having little binding capacity for sodium cholate as was shown in Table 2. The inhibited intestinal absorption of nadolol by sodium cholate was also restored by DE-32 and Cellex QAE. Under the absence of sodium cholate, the absorption of nadolol was not altered (69–74%) by the addition of resins (400 mg/kg), except for Cellex QAE. It reduced the absorption to 53.5% of the dose, presumably due to the addition of a large volume of resin (low specific gravity) into the ligated loop.

TABLE 2

Bile salt binding capacity of anion exchange resins at 37°C in pH 6.5 isotonic buffer

Resin	Binding capacity (mequiv./g resin)		
	Sodium cholate	Sodium taurocholate	Sodium glycocholate
Dextrane			
DEAE Sephadex	1.6	1.3	1.4
QAE Sephadex	1.6	1.4	1.4
Polystyrene			
Dowex 1×2	0.9	0.9	1.2
Dowex 1×8	0.1	0.2	0.2
Dowex 2×8	0.2	0.1	0.2
Cellulose			
Cellex QAE	0.4	0.4	0.4
Cellex T	0.2	0.3	0.4
DE-32	0.6	0.5	0.7

Results are expressed as the mean value of the triplicate experiments.

TABLE 3

Effect of anion exchange resins on in situ intestinal absorption of nadolol in rats with jejunum loop

Resin	Absorption in 4 h (% of dose)		
Dose of resin: (mg/kg)	100	200	400
DEAE Sephadex	71.4 ± 3.7 **	76.2 ± 1.8 **	67.4 ± 5.2 *
QAE Sephadex	70.4 ± 3.1 **	71.2 ± 1.8 **	71.1 ± 4.4 **
Dowex 1×2	49.9 ± 2.9	65.4 ± 2.4 **	75.1 ± 2.0 **
Dowex 1×8	–	47.3 ± 2.2	51.0 ± 4.2
DE-32	58.2 ± 2.4 *	67.3 ± 3.8 **	68.8 ± 2.8 **
Cellex QAE	56.1 ± 1.8 *	53.5 ± 2.8	48.4 ± 2.9

Results are expressed as the mean ± S.E. of 4–5 rats. * $P < 0.05$, ** $P < 0.01$, compared to control (with sodium cholate, 46.1 ± 3.8% shown in Table 1).

Effect of anion exchange resins (100–400 mg/kg) on plasma levels of nadolol (20 mg/kg) was investigated in rats (Table 4). A typical example of plasma levels of nadolol in DEAE Sephadex- and Dowex 1 × 2-treated rats is shown in Fig. 2. As is evident from the figure, plasma levels of nadolol were significantly increased by the oral ingestion of resins in a dose-related manner. In addition, QAE Sephadex and DE-32 also showed the pronounced effect on the intestinal absorption

TABLE 4

Effect of anion exchange resin on oral absorption of nadolol (20 mg/kg) in rats

Resin	Dose (mg/kg)	Absorption (% of dose)	Significance ($P <$)
Control		18.0 ± 0.8	
DEAE Sephadex	100	24.6 ± 3.7	N.S.
	200	41.1 ± 4.0	0.01
	400	63.0 ± 3.9	0.01
QAE Sephadex	200	50.8 ± 3.9	0.01
	400	59.1 ± 4.5	0.01
Dowex 1×2	100	20.7 ± 1.3	N.S.
	200	46.3 ± 5.2	0.01
	400	59.6 ± 5.4	0.01
DE-32	400	43.2 ± 4.1	0.01
Cellex QAE	400	20.6 ± 2.1	N.S.

Results are expressed as the mean ± S.E. of 5 rats.

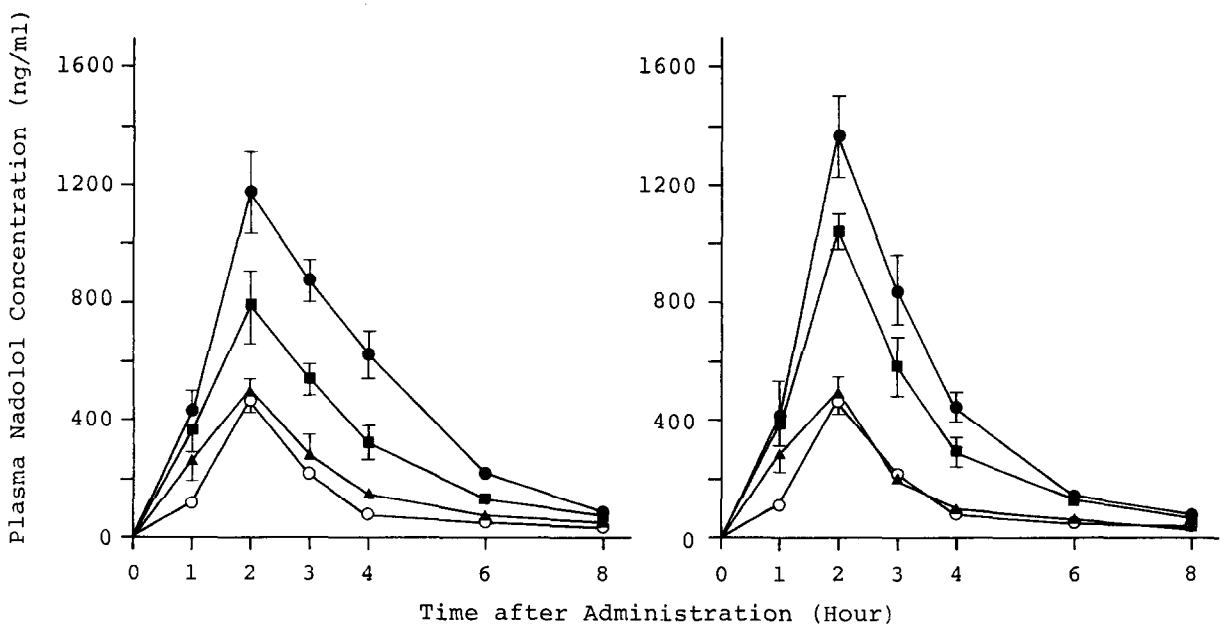

Fig. 2. Effect of DEAE Sephadex (left) and Dowex 1 × 2 (right) on plasma levels of nadolol in rats. ○, control; ▲, 100 mg/kg of resin; ■, 200 mg/kg; ●, 400 mg/kg nadolol (20 mg/kg) was orally administered just after the oral ingestion of anion exchange resin (100–400 mg/kg). Each point represents the mean ± S.E. of 5 rats.

of nadolol after oral administration. However, Cellex QAE was without effect. The percentage absorption in DEAE Sephadex-, QAE Sephadex- and Dowex 1 × 2-treated rats was about 60% of the dose, which was 3.3–3.5 times higher than that in control rats. DE-32 revealed the moderate effect, 43.2% of the dose being absorbed, 2.4-fold excess.

Discussion

From the results of our investigation on the intestinal absorption of nadolol (Yamaguchi et al., 1986a, b and c), it is possible that the inhibited absorption of nadolol by sodium cholate is restored by decreasing the micellar complex formation, since the nadolol micelle is stable and free nadolol is hardly dissociated from the micelle (Yamaguchi et al., 1986b). To ascertain the possibility, two approaches were performed by using: (a) relatively lipophilic endogenous materials (fatty acids, glycerides, cholesterol and lecithin); and (b) bile salt binding sequestrants (anion exchange resins).

In the present study, lipids and anion exchange resins were found to restore the inhibited intestinal absorption of nadolol by sodium cholate in rats. It is well known that lipids form the micellar complex with bile salts (Hofmann and Mekhjian, 1973). When nadolol and lipid are co-administered, both compounds may competitively form the micellar complex with sodium cholate, and attain equilibrium in the intestinal lumen. Thus, the facility of lipid in forming micellar complex is considered to be an important factor for the enhancement of nadolol absorption. The fraction of micellar complex of nadolol at 20 mM sodium cholate was 50% (Yamaguchi et al., 1986b). The fraction of fatty acids and glycerides was more than 90%, similar to that (98%) for oleic acid at 10 mM sodium taurocholate (Siau and Levine, 1980), indicating that fatty acids and glycerides form the micellar complex with sodium cholate with greater facility than nadolol. Lecithin and cholesterol are also known to form micellar complex with bile

salts (Spink et al., 1982; Mazer and Carey, 1983), but do not affect the apparent percentage absorption of nadolol from the ligated loop (Table 1). This may be interpreted in terms of the alteration of the membrane permeability to nadolol by the addition of a large amount of lecithin and cholesterol. On the other hand, the anion exchange resins may bind to sodium cholate and inhibit the micellar formation of nadolol. The resins showed a wide range of binding capacity for sodium cholate (0.1–1.6 mequiv./g resin, Table 2). The capacity was independent of the functional group of resin, and seemed to depend upon the basic structure of resin, in the order of dextran, polystyrene and cellulose. DEAE Sephadex, QAE Sephadex and Dowex 1×2 have a high binding capacity (0.9–1.6 mequiv./g resin), and significantly increase the nadolol absorption in the presence of sodium cholate. However, Dowex 1×8 has very poor binding potency for sodium cholate (0.1 mequiv./g resin), and does not alter the nadolol absorption. Thus the enhancing effect of anion exchange resin on nadolol absorption seems to depend upon the binding capacity for sodium cholate.

At all doses (100–400 mg/kg) in the in situ studies used, DEAE Sephadex and QAE Sephadex showed the maximal effect on nadolol absorption but showed a dose-dependency in the in vivo studies with corresponding doses. A marked difference was observed in the case of monoolein, which restored the in situ absorption at a dose of 0.02 mmol/rat, corresponding to about 35 mg/kg. On the other hand, the in vivo absorption was constant at doses of 100 and 250 mg/kg, but was enhanced at a dose of 500 mg/kg. These discrepancies may be attributed to the difference of the intestinal motility or the difference of the availability of nadolol and bile salts in the in situ and in vivo experiments.

The specific interaction of nadolol and trihydroxy bile salts in the intestinal lumen has been suggested, especially after oral administration of nadolol; plasma levels of nadolol in bile duct-ligated rats were found to be significantly higher than those in sham-operated rats (Yamaguchi et al., 1986a and b). Based on the in situ experiments, lipids and anion exchange resins are considered to interfere with the micellar formation between nadolol and sodium cholate. The in vivo experiments confirmed the interference in the intestinal lumen; namely, the intestinal absorption of nadolol after oral administration (20 mg/kg) was enhanced by lipids and anion exchange resins with extremely high dose. The percentage absorption of oral nadolol was increased to about 40% of the dose with the oral ingestion of lipids (mono- and triglycerides, 500 mg/kg), 2.2-fold excess compared to control (18.0%). Anion exchange resins (DEAE Sephadex, QAE Sephadex and Dowex 1×2, 400 mg/kg) exhibited the marked enhancing effect in 3.3–3.5-fold excess on the absorption of oral nadolol, about 60% of the dose being absorbed. The value was higher than that of oral atenolol in rats (48–56% of the dose; Reeves et al., 1978), corresponding to the previous finding that the in situ intestinal absorption of nadolol was better than that of atenolol in rats (Yamaguchi et al., 1986a). It is concluded that the oral ingestion of lipids and anion exchange resins interfere with the micellar formation between nadolol and trihydroxy bile salts in the intestinal lumen, resulting in the restoration of the oral nadolol absorption. The results also support the proposed mechanism underlying the inhibited absorption of nadolol by the stable micellar formation with trihydroxy bile salts (Yamaguchi et al., 1986b).

Since the bile acids composition in man is qualitatively similar to that in rats (Hofmann and Mekhjian, 1973), it is suggested that the oral absorption of nadolol in man may also be inhibited by the same manner in rats (Yamaguchi et al., 1986a). This means that the oral absorption of nadolol in man may be enhanced by a large amount of lipids and anion exchange resins in a similar manner as described in rats. Fatty acids and glycerides generally have pharmacological or toxic properties which preclude their use as the enhancing agents of nadolol absorption with a long-term treatment. In addition, plasma levels of nadolol in man were not affected by standard food after an oral therapeutic dose of 80 mg (unpublished results from Squibb Institute). Anion exchange resins are little absorbed from the gastrointestinal tract, due to their high molecular weight and extreme insolubility in water (Thomas

et al., 1978). Some anion exchange resins, cholestyramine (Dowex 1 × 2) and colestipol, showed no toxic effect in man for at least one year (Ryan and Jain, 1972). They are now in clinical use in the treatment of hypercholesteremia with the usual dose of 4 g (about 80 mg/kg). By decreasing the enterohepatic circulation of bile salts and increasing the fecal excretion, the resins stimulate the hepatic conversion of cholesterol to bile salts, and lower the blood and tissue cholesterol levels. However, the dose of 80 mg/kg in man was one-fifth lower than that (400 mg/kg) in rats showing the enhancing effect on the oral nadolol absorption. Moreover, plasma levels of nadolol in rats were not increased by the oral ingestion of 100 mg/kg of resins (Fig. 2). Accordingly, it is considered that the intestinal absorption of nadolol in man may be not affected by normal food or usual dose of anion exchange resins.

Acknowledgements

The authors wish to express their gratitude to Dr. M. Shimizu, Managing Director of our Research and Development Division, and to Dr. M. Hashimoto, Director of these laboratories, for their continued encouragement.

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