Effects of lovastatin on biliary lipid secretion and bile acid metabolism in humans[1]

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Abstract Lovastatin, an inhibitor of HMG-CoA reductase, lowers cholesterol saturation of bile. To determine the mechanism of this effect and further define the role of cholesterol synthesis in regulation of biliary lipid metabolism, we studied ten human volunteers in a control period and again after 5–6 weeks on lovastatin, 40 mg b.i.d. Mean sterol production from acetate in mononuclear leukocytes fell from 1.18 to 0.84 pmol/min per 10^6 cells on lovastatin ($P < 0.02$). Concommitantly there was reduction in mean biliary secretion of cholesterol from 143 to 96 μmol/h ($P < 0.02$). On lovastatin, mean pool size of bile acids by the Lindstedt method fell from 3193 to 2917 μmol (one-sided $P = 0.05$) and mean pool size by the one-sample method fell from 5158 to 4091 μmol ($P < 0.002$). Lovastatin had no effect on mean fractional turnover rate of either cholic acid (0.77 vs. 0.74 day^{-1}) or chenodeoxycholic acid (0.51 vs. 0.54 day^{-1}). Mean total bile acid synthesis was lower on lovastatin (1443 vs. 1240 μmol/day), but the difference did not quite achieve statistical significance. In humans, inhibition of cholesterol synthesis by lovastatin lowers biliary cholesterol saturation by reducing cholesterol secretion into bile. Bile acid pool size, and perhaps bile acid synthesis, are also reduced by this inhibition. —**Mitchell, J. C., G. M. Logan, B. G. Stone, and W. C. Duane.** Effects of lovastatin on biliary lipid secretion and bile acid metabolism in humans. *J. Lipid Res.* 1991. **32:** 71–78.

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Lovastatin is one of a new class of drugs that lower serum cholesterol by competitive inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in biosynthesis of cholesterol (1, 2). These drugs exert prompt and striking changes in serum low density lipoprotein (LDL) cholesterol, often reducing levels by 35–40% in 1–2 weeks.

Recently we have reported that both lovastatin and an analogue, simvastatin, have potentially beneficial effects on biliary cholesterol as well (3, 4). These studies with human volunteers showed that both drugs lowered the cholesterol content of gallbladder bile relative to the two solubilizing lipids, bile acid and lecithin. Because cholesterol supersaturation of bile predisposes to development of cholesterol gallstones, this effect may have implications for pathogenesis and treatment of cholelithiasis.

The most likely explanation for the effect of lovastatin and simvastatin on bile lipid composition is that inhibition of cholesterol synthesis resulted in reduced output of cholesterol into bile. However, the relationship between cholesterol synthesis and biliary cholesterol secretion has not been clearly defined. In the rat, acute reduction in cholesterol synthesis by inhibitors of HMG-CoA reductase has been shown to lower biliary cholesterol secretion (5, 6). However, more long-term changes in cholesterol synthesis induced by fasting, cholesterol feeding, and cholestyramine administration have failed to alter biliary cholesterol secretion (7). In humans certain conditions, namely obesity and administration of chenodeoxycholic acid, result in parallel changes in cholesterol synthesis and biliary cholesterol secretion (8–12). However, the cause-and-effect relationship of these changes has not been established. Primary inhibition of cholesterol synthesis with an inhibitor of HMG-CoA reductase provides an ideal experimental opportunity to separate cause from effect in the association between cholesterol synthesis and secretion.

Moreover, a variety of studies both in vitro and in vivo suggest that reduction of cholesterol synthesis by inhibitors of HMG-CoA reductase may also lower bile acid synthesis (13, 14). Thus, even if lovastatin administration does reduce biliary cholesterol secretion, it might also reduce bile acid secretion, which would tend to minimize the change in cholesterol saturation of bile. Such a phenomenon has been reported in bile fistula rats (5), but has not been studied in human subjects.

Abbreviations: HMG, 3-hydroxy-3-methylglutaryl; LDL, low density lipoprotein; HDL, high density lipoprotein.

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To better understand the relationship between inhibition of cholesterol synthesis and biliary lipid composition and metabolism, we have measured both biliary lipid secretion and parameters of bile acid metabolism in human volunteers on and off lovastatin.

METHODS

Ten male volunteers were studied twice: once in a control period and once after 5–6 weeks on lovastatin 40 mg b.i.d. This relatively high dose of lovastatin was chosen to maximize the possibility of measuring changes induced by the drug.

Three of the ten volunteers had also participated in a study of effects of lovastatin and ursodeoxycholic acid on cholesterol saturation index (15). The volunteers ranged in age from 44 to 68 years and in percent ideal body weight from 98 to 133. Except for elevation of serum lipids in some subjects (**Table 1**), all were without significant medical problems as judged by previously published criteria (16). Because sampling procedures for these studies were arduous and uncomfortable for the volunteers, it was not possible to recruit and maintain ten subjects with perfectly normal lipid levels. However, those subjects with elevated lipids (primarily triglycerides) did not appear to respond differently to lovastatin with respect to any of the metabolic parameters measured (Results). Each subject provided a detailed dietary history. Each was then instructed to continue his customary diet throughout the study, and periodic interviews were conducted to ensure that these instructions were being followed. Informed consent was obtained from all volunteers prior to study. All study protocols were approved by the Subcommittee on the Use of Human Subjects in Research of the Minneapolis VA Medical Center.

Secretion rates of biliary lipids were measured as described by Grundy and Metzger (17) using β-sitosterol (ICN Pharmaceuticals, Cleveland, OH) as the marker. Four hours after the start of this infusion, eight hourly samples were collected and analyzed for cholesterol and β-sitosterol by gas-liquid chromatography (18), for total bile salt by the enzymatic method (18, 19), and for phospholipid by colorimetry (20). Hourly secretion rates of the three biliary lipids were calculated from these results using the equations of Grundy and Metzger (17). Values reported here are the means of these eight 1-h determinations.

Bile acid pool sizes, turnover rates, and synthetic rates were determined by isotope dilution as described in previous publications (16, 18) using both [24-^{14}C]cholic acid and [24-^{14}C]chenodeoxycholic acid (New England Nuclear, Boston, MA). Samples of gallbladder bile were obtained after administration of 20 ng/kg cholecystokinin octapeptide (Kinevac, Squibb & Sons, Inc., Princeton, NJ) and were analyzed in duplicate for cholesterol, phospholipid, and total bile salt as indicated above. These were used to calculate lipid molar ratios and cholesterol saturation index as described previously (4). In addition, duplicate determinations of specific activity of cholic acid and chenodeoxycholic acid were performed after isolation of these two bile acids by thin-layer chromatography as previously described (18). Individual bile acid composi-

TABLE 1. Serum lipids

	Cholesterol							
	Total		LDL		HDL		Triglyceride	
Subject	Control	Lovastatin	Control	Lovastatin	Control	Lovastatin	Control	Lovastatin
	mg/dl							
1	155	100	74	44	31	38	247	90
2	195	108	136	60	27	32	158	80
3	140	89	71	31	30	33	193	123
4	210	145	121	55	50	55	195	175
5	175	104	56	40	23	23	478	201
6	180	125	124	65	40	41	80	91
7	232	144	171	85	41	42	99	83
8	184	120	118	59	35	37	154	116
9	215	148	157	85	28	28	149	172
10	146	104	42	39	21	27	412	189
Mean	183	118[a]	107	56[a]	32	35[b]	216	132[c]
Mean Δ		−65		−51		3		−85
SEM Δ		5		9		1		32

Abbreviations: LDL, low density lipoprotein; HDL, high density lipoprotein; Δ, difference between lovastatin and control.
[a] $P < 0.001$.
[b] $P < 0.01$.
[c] $P < 0.05$.

tion was determined by gas–liquid chromatography (18). Fractional turnover rate, pool size, and synthesis rate of the two primary bile acids were determined using semilogarithmic regression analysis of the specific activity–time relation as described by us (18) and originally by Lindstedt (21). Total "Lindstedt" bile acid pool was calculated from these data by averaging the ratio of (chenodeoxycholic acid pool)/(fraction of chenodeoxycholic acid in bile) and the ratio of (cholic acid pool)/(fraction of cholic acid in bile). Finally, from direct measurement of radioactivity and total bile salt in the first bile sample, we calculated total "one-sample" bile acid pool as described and validated previously (22).

Sterol synthesis in mononuclear cells was measured exactly as previously described (23) using a method based on that reported by McNamara, Davidson, and Fernandez (24).

Statistical analysis was done by paired *t*-test using two-sided *P*-values unless otherwise specified. Because all comparisons were paired, we have expressed variability as the standard error of the mean difference, rather than standard error of the mean value, which would be appropriate for unpaired, group comparisons.

RESULTS

Table 1 presents serum lipid values before and after 5–6 weeks of lovastatin. Mean serum cholesterol fell from 183 to 118 mg/dl ($P < 0.01$), mean LDL cholesterol fell from 107 to 56 mg/dl ($P < 0.001$), and mean HDL cholesterol increased slightly from 32 to 35 mg/dl ($P < 0.01$). Mean triglycerides decreased from 216 to 132 mg/dl ($P < 0.05$). All these changes are consistent with previously published studies of HMG-CoA reductase inhibitors (1, 2), although changes in HDL cholesterol and triglycerides have not reached statistical significance in many studies.

Fig. 1 shows the effect of lovastatin on incorporation of acetate into sterols in mononuclear leukocytes in nine of the ten subjects. (Analysis of leukocytes from subject #5 was not accomplished because of a technical error.) In the control period, mean incorporation rate was 1.18 pmol/min per 10^6 cells. After 5–6 weeks of lovastatin, mean incorporation rate fell to 0.84 pmol/min per 10^6 cells ($P < 0.02$). This 29% reduction in leukocyte sterol production is similar to the 16–20% reduction we found in an earlier study of prolonged lovastatin administration (23).

As expected from previous studies (3, 4), cholesterol saturation index of gallbladder fell significantly (1.15 vs. 0.94) on lovastatin ($P < 0.02$). Similarly, in stimulated hepatic bile mean cholesterol saturation index was lower on lovastatin compared to control (1.13 vs. 1.00), but the change was significant at $P < 0.05$ only by one-sided testing.

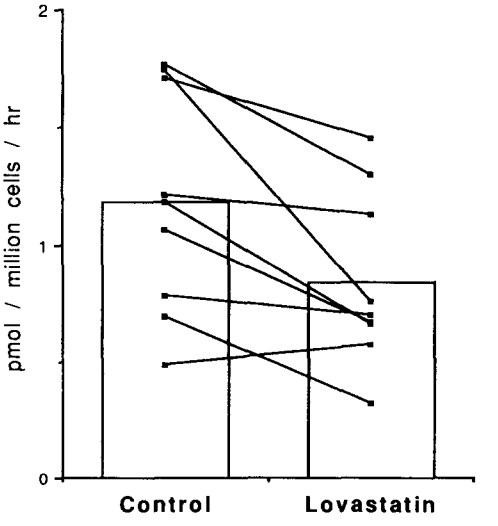

Fig. 1. Sterol synthesis from radiolabeled acetate in mononuclear leukocytes. Nine subjects were studied in a control period and again after 5–6 weeks on lovastatin. Measurements on one of the ten subjects were not successful because of a technical error. Mean sterol production fell from 1.18 to 0.84 pmol/min per 10^6 cells on lovastatin ($P < 0.02$).

Biliary lipid secretion rates are presented in **Table 2**. The most striking and consistent change on lovastatin was in cholesterol secretion which fell from a mean of 143 μmol/h in the control period to 96 μmol/h after treatment with lovastatin ($P < 0.02$). Mean bile salt secretion also fell on lovastatin, but to a lesser extent (1207 vs. 914 μmol/h) and the change was significant at $P < 0.05$ only by one-sided testing. Mean lecithin secretion was lower after lovastatin (338 μmol/h) than in the control period (434 μmol/h), but the difference did not achieve statistical significance.

Data for total bile acid pool size are presented in **Fig. 2**. Mean total bile acid pool measured by the Lindstedt method fell from 3193 μmol in the control period to 2917 μmol after lovastatin treatment, but the change was significant only by one-sided testing ($P = 0.05$). Mean total bile acid pool measured by the one-sample method fell from 5158 μmol to 4091 μmol on lovastatin, a result that was highly significant ($P < 0.002$). We have previously shown that the one-sample method is more reproducible than the Lindstedt method (22), which may explain the ability of the one-sample method to achieve higher statistical significance than the Lindstedt technique. The higher values for pool size measured by the one-sample method as compared to the Lindstedt method have been analyzed in detail previously and are largely a result of extrapolation of specific activity to time zero in one method and not the other (22).

Frequency of cycling of the pool in the enterohepatic circulation, calculated by multiplying hourly bile acid secretion rate by 24 and dividing by total Lindstedt bile

TABLE 2. Biliary lipid secretion rates

Subject	Cholesterol		Lecithin		Bile Salt	
	Control	Lovastatin	Control	Lovastatin	Control	Lovastatin
			μmol/h			
1	206	80	680	241	1462	890
2	208	170	491	471	1186	1107
3	139	153	497	672	1406	1457
4	122	113	413	405	932	1082
5	95	51	207	224	629	595
6	105	120	412	418	1410	1144
7	114	64	354	212	816	549
8	132	59	369	188	945	417
9	163	48	558	175	1971	483
10	141	95	356	366	1304	1408
Mean	143	96[a]	434	338	1207	914[b]
Mean Δ		−47		−97		−293
SEM Δ		15		61		154

Abbreviations: Δ, difference between lovastatin and control.
[a] $P < 0.02$.
[b] One-sided $P < 0.05$.

acid pool, was 9.2 cycles/day in control period versus 8.3 cycles/day during lovastatin treatment.

Pool sizes of individual primary bile acids measured by the Lindstedt method are presented in **Table 3**. For cholic acid, mean pool size in the control period was 1162 μmol and remained essentially unchanged at 1131 μmol (N.S.). For chenodeoxycholic acid, mean pool size fell significantly from 1101 μmol in the control period to 977 μmol on lovastatin ($P < 0.05$). The apparent difference in effects of lovastatin on these two primary bile acid pools is of uncertain significance. Composition of the bile acid pool measured by gas-liquid chromatography did not change significantly (**Table 4**). Mean percent cholic acid in the pool was 36.1% in the control period and 37.5% during lovastatin treatment, while that of chenodeoxycholic acid was 33.0% and 33.3%, respectively. When primary bile acid pools sizes were calculated by multiplying the one-sample pool by the fraction of each bile acid in the pool, there were statistically significant reductions in both cholic acid pool (1951 vs. 1557 μmol, $P < 0.05$) and chenodeoxycholic acid pool (1255 vs. 959 μmol, $P < 0.05$).

Pool size of the secondary bile acid, deoxycholic acid, did not change significantly between control and lovastatin periods when calculated by multiplying the total Lindstedt pool times fraction of deoxycholic acid (768 vs. 643 μmol), but was significantly reduced when

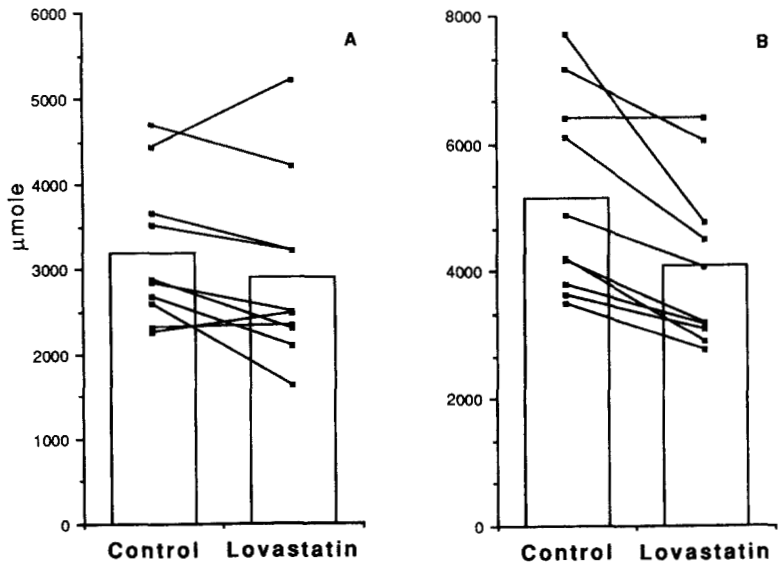

Fig. 2. Total bile acid pool sizes measured by two isotope dilution methods in the control period and again after 5–6 weeks on lovastatin. On lovastatin mean bile acid pool measured by the Lindstedt method (A) fell from 3193 to 2917 μmol (one-sided $P = 0.05$). Mean bile acid pool measured by the one-sample technique (B) fell from 5158 to 4091 μmol on lovastatin ($P < 0.002$).

TABLE 3. Primary bile acid turnover and pools

	Fractional Turnover				Pool Sizes			
	CA		CDCA		CA		CDCA	
Subject	Control	Lovastatin	Control	Lovastatin	Control	Lovastatin	Control	Lovastatin
	day^{-1}				*μmol*			
1	0.77	0.66	0.43	0.49	474	728	669	483
2	0.97	1.26	0.67	1.03	986	914	693	720
3	1.28	1.29	0.89	1.11	1502	1069	913	551
4	0.59	0.57	0.42	0.34	694	762	874	867
5	0.91	1.10	0.52	0.46	952	630	601	526
6	0.70	0.46	0.50	0.32	1737	1466	1607	1222
7	0.76	0.46	0.50	0.35	705	912	740	825
8	0.50	0.61	0.44	0.64	1332	1406	1425	1159
9	0.82	0.57	0.43	0.26	1616	2026	2332	2406
10	0.44	0.43	0.34	0.37	1619	1393	1155	1007
Mean	0.77	0.74	0.51	0.54	1162	1131	1101	976[a]
Mean Δ		− 0.03		0.02		− 31		− 125
SEM Δ		0.06		0.06		88		55

Abbreviations: CA, cholic acid; CDCA, chenodeoxycholic acid; Δ, difference between lovastatin and control.
[a] $P < 0.05$.

calculated from the one-sample total pool (1713 vs. 1359 μmol, $P < 0.05$). Pool size of lithocholic acid was not different in control versus lovastatin periods whether calculated from the Lindstedt total pool (49.8 vs. 58.4 μmol) or the one-sample total pool (77.1 vs. 78.6 μmol). Similarly, for ursodeoxycholic acid, pool size was not significantly different in control and lovastatin periods calculated from either the Lindstedt total pool (109 vs. 108 μmol) or the one-sample pool (162 vs. 137 μmol).

Turnover rates of individual primary bile acid pools are also presented in Table 3. For cholic acid, mean fractional turnover rates in control and lovastatin periods were 0.77 and 0.74 day^{-1}, respectively. Corresponding values for chenodeoxycholic acid were 0.51 and 0.54 day^{-1}. Neither of these slight changes was statistically significant.

Effects of lovastatin on bile acid synthesis rates are presented in **Table 5**. Mean synthesis rate of cholic acid fell from 899 to 785 μmol/day and of chenodeoxycholic acid fell from 544 to 455 μmol/day. Neither change was statistically significant. Mean total bile acid synthesis was 1443 μmol/day in the control period and fell to 1240 μmol/day on lovastatin. This change approached statistical significance, but did not reach it (one-sided $P < 0.10$).

There was no significant correlation between change in mononuclear leukocyte sterol synthesis and change in cholesterol secretion ($r = 0.08$), one-sample bile acid pool size ($r = 0.34$), or bile acid synthesis rate ($r = 0.26$).

TABLE 4. Percentage individual bile acids in gallbladder bile

	LCA		DCA		CDCA		UDCA		CA	
Subject	Control	Lovastatin	Control	Lovastatin	Control	Lovastatin	Control	Lovastatin	Control	Lovastatin
1	3.8	4.5	52.5	37.7	21.8	27.9	1.3	0.4	20.6	29.5
2	1.3	1.5	38.0	31.2	26.8	29.7	2.2	1.9	31.7	35.6
3	0.6	0.9	15.2	28.0	32.4	24.7	0.8	1.1	51.0	45.3
4	1.6	0.9	26.9	26.1	39.8	36.9	3.3	3.5	28.4	32.6
5	1.0	0.6	37.9	25.8	25.2	36.2	2.2	2.1	33.7	35.3
6	0.8	1.2	24.8	34.1	32.0	31.1	2.8	1.0	39.6	32.6
7	2.2	2.3	30.0	25.4	30.1	32.1	3.1	1.8	34.6	38.4
8	1.1	1.4	15.2	14.2	44.7	40.9	4.5	4.3	34.5	39.2
9	1.9	4.0	0.0	0.0	43.8	41.8	8.8	10.5	45.4	43.7
10	1.8	1.1	20.7	20.5	33.8	31.6	2.3	3.6	41.4	43.1
Mean	1.6	1.9	26.1	24.3	33.0	33.3	3.1	3.0	36.1	37.5
Mean Δ		0.2		− 1.8		0.2		− 0.1		1.4
SEM Δ		0.2		2.7		1.7		0.3		1.6

Abbreviations: LCA, lithocholic acid; DCA, deoxycholic acid; CDCA, chenodeoxycholic acid; UDCA, ursodeoxycholic acid; CA, cholic acid; Δ, difference between lovastatin and control.

TABLE 5. Bile acid synthesis rates

Subject	CA		CDCA		Total	
	Control	Lovastatin	Control	Lovastatin	Control	Lovastatin
			μmol/day			
1	366	484	289	237	655	721
2	958	1150	467	741	1425	1892
3	1928	1382	811	610	2740	1992
4	408	433	363	291	771	724
5	863	693	309	241	1173	934
6	1218	675	808	389	2026	1064
7	537	418	369	290	906	709
8	660	864	629	741	1289	1605
9	1332	1152	1005	630	2337	1782
10	716	598	394	376	1111	975
Mean	899	785	544	455	1443	1240
Mean Δ		− 114		− 90		− 203
SEM Δ		85		65		142

Abbreviations: CA, cholic acid; CDCA, chenodeoxycholic acid; Δ, difference between lovastatin and control.

DISCUSSION

While the effects of HMG-CoA reductase inhibitors on bile lipids may have some potential clinical applicability in the management of cholesterol cholelithiasis (3, 4), these inhibitors also provide a powerful probe for better defining the role of cholesterol synthesis in regulation of biliary lipid secretion and metabolism. In previous studies of this important question, cholesterol synthesis has often been altered by such perturbations as fasting, cholesterol feeding, and cholestyramine administration, which are indirect and may themselves alter secretion and metabolism of biliary lipids (7, 25, 26). In contrast, direct competitive inhibition of HMG-CoA reductase is unlikely to alter other metabolic parameters apart from changes exerted by reduced cholesterol synthesis itself. Such inhibitors have been shown to lower biliary cholesterol secretion in animal models after acute administration (5, 6), but more prolonged effects on cholesterol secretion have not yet been studied in either animals or humans. In the present study we evaluated effects of a sustained reduction of cholesterol synthesis by lovastatin on biliary lipid secretion and metabolism. These studies were performed in human volunteers to eliminate any need to speculate about suitability of animal models.

This approach could not be used, however, if the liver could synthesize enough additional HMG-CoA reductase to completely offset the inhibitory effect of lovastatin. This appears to be the case for the rat, a species in which inhibitors of HMG-CoA reductase do not lower serum cholesterol (27–29). In humans, however, the consistent and striking reduction in serum cholesterol levels on lovastatin indicates that compensation by increased production of HMG-CoA reductase must be incomplete. Moreover, in both the present study and a previous study (23) we have documented a 20–30% reduction in sterol synthesis by mononuclear leukocytes from subjects on lovastatin. The only other study of cholesterol synthesis in human subjects taking lovastatin showed a statistically significant reduction in fecal sterol balance in three of five subjects, a reduction not achieving significance in the fourth subject, and no change in the fifth subject (30). Thus, the available evidence to date strongly suggests that, after several weeks on lovastatin, human subjects maintain an appreciable reduction in cholesterol synthesis.

Interest in the role of cholesterol synthesis in regulation of biliary cholesterol secretion was especially aroused by the early appreciation that administration of chenodeoxycholic to human subjects lowered both biliary cholesterol secretion and HMG-CoA reductase activity (8–10). Also, in obese subjects there are parallel changes in cholesterol synthesis and secretion, both being abnormally high (10, 11). It is still uncertain, however, whether these changes in cholesterol synthesis caused a parallel change in cholesterol secretion or vice versa. The present study shows for the first time in human subjects that primary inhibition of HMG-CoA reductase does lower biliary cholesterol secretion (Table 2). This indicates that if conditions such as obesity and administration of chenodeoxycholic acid alter cholesterol synthesis, then one would expect a corresponding change in cholesterol secretion.

The data in Table 2 also demonstrate that, although lovastatin may have lowered secretion of bile acid and perhaps lecithin, it lowered secretion of cholesterol out of proportion to that of the other two lipids. This relatively selective reduction in cholesterol secretion explains the reduction in gallbladder bile saturation index by HMG-CoA reductase inhibitors described earlier (3, 4) and confirmed in this study (Results).

Lovastatin administration also affected bile acid metabolism. This was most clearly demonstrated for bile acid

pool size, which was significantly reduced by lovastatin (Fig. 2). In addition, there was reduction in mean hepatic secretion of bile acid, which was significant only by one-sided testing. It seems likely that any reduction in bile acid secretion occurred because a smaller bile acid pool continued to cycle in the enterohepatic circulation with about the same frequency in control and lovastatin periods. Calculated cycling frequency was nearly identical in control and lovastatin periods (Results), and there is no reason to expect lovastatin to alter enterohepatic cycling frequency.

Why then was bile acid pool size reduced by lovastatin? Table 3 shows virtually identical mean fractional turnover rates during control and lovastatin periods for both cholic acid and chenodeoxycholic acid, suggesting that loss from the pool was unaffected. On the other hand, our data do not demonstrate a statistically significant reduction in bile acid synthesis during lovastatin treatment (Table 5), although mean synthesis rates of both cholic acid and chenodeoxycholic acid were substantially lower during lovastatin treatment. The most rigid interpretation of this finding would be that lovastatin caused no change in bile acid synthesis. This conclusion may not be correct, however, in view of the clear-cut reduction in pool size unexplained by a change in fractional turnover. Perhaps more likely is that lovastatin caused a reduction in bile acid synthesis, at least in some subjects, but that this change was more variable than the change in pool size, either because of greater inherent variability in measurement of synthesis (which, unlike the one-sample pool measurement, depends on extrapolation of a linear regression equation) or because a few individual subjects (e.g., subjects 2 and 8, Table 3) responded to lovastatin with a change in fractional turnover in place of or in addition to a change in bile acid synthesis. Our recent observation that a single dose of lovastatin significantly lowered bile acid synthesis [measured by release of $^{14}CO_2$ from [^{14}C-26]cholesterol (31)] lends some support to this explanation in as much as it shows that lovastatin can lower bile acid synthesis under some circumstances.

There are several possible mechanisms by which lovastatin could lower bile acid synthesis. The first is by limiting availability of substrate by reduction in cholesterol synthesis. This possibility would be compatible with (but not follow necessarily from) reports that newly synthesized cholesterol is a preferential substrate for bile acid synthesis (32–34). On the other hand, recent studies in both rat and human liver suggest that bile acid synthesis is not substrate-limited except in circumstances where cholesterol availability is sharply reduced (35, 36).

A second alternative would be that lovastatin might inhibit 7α-hydroxylase. Indeed, in the rat inhibitors of HMG-CoA reductase, including lovastatin, have been reported to inhibit activity of this enzyme (14, 19). However, a recent study of pravastatin, a related drug, in human subjects reported no significant change in activity of 7α-hydroxylase, although mean activity was lower during pravastatin treatment (37). Any inhibition of this enzyme that might occur during lovastatin treatment is likely to be indirect because studies in vitro show that lovastatin does not directly inhibit activity of 7α-hydroxylase (14).

A final possibility is that the reduced input of cholesterol resulting from inhibition of HMG-CoA reductase increases the sensitivity of bile acid synthesis to feedback inhibition from bile acid returning to the liver. This hypothesis would explain a reduction in bile acid synthesis as well as any reduction of 7α-hydroxylase activity. It would also be compatible with the observation that bile acid synthesis did not increase despite a probable reduction in bile acid return to the liver (equivalent to bile acid secretion, Table 2). Nevertheless, the present study neither proves nor refutes this hypothesis, but provides an interesting speculation that warrants further investigation.

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