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Medication compliance and serum lipid changes in the Helsinki Heart Study

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1 To control the bias caused by poor medication compliance in the Helsinki Heart Study three methods were used to measure medication compliance during the total 5 years follow up time: continuous capsule counting, semi-annual urine gemfibrozil analysis and a new method, the digoxin marker at the end of the third and fifth study years.

2 The serum lipid responses to gemfibrozil treatment varied linearly with the level of medication compliance, e.g. the mean change in serum total cholesterol was −11.4% among those whose apparent capsule consumption was ≥90% of the scheduled dosage, −11.2% among those who had ≥90% positive gemfibrozil analyses and −11.4% among those with good compliance according to both digoxin marker measurements. In contrast the mean serum cholesterol change was only −0.02% if the mean daily capsule count was less than 50%, −1.7% with fewer than 50% positive gemfibrozil analyses and −1.1% if the result was poor in both digoxin marker measurements.

3 Combining the different method findings revealed that the cholesterol changes tended to be small in those groups who had poor compliance classification measured by any of the methods, even if the other results showed good compliance.

Keywords capsule counting digoxin gemfibrozil medication compliance study adherence

Introduction

Results from clinical trials are not only dependent on the actual effect of the treatment studied but also on the difference between subjects' behaviour as expected in the protocol and their behaviour in reality, i.e. study adherence. The well-documented effects of poor compliance on interpretation of study results frequently lead to underestimation of the treatment (Feinstein, 1979).

In the Helsinki Heart Study (HHS), a coronary primary prevention trial using gemfibrozil, special attention was focused on compliance with medication. The present study describes the effects of medication compliance on serum lipid changes induced by gemfibrozil. Medication compliance was measured by capsule counting, by urine analysis for gemfibrozil and by digoxin marker, used for the first time in the HHS.

Methods

In this study the effect of medication compliance on serum lipid changes induced by gemfibrozil medication and dietary counselling was studied among participants of the Helsinki Heart Study (HHS). The HHS was a 5-year double-blind randomized study which tested the effect of lowering serum total cholesterol and triglycerides and elevating serum HDL cholesterol on the incidence of coronary heart disease among healthy middle-aged men with hypercholesterolaemia (Frick *et al.*, 1987). There were 2046 subjects in the gemfibrozil group and 2035 subjects in the placebo group.

Serum lipid determinations

In the HHS, serum total and HDL cholesterol were measured at every 3 monthly follow-up visit. Serum triglycerides were measured at 6 month intervals, i.e. every other visit. LDL cholesterol was calculated using the formula: LDL cholesterol = total cholesterol minus HDL cholesterol minus triglycerides divided by 2.2 (Friedewald *et al.*, 1972). The baseline values for total and HDL cholesterol were obtained from the third pretreatment visit when gemfibrozil or placebo capsules were given for the first time. The baseline value for

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serum triglycerides was taken from the second pretreatment visit. Baseline serum LDL chlesterol was calculated from total and HDL cholesterol values at the third pretreatment visit and the triglyceride value at the second screening visit (Manninen *et al.*, 1988). For each subject the mean differences between baseline lipid parameters and those of each follow-up visit were expressed as percentage changes from the baseline value.

Capsule counting

Subjects were given a pack of 400 capsules each containing 300 mg gemfibrozil or matching placebo for each 3 month follow-up period. The daily dosage was two capsules twice daily. Unused capsules were returned at the following visit. The estimates for compliance according to capsule count were made as follows: For each 3 month period the number of unreturned capsules were divided by four times the number of days between visits. A mean of these ratios was used to form the mean daily capsule count (MDCC) for the total follow-up period of each subject. MDCC is here expressed as the percentage of the scheduled daily dose of four capsules. The HHS subjects were divided into four compliance groups with MDCC cut-off points of 50%, 75% and 90%. Eighty-three gemfibrozil subjects and 73 placebo subjects were excluded from analysis because of early drop out, i.e. they interrupted the study at their first visit without returning their leftover capsules.

Urine gemfibrozil analysis

The presence of gemfibrozil in a urine sample was detected by a colour forming reaction: 1 ml hydrochloric acid (6 N) was mixed with 2 ml of urine. Dichlormethane (3 ml) was then added and mixed (Vortex, 30 s). The mixture was then centrifuged (2500 rev min^{-1}, 5 min, + 4 °C) and the supernatant removed and extracted. Two drops of 16% formaldehyde and 2 ml sulphuric acid (28 N) were added. If gemfibrozil was present in the sample, a red colour formed. When tested with six male volunteers during regular dosing of 600 mg gemfibrozil twice daily, no false negative results were obtained. But after 12 h had elapsed from the last dose, the assay soon turned negative (after 13–20 h). Thus the method gave information about the intake of the preceding one or two doses.

In the HHS a urine sample was taken for gemfibrozil analysis at 6 month intervals. A urine sample was not available for measurement on 3% of occasions. To measure medication compliance from the total follow-up time for each gemfibrozil subject the proportion of positive gemfibrozil results from among all his measurements was expressed as a percentage. The subjects were divided into four groups with cut-off points of 50%, 75% and 90% of positive urine gemfibrozil results. Because of early drop-out 134 gemfibrozil subjects had no gemfibrozil analyses.

The digoxin marker

For this compliance measurement 2.2 μg digoxin was added to each gemfibrozil and placebo capsule (Mäenpää *et al.*, 1987a,b). Urine digoxin and creatinine concentrations were measured and their ratio calculated. Urine digoxin was measured by a radioimmunologic assay (Digoxin ^{125}I RIA Kit, Farmos Diagnostica, Finland). Urine creatinine concentration was measured enzymatically (Boehringer Mannheim Gmb Diagnostic Kit 441716). Digoxin concentration was divided by creatinine concentration to compensate for the effect of urine volume variation. On the basis of this ratio the samples were classified into three compliance groups: good, intermediate and poor.

The two cut-off points used in this classification were tested in a pilot study of 15 male volunteers who took two capsules marked with 2.2 μg digoxin twice daily for 11 days providing three urine samples per day. After 2 days of regular drug intake none of them was classified as poor compliers. On the other hand, a two day pause in drug intake was not enough to lower the ratio below the cut-off point between poor and intermediate compliers. Only a week's pause led to the poor complier classification for all volunteers. During the third day of regular dosing 50% of samples showed good compliance. After 9 days of regular drug intake 97% of samples put the donor in the good complier group. After a subsequent 2 day pause only 1% of samples were still in this group.

Medication compliance was measured by this method at the end of the third and fifth study years, when 2.2 μg digoxin was added to both gemfibrozil and placebo capsules for 3 month follow-up periods. At the end of these periods a urine sample was obtained at the routine clinic visit to measure urine digoxin and creatinine concentrations.

There were 1384 gemfibrozil and 1424 placebo subjects with a result from both digoxin measurements. Others had dropped out before the 5 year measurement. According to these results the subjects were classified into one of four groups: poor compliers at both measurements, poor at one and intermediate at the other, good and poor compliers, twice intermediate, intermediate and good compliers, and finally twice good compliers.

Results

Capsule counting

There were no major differences between gemfibrozil and placebo subjects in terms of distribution among the four compliance groups separated by cut-off points of 50%, 75% and 90% of the mean daily capsule count (Table 1). The largest compliance group, with MDCC 90% or more, consisted of 776 gemfibrozil (39.5%) and 813 placebo (41.4%) subjects. In the group where MDCC was less than 50% there were only 96 gemfibrozil (4.9%) and 93 placebo (4.7%) subjects.

Serum total cholesterol, LDL and HDL cholesterol and triglyceride changes in these four compliance groups are presented in Figure 1, which shows that the mean changes in each lipid parameter varied with the compliance group. In the gemfibrozil group the change in serum total cholesterol ranged from −0.02% (MDCC <

50%) to −11.4% (MDCC ≥ 90%), in LDL cholesterol from +2.6% to −10.1%, in HDL cholesterol from +2.7% to +13.3% and in triglycerides from −6.2% to −40.0%, respectively. No variation in lipids associated with medication compliance could be detected in the placebo group, where any mean changes were mostly in adverse directions.

Urine gemfibrozil analyses

There were 677 gemfibrozil subjects (35.4%) whose results were positive in at least 90% of the semiannual gemfibrozil measurements. The groups with less than 50%, 50–74% and 75–89% positive results had 470 (24.6%), 428 (22.4%) and 337 (17.6%) subjects, respectively. Mean changes in serum total cholesterol, LDL and HDL cholesterol and triglycerides in the four compliance groups are shown in Figure 2. Again, better medication compliance tends to be reflected in greater lipid changes. The lowest compliance group differed clearly from others by a mean change in serum total cholesterol of only −1.7%, in LDL cholesterol of −0.1%, in HDL cholesterol of +6.5% and in serum triglycerides of −11.4%. The range of the gemfibrozil effect across the other groups was −8.5% to −11.2% for serum total cholesterol, −7.1% to −9.0% for LDL cholesterol, +11.8% to +13.3% for HDL cholesterol and −31.6% to −39.3% for triglycerides.

The digoxin marker

Six compliance groups were formed by combining the results from the digoxin marker analyses made at the end of the 3rd and 5th study years (Table 2). There were

Table 1 The mean daily capsule count (MDCC) of 1963 gemfibrozil subjects and 1962 placebo subjects in the HHS

MDCC	*Gemfibrozil group* n	%	*Placebo group* n	%
< 50%	96	4.9	93	4.7
≥ 50 – < 75%	394	20.1	360	18.3
≥ 75 – < 90%	697	35.5	696	35.5
≥ 90%	776	39.5	813	41.4

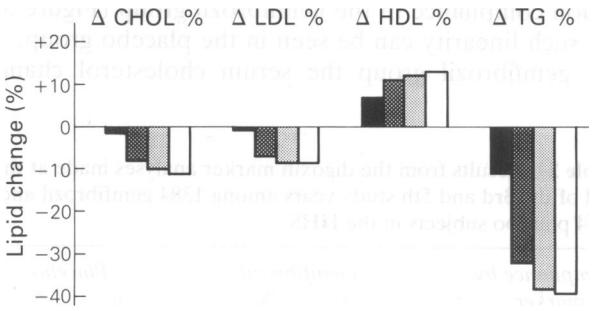

Figure 2 Mean serum total cholesterol changes (ΔCHOL%), LDL cholesterol (ΔLDL%), HDL cholesterol (ΔHDL%) and triglyceride changes (ΔTG%) among 1912 gemfibrozil subjects of the HHS in four groups of medication compliance measured by urine gemfibrozil analyses. ■ < 50%, ▩ ≥ 50% – < 75%, ▨ ≥ 75% – < 90% and □ ≥ 90% samples positive.

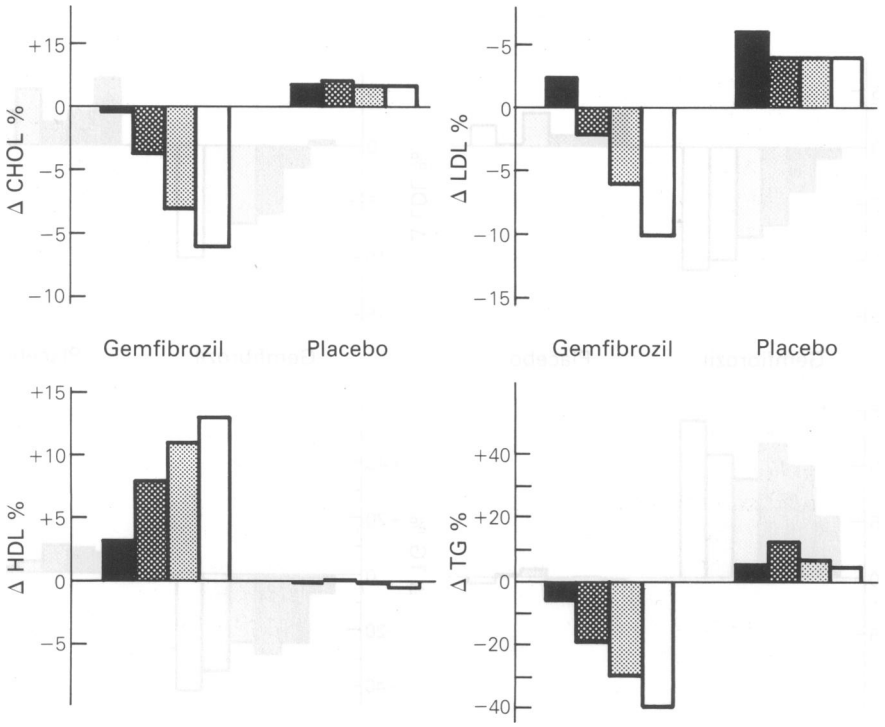

Figure 1 Mean serum total cholesterol changes (ΔCHOL%), LDL cholesterol (ΔLDL%), HDL cholesterol (ΔHDL%) and triglyceride changes (ΔTG%) among 1963 gemfibrozil and 1962 placebo subjects of the HHS in four groups of medication compliance measured by mean daily capsule count (MDCC) from the total follow-up time of 5 years. ■ MDCC < 50%, ▩ MDCC ≥ 50% – > 75%, ▨ MDCC ≥ 75% – < 90% and □ MDCC ≥ 90%.

582 gemfibrozil subjects (42.1%) and 709 placebo subjects (49.8%) classified as good compliers at both measurements. One hundred and ninety-four gemfibrozil and 169 placebo subjects (14.0% and 11.9%, respectively) were classified as poor compliers twice, 243 gemfibrozil and 271 placebo subjects (17.5% and 19.0%, respectively) once. Other result combinations (i.e. twice intermediate compliance or intermediate and good compliance) were recorded for 365 (26.4%) gemfibrozil subjects and 275 (19.3%) placebo subjects. Altogether, 662 gemfibrozil and 611 placebo subjects were excluded from the digoxin analysis because of drop-out before the analysis at the end of the fifth study year.

As before, it can easily be seen that changes in serum lipid parameters tended to be larger with better medication compliance in the gemfibrozil group (Figure 3). No such linearity can be seen in the placebo group. In the gemfibrozil group the serum cholesterol change ranged from −1.1% to −11.4%, LDL cholesterol from +0.4% to −10.0%, HDL cholesterol from +5.4% to +14.4% and triglycerides from −7.2% to −42.0%. As before, there was no association between level of compliance and serum lipid changes in the placebo group.

Table 2 Results from the digoxin marker analyses made at the end of the 3rd and 5th study years among 1384 gemfibrozil and 1424 placebo subjects in the HHS

Compliance by the marker	*Gemfibrozil* n	%	*Placebo* n	%
Twice poor	194	14.0	169	11.9
Poor and intermediate	114	8.2	101	7.1
Poor and good	129	9.3	170	11.9
Twice intermediate	92	6.6	58	4.1
Intermediate and good	273	19.7	217	15.2
Twice good	582	42.1	709	49.8

Method combinations

The effect of gemfibrozil on serum total cholesterol was also analyzed by combining capsule counting and urine gemfibrozil findings and then capsule counting and the digoxin marker results. Because of the small size of the lowest MDCC group, the capsule counting results were split into only three groups, with cut-off points of 75% and 90%. The urine gemfibrozil results were in four groups as in the previous analyzes. The digoxin marker findings were analysed in four groups: twice poor, once poor, twice good and other combinations of compliance results.

Distributions of the gemfibrozil subjects into subgroups formed by the method combinations are presented in Tables 3 and 4. The serum total cholesterol changes in the subgroups formed by combining capsule counting and urine gemfibrozil results are shown in Figure 4, and the corresponding results from the combination of capsule counting and the digoxin marker in Figure 5. It can be seen that classification into the poorest complier group by any of the methods tended to mean low cholesterol change irrespective of the other findings. This phenomenon was strongest among those classified as poor compliers twice, or even once, by the digoxin marker analyses.

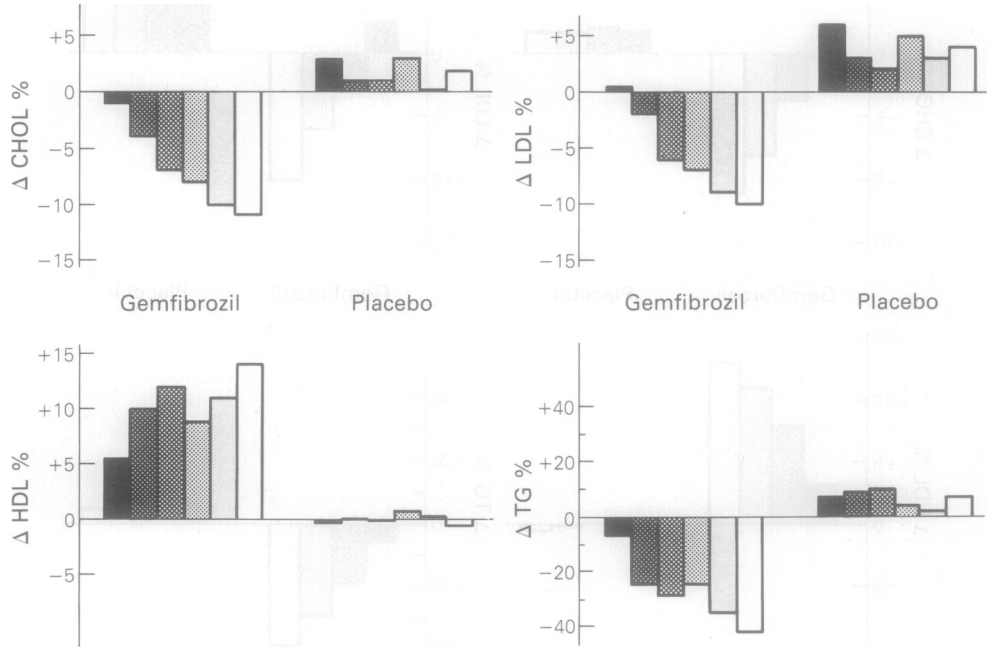

Figure 3 Mean serum total cholesterol (ΔCHOL%), LDL cholesterol (ΔLDL%), HDL cholesterol (ΔHDL%) and triglyceride changes (ΔTG%) among the 1384 gemfibrozil subjects of the HHS who were divided into six compliance groups according to the combination of results in the digoxin marker analyses at the end of the third and fifth study years: ■ twice poor, ■ poor and intermediate, ■ poor and good, ▨ twice intermediate, ▨ intermediate and good and finally □ twice good compliance.

Discussion

The issue of adherence to medication looms large over all clinical studies. In clinical practice, 25–50% of patients are commonly poor compliers (Sackett & Snow, 1979), and there is no reason to suggest the situation is any better during trials. Indeed, the clinical setting may weaken patient resolve still further via factors such as the change of receiving placebo medication, and insecurity about side-effects. Primary prevention studies, moreover, can last many years, with the intervention tested often having no immediate effect on well-being. It was for all these reasons that special attention was focused on compliance measurement in the Helsinki Heart Study. Originally, four different methods were used, but only capsule counting, urine gemfibrozil analysis and the digoxin marker were completed. The fourth method, a compliance questionnaire, proved a very poor detector of poor medication compliance at the 3 year analysis (Mäenpää *et al.*, 1987b). All methods involving patient activity are vulnerable to compliance overestimation including capsule counting, where the fate of the unreturned capsules can never be known for sure. This is why two objective methods were incorporated into the Helsinki Heart Study.

Gemfibrozil was analyzed semi-annually in urine with a simple and rapid colour reaction. Because of the short half-life of gemfibrozil, urine analysis can only monitor intakes from one or two preceding gemfibrozil doses. A marker was needed to indicate drug intake over longer periods and to chart medication compliance in the placebo group. A microdose (2.2 μg) of digoxin was

Table 3 Combination of the mean daily capsule count (MDCC) and urine gemfibrozil results among 1909 gemfibrozil subjects in the HHS

	Percent of positive urine gemfibrozil analyses							
	< 50%		*≥ 50% – <75%*		*≥ 75% – <90%*		*≥ 90%*	
MDCC	n	%	n	%	n	%	n	%
< 75	236	12.4	104	5.4	53	2.8	66	3.5
≥ 75% – < 90%	146	7.6	180	9.4	113	5.9	245	12.8
≥ 90%	85	4.5	144	7.5	171	9.0	366	19.2

Table 4 Combination of the mean daily capsule count (MDCC) and urine digoxin results among 1384 gemfibrozil subjects in the HHS.

	Compliance classification by the digoxin marker							
	Twice poor		*Once poor*		*Twice intermediate, good and intermediate*		*Twice good*	
MDCC	n	%	n	%	n	%	n	%
< 75%	80	5.8	80	5.8	68	4.9	35	2.5
≥ 75% – < 90%	78	5.6	96	6.9	152	11.0	188	13.6
≥ 90%	36	2.6	67	4.8	145	10.5	359	25.9

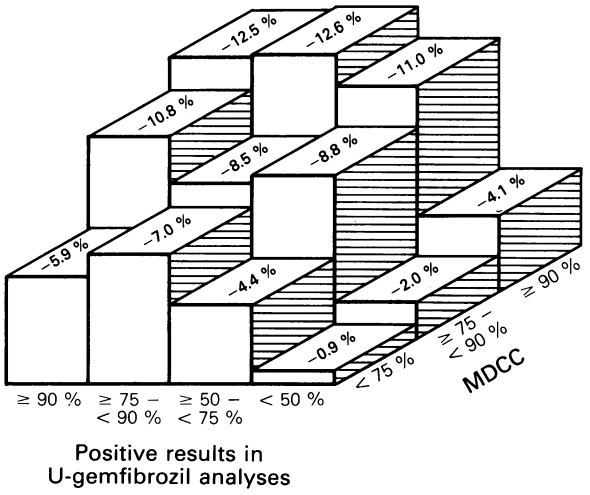

Figure 4 Mean serum total cholesterol changes among the 1909 gemfibrozil subjects of the HHS whose medication compliance was analyzed by combining the results of mean daily capsule count (MDCC) and urine gemfibrozil analyses.

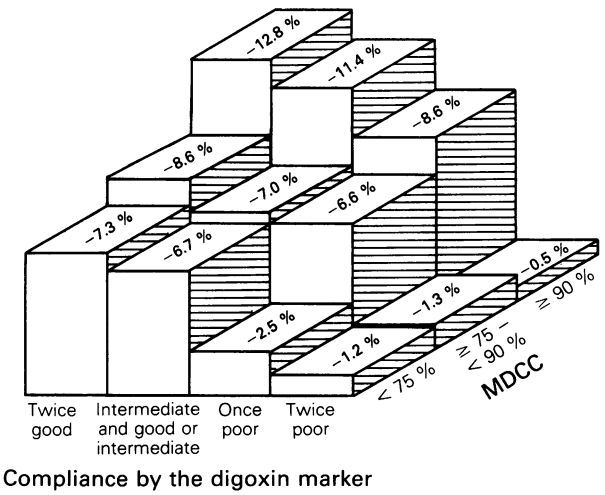

Figure 5 Mean serum total cholesterol changes among the 1384 gemfibrozil subjects of the HHS whose medication compliance was analyzed by combining the results of mean daily capsule count (MDCC) and the two digoxin marker measurements.

tested and approved for this purpose, the daily dose (8.8 μg) thus being only 3.5% of the normal therapeutic dose.

The digoxin marker appeared to be very reliable for detecting poor compliance. After 2 days scheduled drug intake in the pre-testing, none of the 15 volunteers were classified as poor compliers, although after a subsequent week's pause all fell to this class. After 9 days regular drug intake 97% of samples were classifying to the good complier group, while after 2 days pause only 1% of samples were still in this group. The digoxin marker method also improved its convenience for large, multicentre trials in that measurements were not affected by prolonged storage at room temperature, or by freezing.

To measure the medication compliance of each HHS subject for the total follow-up time three variables were formed, namely mean daily capsule count (mean of each 3 month period), percentage of positive urine gemfibrozil analyses from all semi-annual measurements, and the combined digoxin marker results from the last quarter of the third and fifth study years. These measurements revealed a wide range of compliance behaviour. At the good end of this range were the 39.5% of gemfibrozil and 41.4% placebo subjects whose mean daily capsule count was 90% or more, the 35.4% of gemfibrozil subjects whose urine gemfibrozil analyses were positive in 90% of measurements, and finally the 42.1% of gemfibrozil and 49.8% of placebo subjects whose digoxin marker analyses showed good compliance in both measurements. At the bad end of the compliance range were the 4.9% of gemfibrozil and 4.7% of placebo subjects whose MDCC was less than 50% of the scheduled dosage, the 24.6% of gemfibrozil subjects who had less than 50% positive urine gemfibrozil results, and finally the 14.0% and 11.9% of respective gemfibrozil and placebo subjects who were twice classified into the poor complier group by their digoxin marker results.

There were 4.5% of gemfibrozil subjects with a MDCC of 90% or more but less than 50% negative results in gemfibrozil analyses. In addition, 2.6% of subjects had the poor compliance classification twice in the digoxin marker analysis despite a MDCC of 90% or more. Roth *et al.* (1970) found that 10 out of 105 patients with duodenal ulcer returned less antacid bottles that would have been expected from their blood marker (sodium bromide) concentrations. The inaccuracy of capsule counting was also evident in a study comparing low-dose phenobarbitone with capsule counting. Among the 161 subjects classified as good compliers by capsule counting there were 32% whose plasma marker levels pointed to poor compliance (Pullar *et al.*, 1989).

In the Helsinki Heart Study there was a 34% reduction in cardiac end points (Manninen *et al.*, 1987). This was achieved by lowering serum total cholesterol by 10% and triglycerides by 35%, and elevating HDL cholesterol by 11% with gemfibrozil compared with placebo. Behind these average changes was a wide variation in the gemfibrozil effect which was strongly associated with the level of compliance as measured by all three methods used. For example, among those whose MDCC was 90% or more the mean reduction in serum total cholesterol was 11.4%, whereas it was only 0.02% among those with an MDCC of less than 50%. It was 11.2% among those who had 90% or more positive urine gemfibrozil analyses, and only 1.7% among those who had less than 50% positive results. Those who were good compliers twice according to the digoxin marker had a cholesterol reduction of 11.4%, whereas those who had poor results twice had a reduction of only 1.1%. It was noticed that the poorest compliers must have taken at least some of their doses because their mean changes were far better than in the placebo group, where the direction of change was mainly opposite. No association between serum lipid changes and medication compliance was detected in the placebo group.

The effect of gemfibrozil was also analyzed by combining capsule counting with either the urine gemfibrozil or the digoxin measurements. This showed that poor compliance by any of the three methods meant only minor cholesterol change, irrespective of the other results. The digoxin marker was strongest in this respect. Subjects whose MDCC was 90% or more had a mean cholesterol reduction of only 0.5% if they were also classified as poor compliers at both digoxin marker measurements; even a single poor result signalled a low cholesterol change. This dominance of poor compliance results was also clear among those whose urine gemfibrozil results were positive in less than half of the measurements. Finally, subjects in the poorest MDCC group (less than 75% of capsules consumed) also tended to have lower cholesterol changes than others, but the dominance here was less obvious. This compliance group contained subjects who had taken sufficient of the drug for some gemfibrozil effect. The discrepancy between capsule counting and urine compliance measurements can be explained by the improved compliance just preceding the visits, known from other studies (Cramer *et al.*, 1990).

In addition to the true pharmacologic effects tested in a clinical trial, the power of an intervention is affected by a human variable, study adherence. In studies of high quality this variable must be controlled as fully as possible. However, the human sources of poor compliance can also influence the compliance results, which is why the Helsinki Heart Study adopted two objective methods, urine analysis for gemfibrozil and the digoxin marker, in addition to capsule counting. The use of method combining improved the detection of poor compliance and reduced the over-estimation of good compliance. These compliance measurement methods made it possible to estimate the variation of intervention which led to an overall 34% reduction in the myocardial infarcts in the Helsinki Heart Study.

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