Compliance with medication in the Helsinki Heart Study

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Received: January 18, 1990/Accepted in revised form: June 19, 1990

Summary. Compliance with medication has a decisive influence on the findings in clinical intervention studies, so the reliable estimation of compliance is vital to the success of such research. This report describes the main findings about compliance in the Helsinki Heart Study, a five-year, double-blind, primary prevention trial of gemfibrozil as a lipid-lowering agent compared with placebo, in 4,081 dyslipidaemic middle-aged men. Three estimation methods were employed: capsule counting at every three-month follow-up visit, urine gemfibrozil analysis at six-month intervals, and, a novel technique, a digoxin marker added to both gemfibrozil and placebo capsules at the end of the third and fifth study years. The estimates of compliance for the study population as a whole generated by these three methods are discussed here.

The mean daily capsule count showed that 36% of patients on gemfibrozil and 39% of those on placebo took more than 90% of their capsules, while only 5% of both groups consumed half or less of the prescribed treatment. According to urinary gemfibrozil analysis, 30% of gemfibrozil subjects had more than 90% positive results and 28% had half or fewer positive. Among study completers, there were 42% gemfibrozil subjects and 50% placebo subjects who on both occasions had the good result in the digoxin marker analysis, while 14% of the gemfibrozil men and 12% of the placebo men scored 'poor' in both marker analyses. Capsule counting revealed a slight deterioration in compliance over the trial period, which was confirmed by the other two methods; for example, the proportion of positive results in the semiannual urine gemfibrozil analyses decreased from 76% to 65%. Medication compliance was slightly better in the placebo group according to capsule counting and digoxin marker methods.

In the Helsinki Heart Study there were 34% fewer cardiac end points among participants in the gemfibrozil group compared to placebo. The reduction occurred in a study group with 30% drop outs and with about 20% of study completers having poor medication compliance, according to all three methods.

Key words: Compliance, Digoxin marker, Helsinki Heart Study; compliance markers, capsule counting, gemfibrozil

The Helsinki Heart Study (HHS) [1, 2] was a primary prevention trial, which used gemfibrozil to investigate the effects of simultaneously lowering serum LDL-cholesterol and triglycerides, and elevating HDL-cholesterol, on the incidence of coronary heart disease among healthy middle-aged men with dyslipidaemia. Special attention was given to the measurement of compliance in order to obtain an accurate picture of compliance at different phases of the study. In addition to conventional capsule counting, two other methods were employed, namely analysis of gemfibrozil in urine, and, a new technique developed for this study, a digoxin marker added to both active and placebo medication. This report presents data on compliance determined by these methods during the 5-year, double-blind, randomized phase of the study.

Materials and methods

All 4,081 participants in the double-blind randomized study had compliance monitored throughout the trial. There were 2,046 subjects in the gemfibrozil group and 2,035 in the placebo group. During the 5 years of follow-up, 640 of the gemfibrozil group men (31.3%) and 582 (28.6%) in the placebo group dropped out of the study. Of the gemfibrozil group 14.7%, and of the placebo group 12.6% stopped during the first year of follow-up, adverse effects and motivational problems being the commonest reasons for dropping-out.

Capsule counting method

The 1200 mg dose of study medication was taken as two capsules twice daily, each containing 300 mg of gemfibrozil or placebo. For each three-month follow-up period the men received a pack of 400 capsules and they were instructed to return the unused capsules. Compliance with medication was calculated as the number of non-returned capsules divided by four-times the number of days in the follow-up period. This mean daily capsule count (MDCC %) was expressed as a percentage of the scheduled dose. A detailed description of the counting method has been published [3]. Capsules were
not returned in 6% of the visits. Altogether, 83 gemfibrozil and 73 placebo subjects left the study too early for compliance to be estimated.

Urine gemfibrozil analysis method

A single urine sample for analysis of gemfibrozil was taken at every other visit, i.e. at six-month intervals, in order to provide a qualitative measure of the intake of the preceding one or two doses. Only in 3% of visits was a urine sample not available. To minimize the possibility of unblinding the study by this procedure, urine samples from all subjects were taken and analysed, and the laboratory personnel were the only members of the study team to see the results before the trial was concluded.

Digoxin marker method

Compliance was further measured by a digoxin marker method developed for the trial. A detailed description of the method has been presented [4]. An average of 2.2 μg digoxin was added to all capsules for the last quarter of the third and fifth years of the study. After these periods, urinary digoxin and creatinine concentrations were measured in single urine sample taken at the regular follow-up visit, and their ratio was calculated. The creatinine value was used to compensate for variation in the digoxin concentration due to fluctuation in urine volume. On the basis of pilot study findings, the participants were classified into three compliance groups - good, intermediate and poor - according to two cut-off points of the urine digoxin creatinine concentration ratio. In the pilot study the cut-off point for good compliance was exceeded in 50% of samples by the third day of regular drug intake. After 9 days of regular intake, 97% of samples were classified as good compliers. After 2 subsequent days with no treatment only 1% of samples was still in this group. The cut-off point for poor compliance was chosen so that a 2 days pause was not enough to lower the ratio beyond this point. Only a break lasting a week led to classification as 'poor compliers' of all the pilot study volunteers. Following 2 days of drug intake, no sample was classified in the poor complier group. In the HHS, a urine sample for measurement was not available from 1% of determinations. Altogether, fewer than 20 subjects were taking digoxin-containing medication.

Results

Compliance determined by the MDCC% revealed that 35.7% of the gemfibrozil group and 38.5% of the placebo group took more than 90% of their capsules (Fig.1). The corresponding proportions for men taking 71–90% of their doses were 43.9% and 44.4%, and for those taking 51%–70% they were 15.2% and 12.0%. Only 5.2% of the gemfibrozil group and 5.1% of the placebo subjects consumed half or less of their capsules.

As measured by capsule counting, compliance was fairly stable over the duration of the study, although among study completers the proportion of those who took less than 75% of their capsules did rise slightly, from 15.6% (first year) to 23.5% (fifth year) in the gemfibrozil group (Fig.2). It rose from 16.7% to 20.8%, respectively, in the placebo group.

The six-monthly urinary gemfibrozil analyses also revealed a slight fall in compliance as the trial progressed (Fig.3); the proportion of positive samples decreased from 75.9% at 3 months to 64.7% at 57 months. Of those taking the active medication, 29.6% had more than 90% positive results, 27.2% had 71–90% positive results, and 15.3% had 51–70% of samples containing gemfibrozil (Fig.4). Half or fewer positive findings were recorded in 27.8% of the group. No positive results were recorded in the placebo group.

The slight decrease in compliance with mediation over time was again evident when measured by the digoxin marker (Fig.5). In the gemfibrozil group the proportion of poor compliers increased from 21.2% at the end of the third year to 25.5% at the end of the fifth study year. The proportion of intermediate compliers decreased...