Editorial

The Present Status of Clofibrate (Atromid-S)

Clofibrate (ethyl-α-p-chlorophenoxyisobutyrate or Atromid-S) has been investigated extensively since its original development, and recent progress now permits examination and appraisal of its role as a means of lowering blood and tissue lipid. The chief effect of Atromid-S is to reduce triglyceride-rich very low-density lipoproteins and, to a lesser extent, cholesterol-rich low-density lipoproteins. It is most effective in correcting those hyperlipoproteinemic states characterized by hyperglycemia and hypercholesterolemia and may be least effective in patients with familial hyperbetalipoproteinemia. The net result in a mixed population of patients with ischemic heart disease is that elevated serum cholesterol levels are reduced by 15 to 20%, on the average, and elevated serum triglyceride levels by 30 to 40%. Atromid-S also lowers serum free fatty acids.

The most impressive clinical effect of Atromid-S is the disappearance of accumulations of tissue lipid. Tuberous xanthomata regress, and hard lipemic exudates in the retinae of diabetics decrease. An increase occurs in fecal excretion of neutral sterols which continues for several months. This is not necessarily reflected in the serum level of cholesterol, although the possibility that it represents reduction of total body cholesterol is consistent with preliminary clinical observations that xanthomata can regress in the absence of consistent reduction in serum cholesterol.

In addition to these effects on lipids, Atromid-S reduces raised plasma fibrinogen and corrects decreased fibrinolysis. Abnormal platelet stickiness, platelet turnover, and platelet survival time are each altered toward normal values. Requirements for coumarin and indanedione anticoagulants are quantitatively and significantly reduced, although Atromid-S does not prolong prothrombin time in subjects not receiving prothrombin-depressant drugs.

The precise mode of action of Atromid-S is not known. It has been established that clofibrate does not require, as was first thought, to be given with androstosterone (this combination was called "Atromid") to reduce hyperlipidemia. Atromid-S is rapidly hydrolyzed by esterases to chlorophenoxyisobutyric acid (CPIB), which is bound to serum albumin and is restricted in distribution to the total albumin space. The half life of CPIB is about 12 hours; it is excreted in urine as the glucuronide. The main hypothesis which has been advanced is that binding of CPIB to albumin reduces its affinity for other acids, including thyroxine and free fatty acids (FFA), leading to an alteration in the intrahepatic and the extrahepatic balance of thyromimetic substances and of FFA. No hypermetabolic effects are seen in man or experimental animals. In rats, liver weight, protein content,
and rate of protein synthesis are increased; the number and size of mitochondria and microbodies increase, and cholesterol, glyceride, and glycogen decrease.\textsuperscript{1,2,4} It has also been suggested from studies\textsuperscript{4,5} in rats that CPIB inhibits cholesterol biosynthesis in the liver at some step prior to the synthesis of mevalonate. Endogenous production of adrenal steroid is not changed.\textsuperscript{1} There is no accumulation of desmosterol or other cholesterol precursors. Carbohydrate tolerance and nitrogen balance are unaltered.

Atromid-S is prepared in capsules and the daily dose is 1.5 or 2 g according to body weight. Nausea and mild diarrhea occur in about 5% of patients soon after they commence to take the drug, but these side effects are usually transient. Indeed, in two large therapeutic trials they have occurred as frequently in control subjects receiving the same quantity of a vegetable oil in dummy capsules. No toxic effects have been reported so far. Increases in serum glutamic-oxalacetic transaminase (SGOT) occur within a few weeks of starting Atromid-S but are transient. Bromsulphalein retention is not significantly altered. Increases in body weight, not due to fluid retention,\textsuperscript{3} occur in a minority of subjects; similar increases in weight have been seen in patients on placebo treatment in controlled trials. Patients on a constant caloric intake in a metabolic ward do not gain weight. A decrease of total white blood cells has been reported, although not beyond the normal range. No specific laboratory tests, apart from serial measurements of serum lipids, are necessary during therapy with Atromid-S.

In the present state of knowledge, Atromid-S can be regarded as an effective and safe drug for lowering elevated lipids without the need for any dietary restrictions. Before it is prescribed for individual patients, an attempt should be made to classify their lipid disorder and determine their suitability for this treatment. A minimum should be the estimation of serum cholesterol and triglycerides, and preferably typing of the lipoprotein abnormality should be included. The principal indications for the use of Atromid-S at present are (1) patients with hypercholesterolemia and hyperglyceridemia with or without xanthomata, (2) patients with fasting lactescent plasma, (3) patients with hypercholesterolemia with or without a family predisposition to vascular disease, although the lipid response in this third category will probably be less than that in the first two, and (4) diabetic patients with lipemic exudative retinopathy in order to prevent further deterioration in visual acuity. There is insufficient evidence of the value of the drug to advocate its use yet for patients with ischemic heart disease or peripheral vascular disease without hyperlipidemia, or those with secondary hyperlipidemias due to myxedema or nephrosis. There are, however, as yet no contraindications for its use. Atromid-S may operate over many months before large tissue cholesterol pools are reduced and therefore should be given for at least a year before it is assumed that a given patient is unresponsive. Serial analysis of serum lipids should be undertaken, and once significant lowering has occurred, the drug should be given indefinitely.

Clinical experience with Atromid-S now extends to 6 years, and it is estimated that 3,000 patients have received the drug for 2 or more years. Personal experience indicates that it produces sustained reduction of serum lipids for periods up to 4 years. Atromid-S is being used as a means of testing whether reduction of hyperlipidemia improves prognosis in patients with ischemic heart disease. In Britain, two large scale trials of its effects on reinfarction and death (secondary prevention trials) have been in progress for 3 years; in a third trial it is being used in patients with peripheral vascular disease. In the U.S.A., Atromid-S is one of four drugs under evaluation in the Cooperative Coronary Heart Disease Drug Project.

The real purpose, however, of any lipid-lowering regime is to reduce the prevalence of ischemic heart disease and this can be demonstrated only through primary prevention trials. Such a trial was started in Edinburgh 2 years ago and will shortly be ex-
tended to Prague and Budapest. Healthy men without ischemic heart disease, mostly blood donors, are being studied. Two thirds of them have been selected on account of hyperlipidemia and have been randomized into two groups receiving either Atromid-S or olive oil as a blind placebo. One third have been selected because of low lipid levels; these men form an additional control group, and all receive olive oil. Clinical and electrocardiographic examinations, serum lipid estimations, and Atromid-S blood levels are made every 6 months. An assessment of progress will be undertaken after 5 years when it should be possible to decide whether correction of hyperlipidemia, by this particular method, provides any degree of control over the incidence of ischemic heart disease. M. F. OLIVER

References

Graves on the Nobility of Physicians (1848)
And thus it will be proved that if man has passions which impel him to the destruction of man, if he be the only animal who despising his natural weapons for attack or defence, has devised new means of destruction,—he is also the only animal who has the desire or the power to relieve the sufferings of his fellow-creatures; the only animal in whom the co-existence of reason and benevolence attests a moral as well as an intellectual superiority.—ROBERT J. GRAVES: Clinical Lectures on the Practice of Medicine, ed. 2, vol. 1. Dublin, Fannin and Co., 1848, p. 44.
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