The influence of mevinolin on the adrenal cortical response to corticotropin in heterozygous familial hypercholesterolemia

(low density lipoprotein/hydroxymethylglutaryl-CoA reductase/hypolipidemic agents)

D. Roger Illingworth and Debra Corbin

Division of Endocrinology-Metabolism and Clinical Nutrition, Departments of Medicine and Biochemistry, and The Clinical Research Center, The Oregon Health Sciences University, Portland, OR 97201

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ABSTRACT The biosynthesis of adrenal corticosteroids in humans depends on a continuous supply of cholesterol, which can be derived from both local synthesis and receptor-mediated uptake of low density lipoproteins (LDL) from plasma. Mevinolin, an inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase [mevalonate:NAD\(^+\) oxido-reductase (CoA-acylating), EC 1.1.1.88] is an effective hypolipidemic agent in patients with heterozygous familial hypercholesterolemia. To determine whether mevinolin influences the adrenal production of corticosteroids, the adenocortical response to a continuous 36-hr infusion of corticotropin (ACTH) was examined in eight patients with heterozygous familial hypercholesterolemia before, and again during, treatment with mevinolin (40–80 mg/day). The drug produced an average decrease of 28% and 34% in the plasma concentrations of total and LDL cholesterol. Serum cortisol levels showed similar increases in response to ACTH stimulation before and during mevinolin treatment, and the rates of excretion of urine-free cortisol were also similar. We conclude that clinically effective doses of mevinolin do not affect corticosteroid production by the adrenal cortex during prolonged ACTH stimulation in patients with heterozygous familial hypercholesterolemia.

METHODS

Study Subjects. All studies were conducted in the Clinical Research Center of The Oregon Health Sciences University. Informed consent was obtained from all patients and the protocol was approved by the Human Research Committee of this institution. The subjects consisted of eight patients with well-characterized heterozygous FH in whom currently available lipid-lowering medications had failed to lower serum cholesterol concentrations below 300 mg/dl. In all patients, the diagnosis of heterozygous FH was based on primary hypercholesterolemia, an inheritance pattern consistent with autosomal dominant, tendon xanthomas, and the presence of primary hypercholesterolemia in other family members with an absence of multiple phenotypes in other relatives. The characteristics of the study subjects (four males and four females) are outlined in Table 1. All the subjects were without clinical or laboratory evidence of renal, hepatic, or endocrine dysfunction, and none was obese. Three patients (cases 1, 4, and 5) were on therapy for hypertension and two (cases 2 and 6) were receiving propranolol and nifedipine for angina. No change in medications occurred in any patient between the base-line period of study and the repeat studies under steady-state conditions during therapy with mevinolin.

Experimental Procedures. Blood samples for lipid studies were drawn into tubes containing EDTA (1 mg/ml), and the plasma was analyzed for cholesterol and triglycerides with the Autoanalyzer II (19). Lipoproteins were separated by heparin manganese precipitation according to Lipid Research Clinic procedures (19). Blood samples for hormone assays were drawn with the patient in a recumbent position and were collected into tubes without anticoagulant. Concentrations of...
To determine whether therapy with mevinolin was associated with any impairment in steroid hormone production in vivo, the adrenal response to ACTH stimulation was evaluated in each patient prior to therapy with mevinolin and again under steady-state conditions on optimal doses of mevinolin. In each case, the adrenal response to a continuous 36-hr infusion of α-ACTH-(1–24) (Cortrosyn) was determined. The initial concentrations of serum cortisol were similar in patients before and during mevinolin therapy, and, as illustrated in Fig. 1, rapid increases in the concentrations of serum cortisol occurred in response to ACTH stimulation in the patients under both basal conditions and during therapy with mevinolin. Under both circumstances, serum concentrations of cortisol increased rapidly over the first 4–6 hr of ACTH infusion and then showed a much slower but progressive increase. Although the mean serum concentrations of cortisol obtained during mevinolin therapy were slightly higher than those obtained under basal conditions, the difference is not statistically significant. Changes in the rates of urinary excretion of free cortisol were also determined in timed collections obtained during ACTH stimulation under basal conditions and upon restudy while the patients were taking mevinolin. As illustrated in Fig. 2, excretion of urine-free cortisol over three consecutive 12-hr time periods as well as the cumulative 36-hr excretion was similar under both circumstances. On an individual basis, total excretion of urine-free cortisol over the 36-hr period of ACTH stimulation decreased in six patients and increased in two during mevinolin therapy, as compared to the rates of excretion during ACTH stimulation under basal conditions.

**DISCUSSION**

The production of adrenal corticosteroids during prolonged ACTH infusion requires a continuous supply of cholesterol, which can be derived from both local synthesis and receptor-mediated uptake of LDL (1–5). Previous studies have established that the adrenal cortical response to prolonged ACTH infusion is impaired in patients with both abetalipoproteinemia (6, 7) and homozygous FH (8), but it is normal in patients with heterozygous FH (9). The relative contributions of de novo cholesterol biosynthesis and receptor-mediated uptake of LDL in the provision of adrenal cholesterol to patients with the latter disorder is, however, unknown. The purpose of the present study was to determine whether or not clinically effective doses of mevinolin, a specific inhibitor of HMG-CoA reductase, influences the adrenal cortical response to prolonged stimulation with ACTH in patients with heterozygous FH.

The possibility that drugs that inhibit cholesterol biosynthesis may also inhibit steroid hormone production has been addressed by several investigators (11, 25, 26), although none have examined whether the adrenal cortical response to

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**Table 1. Characteristics of the study subjects**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Xanthoma</th>
<th>Corneal arcus</th>
<th>CAD</th>
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<tbody>
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<td>31</td>
<td>68</td>
<td>+</td>
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</table>

CAD, coronary artery disease: +, present; −, absent.

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**Table 2. Plasma lipid and lipoprotein concentrations at base line and during mevinolin treatment**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total cholesterol</th>
<th>VLDL cholesterol</th>
<th>LDL cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglyceride</th>
<th>Mevinolin dose, mg/day</th>
<th>Duration of therapy, weeks</th>
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<td>18</td>
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VLDL, very low density lipoprotein; HDL, high density lipoprotein.
prolonged ACTH infusion is impaired. The importance of providing a sustained maximal stimulus to the adrenal cortex is well illustrated by our previous studies in patients with abetalipoproteinemia (6, 7) and homozygous FH (8) in whom the basal rates of excretion of adrenal corticosteroids were normal but the response to prolonged ACTH infusion was impaired. In studies conducted two decades ago, Ford (25) documented a small decrease in the urinary excretion of corticosteroids and in the serum concentrations of hydrocortisone following ACTH stimulation in a group of hypercholesterolemic patients treated with Triparanol [MER29, an agent that inhibits a late stage in the biosynthesis of cholesterol (27)] as compared to parallel studies conducted in the same patients studied on no medications. Tobert et al. (11) noted small decreases in the rates of excretion of 17-hydroxy and 17-ketosteroids as well as in the plasma concentrations of testosterone and cortisol in a group of normal male subjects given mevinolin for a period of 1 month. In a recent study, Yamaguchi et al. (26) performed rapid ACTH tests in 11 hypercholesterolemic patients studied on no medications and then restudied under steady-state conditions during therapy with compactin. Serum cortisol concentrations were determined prior to administration of ACTH and 1 hr later; the mean increment in serum cortisol after ACTH was found to be higher when the patients were receiving compactin than prior to therapy with this drug. These results, which were obtained in a heterogeneous group of patients, differ from those obtained in the present study in which the rates of increase in serum cortisol following ACTH stimulation were similar in patients studied under basal conditions and then restudied under steady-state conditions on optimal doses of mevinolin. Similarly, we found no differences between the rates of excretion of urine-free cortisol during prolonged ACTH infusion in FH patients studied under basal conditions and during mevinolin therapy. These results demonstrate that clinically effective doses of mevinolin exert no adverse effect on the adrenal cortical response to prolonged ACTH stimulation in patients with heterozygous FH.

Recent studies have indicated that the hypocholesterolemic effects of mevinolin in patients with heterozygous FH result primarily from an increased rate of receptor-mediated catabolism of LDL but that a small reduction in LDL synthesis may occur concurrently (16). The stimulation of receptor-mediated LDL catabolism is believed to result from an increased number of high-affinity LDL receptors present on the plasma membrane of cells, within which mevinolin has inhibited cholesterol biosynthesis. The extent to which HMG-CoA reductase is inhibited in different tissues of the body is, however, unknown and the normal adrenal cortical response to ACTH stimulation observed in the present study may be attributable to at least two possibilities. First, cellular uptake of mevinolin by the adrenal cortex may be very low, and at clinically effective doses (20-40 mg daily) the drug may exert no effect on HMG-CoA reductase in the adrenal cortex. Alternatively, if HMG-CoA reductase in the adrenal cortex of FH patients is inhibited by mevinolin, compensatory increases in the number of high-affinity LDL receptors on adrenal cortical cell membranes (or possibly in the mass of enzyme protein) are sufficient to ensure an adequate supply of cholesterol for corticosteroid production. The lack of effect of mevinolin on ACTH-stimulated adrenal corticosteroid production is also consistent with a recent report in which the hypocholesterolemic effects of mevinolin were found to occur without significant reductions in whole body cholesterol biosynthesis assessed by sterol balance techniques (28).

Although our data indicate that clinically effective doses of mevinolin do not adversely influence the adrenal cortical response to ACTH stimulation in patients with heterozygous FH, we believe further studies are needed to assess whether this is also true in patients homozygous for this disorder. Patients with homozygous FH show a modest impairment in adrenal cortical response to prolonged ACTH stimulation (8), and in these patients, provision of cholesterol necessary for adrenal corticosteroid production is dependent on de novo synthesis and, possibly, low-affinity receptor-mediated uptake of LDL from plasma. If significant uptake of mevinolin by adrenal cortical cells occurs in these patients, inhibition of HMG-CoA reductase would not result in compensatory increases in the number of high-affinity LDL receptors, and adrenal corticosteroid production under stimulated conditions may be compromised.

![Graph](image-url)  
**Fig. 1.** Changes in the serum concentrations of cortisol during ACTH infusion in patients with heterozygous FH studied before (O) and during (•) treatment with mevinolin. Results are expressed as the mean ± SEM from studies in eight patients.

![Graph](image-url)  
**Fig. 2.** Excretion of urine-free cortisol during ACTH infusion in patients with heterozygous FH studied before and during treatment with mevinolin. Cumulative excretion over the 36-hr infusion in individual patients is shown by the single lines and the mean ± SEM from all eight patients is shown by the bar graph.
In conclusion, our results indicate that mevinolin in clinically effective doses of 20–40 mg twice daily does not influence the adrenal cortical response to prolonged ACTH infusion in patients with well-characterized heterozygous FH. These results strengthen the view (28) that treatment with mevinolin lowers LDL cholesterol levels without leading to a significant depletion of cellular cholesterol in patients with heterozygous FH.

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