Hypocholesteremic Effect in Man of Benzmalecene: An Inhibitor of Cholesterol Biosynthesis. (25404)

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Benzmalecene, N-(1-methyl-2,3-di-p-chlorophenylpropyl)-meleamic acid (α isomer), has been shown by Huff and Gilfillan(1) to inhibit *in vitro* incorporation of mevalonic acid into cholesterol. These investigators also have demonstrated that benzmalecene lowers serum cholesterol when administered to rats(1). To determine the effect of benzmalecene in human subjects, it was administered to a group of patients for periods varying from one to 7 weeks.

Procedure. Nine patients were given 500-1000 mg of benzmalecene (free acid or the sodium salt)* per day for 10 to 53 days. Serum cholesterol levels were determined and measurements of hepatic, renal and hematopoietic function were made before, during and after benzmalecene treatment. Temperature, blood pressure, pulse, weight, appetite and urinary output were closely followed. Patients were studied in the hospital and were on the regular hospital diet, except when salt restriction was necessary. No other medications or dietary supplements known to have a hypocholesteremic effect were administered during study. All 9 patients had coronary artery disease; in addition, one had primary bronchogenic carcinoma, and one diabetes mellitus. Six had elevated serum cholesterol levels. Ages of the patients ranged from 37 to 81 years. Benzmalecene was administered either as the sodium salt or the free acid in amounts of 250 or 500 mg twice a day, after breakfast and in the afternoon. Two or more serum total cholesterol and cholesterol ester determinations were made before starting benzmalecene. Thereafter, determinations were made 2 or 3 times a week while patients were receiving benzmalecene, and at periodic intervals after cessation of treatment. Tests of renal, hepatic and hematopoietic function were performed once a week. Serum total cholesterol and cholesterol ester levels were done by the Schoenheimer-Sperry method(2).

Results. The effect of benzmalecene on serum cholesterol was evaluated in 6 of the 9 subjects studied. One patient began to show a lowering of serum cholesterol while on benzmalecene but left the hospital after only 8 days of treatment. Two patients developed laboratory evidence of possible toxic side-effects of benzmalecene and its effect on serum cholesterol was therefore obscured. In 6 patients serum total cholesterol levels were lowered 11.4 to 25.3%, the average being 18 $\pm$ 4.67% (Table I). This drop was statistically significant at the 0.01 level. The 5 patients receiving either 1000 mg of the benzmalecene free acid or 500-1000 mg of the sodium salt per day had decreases of 15% or more. Depression of serum cholesterol level occurred within a week after the drug was begun; after discontinuance of benzmalecene it took approximately a week for serum cholesterol to return to control values. None of the patients who received the benzmalecene had any complaints attributable to the drug. Appetite and body weight were not affected. The 2 patients who developed laboratory evidence of possible toxicity had ester decreases to a greater degree than total cholesterol and an eosinophilia of 12% and 16% respectively. One patient became slightly icteric and complained of generalized pruritis. He was receiving chlorpromazine concurrently and withdrawal of both medications was followed by clearing of jaundice and disappearance of pruritis. These manifestations may have been due to chlorpromazine since they did not recur with a subsequent 4 day "challenge" with benzmalecene. The other patient was on no other medication at time of study and sodium sulfobromophthalein (BSP) retention at 45 minutes increased from 8% to 21% during benzmalecene treatment. Three

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TABLE I. Changes in Serum Total Cholesterol during Administration of Benzmalecene.

Age (yr) and sex of patients		Medication	Dose/day	Avg control* serum total cholesterol, mg % (range)	Avg % decrease	Range of levels during treatment, mg %
72	♂	Sodium benzmalecene	1000	278 (274–282)	19.4	257–208
81	♀	Benzmalecene (free acid)	750	200 (198–202)	11.4	202–164
58	♂	*Idem*	1000	299 (293–308)	17.0	256–240
68	♀	"	"	318 (304–332)	25.3	245–229
53	♀	"	"			
		Sodium benzmalecene	500–1000	274 (255–292)	15.5	293–189
66	♀	*Idem*	500	282 (275–290)	19.8	256–202

* Two or more successive determinations.

other patients had depressions of serum alkaline phosphatase levels from control values of 7-10 to 1.5-3.0 King-Armstrong units.

Discussion. Benzmalecene appears to be an effective hypocholesteremic agent in man. There was no evidence of escape from the effect of the medication in these studies, but there seemed to be a definite minimal dose level below which an appreciable hypocholesteremic response could not be obtained. Two of the benzmalecene treated patients (one on chlorpromazine concurrently) developed evidence of possible liver toxicity and eosinophilia. Blondheim(3) has reported probenecid inhibition of BSP excretion in normal human subjects receiving probenecid. The similar pharmacologic action of benzmalecene and probenecid may well explain this effect of benzmalecene. However, the excessive reduction in esterified cholesterol and the eosinophilia occurring in 2 of the patients under study seem best explained as possible toxic manifestations of the drug. Peck has noted elevation of alkaline phosphatase levels and increased BSP retention in dogs given benzmalecene orally in relatively high doses. In these animals the alkaline phosphatase elevations returned to control levels on continued therapy with the same dose (personal communication).

Summary. Benzmalecene in 0.5-1.0 g/day of the free acid (or sodium salt) was studied in 6 patients for 10 to 53 days. Serum total cholesterol levels in this group were decreased by an average of 18%. Accordingly, this drug shows promise as serum cholesterol depressant. However, treatment with benzmalecene was associated with decreases in serum alkaline phosphatase and a drop in cholesterol ester levels in disproportion to decrease of serum total cholesterol. These changes as well as occurrence of eosinophilia in 2 subjects suggest that benzmalecene in amounts used in this study may prove to be too toxic for clinical use.

1. Huff, J. W., Gilfillan, J. L., PROC. SOC. EXP. BIOL. AND MED., 1960, v103,

2. Schoenheimer, R., Sperry, W. M., *J. Biol. Chem.*, 1934, v106, 745.

3. Blondheim, S. H., *J. Appl. Physiol.*, 1955, v7, 529.

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