FONDAZIONE
GIOVANNI
LORENZINI

IX INTERNATIONAL SYMPOSIUM ON
DRUGS AFFECTING LIPID METABOLISM

Fiorence (Italy), October 22-25, 1986

Palazzo dei Congressi
Piazza Adua, 1

ABSTRACT BOOK

EFFECT OF MK-733, AN INHIBITOR OF HMG-CoA-REDUCTASE, ON SERUM LIPIDS IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

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Recently a new class of fungal metabolites that are potent competitive inhibitors of HMG-CoA-reductase have been shown to be effective on lowering plasma concentrations of LDL-cholesterol. The purpose of this study was to estimate tolerability and efficacy of various doses of Synvinolin (MK-733, [1S-[1α,3α, 7β, 8β(2S*, 4S*), 8αβ]]-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2,2-dimethylbutanoate) in hypercholesterolemic patients.

16 patients (5 ♀, 11 ♂), aged 21 - 62 years, with hypercholesterolemia type II a (10 x) and type II b (6 x) were treated after giving informed consent. After being at least for 12 weeks on diet and after a single-blind placebo period of 2 weeks patients received on a double-blind basis 1.25, 2.5, 5.0, 10.0, 20.0 and 40.0 mg twice daily, or placebo. Safety, tolerability and efficacy were assessed by clinical and laboratory measurements weekly. Doses of 5, 10, 20 and 40 mg b.i.d. for 4 weeks induced a mean reduction of total cholesterol of 33.2 % (26.6 - 46.6 %) in 8 patients. Mean reduction of LDL-cholesterol amounted to 41.9 (29.5 - 46.6 %). The decrease of cholesterol was evident after one week of treatment and nearly complete after two weeks. The effect of the 40.0 mg b.i.d. dose was only slightly greater than the 10.0 and 20.0 mg b.i.d. dose. HDL-cholesterol and triglycerides were not influenced significanty. The compound was tolerated well and no serious clinical and laboratory side effects were observed, but the present study is considered as not informative as to the safety of the drug. Its safety would have to be clearly established before routine clinical use of Synvinolin is serious contemplated in the treatment of hypercholesterolemia.

SRI-62320: HYPOLIPOPROTEINEMIC EFFECTS OF A POTENT HMG-CoA REDUCTASE INHIBITOR

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Since the results of Lipid Research Clinic's Coronary Primary Prevention Trial with Cholestyramine, there has been heightened interest in the development of safe and effective hypolipoproteinemic agents. Efforts at Sandoz Research Institute in the design and synthesis of novel HMG-CoA reductase inhibitors have led to SRI-62320: [R*,S*-(E)]-(±)-Sodium-3,5-dihydroxy-7-[3-(4-fluorophenyl)-1(1-methylethyl)-1H-indol-2-yl]-hept-6-enoate, which shows marked effects in lowering several lipid parameters in rats, dogs and monkeys. The hypolipoproteinemic properties of SRI-62320, in comparison to compactin, will be the subject of this presentation.