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RESPONSE OF ISCHEMIC HEART DISEASE TO CHONDROITIN SULFATE-A*

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ABSTRACT: **One hundred and twenty patients with demonstrable ischemic heart disease (IHD) or coronary heart disease (CHD) —suggested designation, ischemic coronary disease (ICD)— were divided into two groups of 60 patients each and observed for a study period of two and a half years. Treatment was randomly assigned, and comparisons were made on the basis of clinical evaluation and mortality and morbidity rates. Sixty patients were treated with the acid mucopolysaccharide, chondroitin sulfate-A (CSA), in addition to regular medicinal and dietary regimens. Sixty comparable patients serving as controls were not given CSA, but otherwise were treated under similar dietary and medicinal regimens. CSA was given orally in tablet form; the initial dosage of 10 gm daily was reduced to 1.5 gm daily, and was well tolerated by all patients. No abnormal laboratory or clinical findings and no toxicity or side effects from CSA were noted.**

At the end of the 2.5-year observation period, 21 of the 60 ICD patients in the control group had experienced acute cardiac episodes or myocardial ischemia; of these, 4 were fatal. The 17 survivors were hospitalized—7 with myocardial infarction, 7 with acute myocardial ischemia or coronary insufficiency, and 3 with non-critical or transient myocardial ischemia. In the matched CSA-treated group of 60 ICD patients, there were 5 deaths. Autopsies were conducted in all cases. One patient with myocardial ischemia died from a myocardial infarction. A

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second patient who died from myocardial infarction had persistent hypertension which often was difficult to control. A third patient, who had chronic atrial fibrillation and flutter, died from coronary insufficiency and cardiac congestive failure following a massive cerebrovascular hemorrhage. Two other patients died from non-cardiac causes—one from a malignant cerebral astrocytoma, and the other from a skull injury which induced ventricular fibrillation. The surviving 55 patients of this group have not required treatment or hospital admission for acute cardiac symptoms or recurrent cardiac illness.

The ratio of 21:3 for coronary episodes in the CSA group versus the non-CSA group warrants further studies with caid mucopolysaccharides such as CSA and CSC. This would involve statistically designed and controlled studies on large groups of patients and possibly on sections of the normal adult population. These data could be invaluable in determining the feasibility of the therapeutic use of acid mucopolysaccharides for the prevention and treatment of ischemic coronary disease.

Ischemic heart disease, coronary heart disease or coronary artery insufficiency of a degree sufficient to impair the blood supply of the heart muscle is but another clinical manifestation of localized atherosclerosis for which no effective therapeutic agent has been found.

This report concerns preliminary impressions gained in a "feasibility" pilot study during which 60 patients with ischemic or coronary heart disease (IHD or CHD) were treated for a period of two and a half years by oral administration of chondroitin sulfate-A (CSA), a naturally-occurring acid mucopolysaccharide.

CSA therapy was started in these patients after Morrison and co-workers observed the anti-atherogenic properties of this naturally-occurring ingredient of connective tissue in rats (1), rabbits (2) and monkeys (3), and its anti-thrombotic effects, both in vivo (4a) and in vitro (4b), in rabbits (2b), dogs (5) and humans with cerebral and/or coronary atherosclerosis (6).

When the data on the therapeutic properties of CSA in the foregoing species of animals are transposed to patients with IHD or CHD, at least two main processes are involved in the clinical manifestations. It is not within the province of this paper to discuss the various concepts of atherosclerosis and thrombosis, in some of which arterial thrombosis is regarded as a preliminary or primary step in the pathogenesis of atherosclerosis.

For the purposes of clinical evaluation, we attached great importance to the following observations: 1) Coronary-artery atherosclerosis is found in at least 90 per cent of cases of coronary occlusion (with or without myocardial infarction), coronary insufficiency, or myocardial ischemia. 2) When the coronary artery is occluded or partially obstructed, a second process is evi-

dent, viz, the formation of an intraluminal thrombus, primarily by elements of the circulating blood.

In this study, no precise clinical distinction could be made between these associated pathological processes. Therefore only a clinical assessment is offered, on the basis of objective observations on acute cardiac and coronary episodes.

The term ischemic coronary disease (ICD) is proposed for describing insufficiency of blood flow to the myocardium, and is employed in this paper. It denotes not only the presence of coronary artery disease ("silent" atherosclerosis involves the coronary arteries in the majority of North American adults) but progression of the atherosclerosis process to the stage of a clinically and/or electrocardiographically demonstrable abnormality. The term ICD is suggested because the term ischemic heart disease may denote abnormal cardiac states other than those due to coronary atherosclerosis.

MATERIAL AND METHODS

The study included 120 patients with electrocardiographically demonstrable coronary-artery heart disease and/or past myocardial infarction, who had been treated for these conditions during periods varying from six months to twenty years. They were divided into two groups of 60 patients each, matched as closely as possible for age, sex, and clinical and laboratory findings. Their order of entry into the study was as they presented themselves in clinical practice. All pre-test comprehensive therapeutic regimens were continued or expanded. These regimens consisted of various combinations of anticoagulant therapy (oral), low-cholesterol diet, low-sugar and unsaturated-fat foods, sodium restriction when indicated, coronary and systemic vasodilators, tranquilizers, sedatives, vitamin supplements and nutritional supplements (including highly unsaturated oils and fats).

Chondroitin sulfate-A was prepared from bovine tracheal cartilage obtained from commercial sources and purified in our laboratories. Analysis of this material showed a typical chondroitin sulfate infrared spectrophotometric adsorption curve. Optical rotation determinations gave values of (a) 24_D-24°. The nitrogen content was 3.95 per cent (average), the sulfur content was 4.3 per cent (average), and the sedimentation constant was 1.6.

Sixty patients were given CSA orally, the daily dose ranging from an intitial 10 gm to the currently employed 3.0 or 1.5 gm in tablet form (*Group I*). Sixty other patients served as non-CSA controls (*Group II*).

The average age of the Group I patients at the beginning of treatment was 65 years (range, 44 to 86 years). There were 44 females and 16 males. Forty patients had angina, and 13 had had one or more myocardial infarctions.

For the 60 patients who served as controls (Group II), the average age was 66 years (range 39 to 83 years) at the start of the study. There were 35 females and 25 males. Thirty-nine patients had angina, and 15 had had one or more myocardial infarctions.

Laboratory estimations were usually performed every one to two months in most patients. These consisted of a complete blood count, erythrocyte sedimentation rate, urinalysis, and determination of serum protein-bound iodine, I^{131}-labeled triiodothyronine, sodium, potassium, thymol turbidity, glutamic oxalacetic transaminase,

TABLE 1

Duration of CSA Treatment and Number of Deaths from Cardiac Cause since Beginning of Study, for 120 Patients with Ischemic Coronary Disease (ICD)

Duration of CSA Treatment (months)	Controls (N = 60)	CSA-Treated (N = 60)
6-11	21	16
12-17	6	6
18-23	7	8
24-30	26	30
Number of deaths	4*	3**
Mean duration of CSA treatment (months)	18.0	17.7
Total months treated (all cases)	1060	1077

* 3 deaths from myocardial infarction and 1 from a ruptured abdominal aneurysm and coronary thrombosis with infarction.

** 2 deaths from myocardial infarction and 1 from acute coronary insufficiency.

glutamic pyruvic transaminase, bilirubin (direct and indirect), calcium, phosphorus, creatinine, total protein, albumin, globulin, blood glucose, urea nitrogen, uric acid, alkaline phosphatase, cephalin flocculation, serum cholesterol and beta-lipoprotein.

Chest roentgenograms and "resting" electrocardiograms were obtained in each case. Master exercise electrocardiograms were obtained on most patients. Ophthalmological examinations were conducted by quality ophthalmologists in all cases. Photographs of the microcirculation in the conjunctival vessels were made in 27 patients.

No abnormal laboratory (including liver function) findings were noted in patients receiving CSA for the 2.5-year period. No toxic or side effects from CSA have been noted to date.

Such coronary risk factors as hypertension, obesity, diabetes, and heavy tobacco smoking appeared to be equal in both groups. No significant preponderance of any one of these risk factors was evident in either group of patients.

Table 1 shows the duration of treatment and the number of cardiac deaths in each series of 60 patients.

RESULTS

Anatomically, ICD reduces the diameter of the lumen (area for free blood flow) of the coronary artery and its branches. The reduction ranges from that caused by a small atherosclerotic plaque to a narrowing significant enough to impair or obstruct the flow of nutrient blood to the heart muscle.

In this study, the acute episodes of ICD were classified according to four grades of severity for both groups of patients. Group II (control, no CSA therapy) is considered first:

Group II—60 control patients with ICD

1. *Fatal coronary occlusion (with myocardial infarction)*; complete obstruction of a coronary artery with ensuing death—4 patients. Each died

suddenly of an acute cardiac attack, registered on 3 of the death certificates by physicians other than the author (2 patients died out of town and 1 died during the author's absence from the city). Two of these patients were males, aged 71 and 76. The 2 females were aged 79 and 65. Three of the patients died during the first year of observation, and 1 died after one and a half years of observation. All 4 had been receiving some combination of the therapeutic regimens for ICD previously described. One patient had been taking an anticoagulant (orally) for a year and had been under the constant care of several cardiologists; blood thrombin levels had been well controlled at 15–30 per cent. All 4 patients had angina pectoris intermittently before death. Three had had a previous myocardial infarction.

2. *Non-fatal myocardial infarction*—7 patients. These 7 patients were hospitalized and treated for their attacks in the intensive coronary-care units of local Los Angeles hospitals. Four were males, average age 63 (range, 49 to 74). Three were females, average age 79 (range, 75 to 83). None was receiving anticoagulant therapy before the attack. Three had had a previous myocardial infarction.

3. *Acute myocardial ischemia or acute coronary insufficiency without myocardial infarction*—7 patients. All were admitted to the intensive coronary-care units of Los Angeles hospitals. Some of the admitting physician's

TABLE 2

Comparison of CSA-Treated and Control (no CSA) Patients, Before and During Study

	CSA-Treated (N = 60)*			Controls (N = 60)*		
	Male	Female	All	Male	Female	All
			Before Study			
Mean age (yrs.)			65			66
Patients with angina	15	25	40	19	20	39
Patients with hypertension	6	20	26	8	19	27
Patients with previous myocardial infarction	7	6	13	12	3	15
Patients receiving anticoagulant therapy	6	3	9	7	3	10
			During Study			
Myocardial infarctions:						
fatal	1	1	2	2	2	4
non-fatal	0	0	0	4	3	7
Patients hospitalized for acute coronary insufficiency	0	1 (fatal)	1	3	4	7
Patients with myocardial ischemia (hospitalized transiently)	0	0	0	0	3	3
Total, acute cardiac incidents	1	2	3	9	12	21

* Current "coronary" treatment program included combinations of oral anticoagulant drugs, vasodilators, diets and other established drugs in approximately equal proportions for both groups of patients.

diagnoses were: "threatened" or "impending" myocardial infarction, "protracted angina pectoris," or "status anginosus." All 7 patients recovered, though a year later one of them had a massive myocardial infarction requiring hospital care. These 7 control patients are still under observation and the previously described therapeutic regimens are being continued. The average age for the 3 males and 4 females was 65 years (range, 29 to 82).

4. *Myocardial ischemia*—3 patients. These patients were admitted to the hospital for treatment but their clinical condition, circulatory state, and ECG and other findings were not sufficiently abnormal to require admission to an intensive coronary-care unit. All 3 were females, average age 63 (range, 55 to 75).

In Table 2 is a summary of the mortality and morbidity data for the 2.5-year observation period on these 60 patients with ICD, of whom 20 required hospitalization for cardiac care.

Group I—60 CSA-treated patients with ICD

1. *Fatal coronary occlusion with myocardial infarction*—2 patients. The first patient was a male aged 68, who had a 20-year history of intermittent angina pectoris and had been treated by several cardiologists other than the author and associates. Autopsy revealed extensive chronic diffuse coronary atherosclerosis. This patient's regimen had included a strict diet (low-sodium, low-cholesterol, low-sugar), coronary-artery vasodilators, sedatives, tranquilizers, vitamins and anticoagulant therapy. Anticoagulants had been given for seven years, with maintenance of blood prothrombin levels between 12 and 30 per cent most of the time. The dosage of CSA had been erratic. CSA had been discontinued twice in the four months before death because the supply was exhausted. Initially the dosage was 3 gm daily, subsequently reduced to 1.5 gm daily.

The second patient was a woman aged 65 who had had persistent hypertension which often was difficult or impossible to control.

2. *Fatal acute coronary insufficiency*—1 patient. This woman, aged 78, died from coronary insufficiency and cardiac congestive failure—the terminal complications of a massive cerebrovascular hemorrhage. She had had chronic atrial fibrillation and flutter, and a history of chronic angina pectoris.

3. *Fatal ventricular fibrillation* after a skull injury—1 patient. This man, aged 77, had a history of chronic intractable atrial fibrillation and flutter, and angina pectoris. His head injury was the result of a fall. He was admitted, unconscious, to an intensive care unit of the Connecticut General Hospital. The autopsy report gave the cause of death as ventricular fibrillation (clinical and electrocardiographic during life), intramural hemorrhages in the coronary arteries, coronary atherosclerosis and lacerations of the skull. For more than a year before death, the patient had been treated with anticoagulants by an out-of-town physician who had discontinued CSA therapy during this period. The patient had been taking 1.5 gm of CSA daily inter-

mittently for more than a year, but discontinued it for the year preceding his death.

Many Group I patients had had to go without CSA medication for short periods (a few days to a few weeks) because of a temporary lack of supplies or because of a transitory episode of upper respiratory-tract or gastrointestinal infection.

4. *Fatal malignant cerebral astrocytoma*—1 patient. At operation and at autopsy, this 63-year-old woman was found to have a malignant cerebral astrocytoma with central-nervous-system necrosis. Symptoms of the intracranial lesion had been evident before CSA therapy was started for ICD. These symptoms had been treated at a local general hospital and a university medical center.

To summarize the data on these 5 deaths among CSA-treated patients—3 deaths had cardiac causes (in 1 of these cases the patient had been receiving CSA only intermittently), and 2 deaths had non-cardiac causes (in 1 of these cases the patient had discontinued CSA for a year before death).

As seen in Table 2, there were no other acute cardiac episodes in the remaining 55 Group I patients treated with CSA.

Any improvement in subjective symptoms which occurred during CSA therapy (including exercise tolerance and well-being) was not considered in this evaluation since such improvement possibly could be induced by placebo, by suggestion, or by the psychotherapeutic factors involved in such a study of a new medication (7). The mortality and morbidity rates, however, were objective and therefore were valid indicators of the pathological processes within the coronary arteries and the heart muscle. This preliminary report concerns only a feasibility or pilot study. A triple-blind, cross-over, statistically controlled study on a large number of patients could not be justified to the exclusion of any therapy except CSA (a hitherto unproved drug) for the treatment of such a life-threatening disease as ICD.

DISCUSSION

The modus operandi of chondroitin sulfate and other acid mucopolysaccharides has been studied by numerous investigators. Morrison and coworkers also have investigated CSA and other acid mucopolysaccharides at the cellular level in both human and animal tissue cultures, and have conducted in vivo studies in rats, rabbits, dogs, monkeys and human subjects. The findings can be summarized as follows:

CSA in relation to atherogenesis

(a) In tissue and organ cultures CSA stimulated cellular growth (animal and human) and "cleared" from coronary and aortic cells and tissues the saturated lipids, lipoproteins and cholesterol which were "loaded" into these cells and tissues in culture media; CSA also increased messenger RNA synthesis at the cellular level and DNA synthesis to a lesser extent (8).

Electron microscope studies with C^{14}-cholesterol showed increased turnover rates for tissue and cellular fatty acids and cholesterol, to the extent that CSA might be described as a cellular regulator of metabolism, acting in a hormone-like manner (5b).

(b) Squirrel monkeys (Saimiri sciurea), sub-human primates of South America, are noteworthy for spontaneous or naturally-occurring atherosclerosis and arteriosclerosis in adult life, analogous to the process observed in humans (9a & b). In an earlier study on 65 of these primates, Morrison and associates (3) observed the inhibition of dietary cholesterol-accelerated aortic atherosclerosis during treatment with CSA (daily subcutaneous injection) for nine months.

(c) Two experiments (one in which x-irradiated cholesterol-fed rats were treated with CSA orally, and another in which rats were fed massive doses of vitamin D and CSA), showed CSA to be strikingly effective in the prevention of coronary atherosclerosis (6b). In another rat study, Morrison et al. (7) found that CSA accelerated the regression of coronary-artery atherosclerosis but not of coronary-artery calcium deposition or fibrosis (7). It is of interest that in earlier experiments with rats, parenteral administration of CSA failed to prevent coronary atherosclerosis whereas oral administration was highly effective.

(d) In rabbits, parenterally administered CSA and chondroitin sulfate-C (CSC) were found effective in inhibiting aortic atherosclerosis, as shown by Ohdoi (10), Murata, Oshima et al. (11a) and Morrison et al. (6b). However, orally administered CSA was found ineffective in preliminary studies by Morrison et al. Parenterally administered CSC was more effective than CSA in the rabbit.

Antithrombogenic or antithrombotic properties of acid mucopolysaccharides such as CSA, CSC and heparin

(a) The anticoagulant or antithrombogenic action of parenterally administered heparin is well known. Chondroitin sulfates and other acid mucopolysaccharides were found to be effective anticoagulants in both rabbits and humans when administered parenterally, according to Oshima and Murata (11b); and when administered either parenterally or orally in rabbits, according to Morrison et al. (2, 6b).

(b) Recently Morrison and associates (5) showed that CSA administered parenterally was an effective antithrombotic agent in dogs; preliminary studies in dogs with CSA administered orally showed a similar trend towards antithrombogenesis as determined by the thrombus-formation time (Chandler method, 12a, b, c).

(c) In rats, Robbins and Morrison (13) found that oral administration of CSA reduced the elevated erythrocyte sedimentation rate induced by toxic doses of vitamin D_2. In subsequent studies Morrison et al. (13) gave rats a purified diet containing 1.25 million U.S.P. units of vitamin D_2 plus 1.5 per cent cholesterol plus 0.5 per cent cholic acid; after six weeks of such

feeding, the blood cells adhered markedly to the walls of the coronary artery and the aorta. This did not occur in rats fed a similar diet supplemented with 1 per cent CSA.

Recent motion-picture films and microphotographs of animal coronary arteries have indicated that one major aspect of the action of CSA involves Coulomb and Van der Maal's electrically charged forces. The electro-negative charges on blood platelets and cells prevent aggregation, adhesion or "stickiness," thereby preventing or delaying thrombus formation. At the same time, electro-negative repellent charges are exerted upon the vascular endothelium lining the artery wall.

(d) In 17 patients with angina pectoris, Morrison et al. (14) found that the thrombus-formation time (adhesiveness or "stickiness" of blood cells) was abnormally short compared to that in the controls, as measured by the Chandler-Poole method. In the anginal patients after the oral ingestion of CSA in a dosage of 10 gm daily for 90-day periods, there was a significant inhibition of thrombus formation, i.e., prolongation of the thrombus-formation time.

Effect of CSA on serum lipids and cholesterol

In squirrel monkeys, a statistically significant lowering of the total serum lipids occurred during the daily parenteral administration of CSA in a dosage of 20 gm per kg of body weight for nine months (3). In rats, no reduction of lipid or cholesterol was noted in either the liver or the blood after three months of oral feeding with a diet containing 0.4 per cent CSA (1). In patients, Izuka, Murata et al. (6a) found a reduction of 20 per cent in serum lipoprotein and cholesterol levels after oral or parenteral administration of CSA and CSC for periods varying from six weeks to twelve months. Our own experience remains to be evaluated in relation to the well known, wide variations of serum lipids and their fractions in ICD patients.

CSA and defense mechanisms

Since CSA is a normal constituent of circulating blood (15) and of human arterial tissue (6a, 16, 17), it may well be that CSA exerts its preventive or protective action upon the vasculature by virtue of participation in a "defense system" to guard the arteries against degenerative or other pathological processes. It is well documented that acid mucopolysaccharides are among the first substances to react to inflammatory or noxious agents which may enter the artery wall (18, 19). Our observations on human and animal arterial tissues lead us to believe that these acid mucopolysaccharides arise in the connective tissue of the arterial wall as part of the first line of defense against the invasion of any foreign or noxious substance which threatens harm or challenges the integrity of the arterial wall. The primary action of certain acid mucopolysaccharides involves repair, regeneration and growth of normal new tissue.

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