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PARENTERAL MAGNESIUM SULPHATE IN CORONARY ARTERY DISEASE

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In September 1956 a preliminary report was published which suggested that intramuscular injections of magnesium sulphate might have beneficial effects in certain types of coronary heart disease.[1] In particular it was reported that in a series of 22 cases selected for treatment because of a high beta-lipoprotein fraction, 14 showed a dramatic reduction in this fraction after treatment, while clinically 20 of the 22 cases were markedly improved. Several reports have since been published which stated that the use of parenteral magnesium sulphate was clinically justified.[2-4]

Because of these findings and other suggestive evidence that magnesium might be associated with atherogenesis,[5-8] another trial of the effect of magnesium sulphate was designed. In contrast with the previous trial,[1] cases were selected on the sole criterion of suffering from angina of effort due to coronary heart disease. The effects of magnesium sulphate and a placebo (saline) were compared by means of the double-blind technique. This paper describes the results obtained.

Material and Methods

Sixteen patients were included in the trial—11 males and 5 females of ages varying from 44 to 78 years. All had typical angina of effort; 8 patients had experienced previous episodes of myocardial infarction; 3 patients suffered also from myxoedema (induced in 2 as a therapeutic procedure), 3 from moderate diastolic hypertension, and 1 from diabetes mellitus. None of the patients had any evidence of any other type of heart disease, and in all there was an abnormal electrocardiogram.

Two sets of apparently identical ampoules containing 50% magnesium sulphate or normal saline were labelled A and B respectively. It was not possible for the person giving the injections to know which solution was being used.

Each patient when accepted for trial was allotted treatment A or B in a random manner. The trial was conducted over a period of 8 weeks. Each patient received a total of 16 intramuscular injections of 1 ml. given twice weekly over 2 consecutive 4-week periods. Half the cases received solution A (8 injections) followed by solution B (8 injections), and the other half solution B followed by solution A.

Blood samples were collected on 5 occasions, immediately before receiving the 1st, 3rd, 9th and 11th injections and 4 days after the last (16th) injection. The specimens were collected in the morning approximately 3 hours after a fat-free breakfast of black tea or coffee and dry toast with jam. The following investigations were carried out: Total lipids (Bloor[9]), total and beta-lipoprotein cholesterol (Sperry and Webb[10]), phospholipids (Fiske and Subbarow[11]), lipoproteins (Durrum[12] as modified by Bersohn[1]), and total fatty acids (Stoddard and Drury[13]).

Throughout the trial there was no change in dietary habits or therapy (thyroid in 3 patients, dicoumarol in 2, peritrate, metamine, benecardin and phenobarbitone).

All patients kept a record of the incidence of anginal attacks and of the number of nitrite tablets consumed each day. At each visit they were asked to report on any subjective change.

Results

The results of the trial were assessed with regard to subjective change, average weekly consumption of glycerine trinitrite tablets and biochemical changes.

Of 8 patients who first received sodium chloride all reported subjective improvement. On changing the injections to magnesium sulphate 5 reported further improvement (cases 1, 3, 6, 7, 8), 2 no change (cases 2 and 4), and one deterioration (case 5). Of the 8 patients who first received magnesium sulphate 6 were improved (cases 9, 10, 12, 13, 14, 15). In these the change to placebo injection was accompanied by further improvement in 3 (cases 12, 14, 15), and maintenance of improvement in 3 (cases 9, 10, 13). Two (cases 11, 16) showed no initial improvement while on magnesium sulphate injections but reported improvement on being changed to placebo injection.

As regards biochemical changes the tables reflect the means of the values observed of the control period on normal saline (C), and the treatment period on magnesium sulphate (T). No obvious trends are apparent. The results were not subjected to statistical analysis. With the possibility in mind that delayed effects of the magnesium sulphate injection might be influencing the observed values during the control period in those subjects who received magnesium

TABLE I. PATIENTS WHO RECEIVED PLACEBO (C) FOLLOWED BY MAGNESIUM SULPHATE (T)

Case	Age	Sex	Total Lipids mg.%		Total Cholesterol mg.%		Phospholipids mg.%		Total Fatty Acids mg.%		Cholesterol/Phospholipid Ratio		Beta-Lipoproteins		Beta-Lipoprotein Cholesterol mg.%		Average Nitrite Tablets/Week	
			C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T
1[a,d]	59	M	761	909	280	285	262	319	414	522	1·09	·90	75	77	231	232	3	6
2[b]	50	F	990	1,137	352	379	381	384	512	657	·92	·99	76	74	303	323	2	1
3	59	F	798	737	246	231	300	290	478	391	·82	·80	64	67	178	171	3	3
4[a,d]	66	M	1,003	896	331	261	339	278	575	545	·98	·94	82	74	298	216	19	9
5[a]	46	M	710	864	246	278	295	309	359	489	·84	·89	73	74	200	217	1	4
6[c]	52	F	807	903	271	315	314	342	416	486	·87	·92	71	74	220	269	9	5
7	56	F	969	944	323	211	353	364	530	516	·92	·87	75	71	268	243	3	2
8[a]	69	M	526	553	179	154	212	219	273	255	·79	·71	66	67	126	112	7	5
Mean			821	867	278	299	307	313	445	481	·90	·88	73	72	228	224	6	4

TABLE II. PATIENTS WHO RECEIVED MAGNESIUM SULPHATE (T) FOLLOWED BY PLACEBO (C)

Case	Age	Sex	Total Lipids mg.%		Total Cholesterol mg.%		Phospholipids mg.%		Total Fatty Acids mg.%		Cholesterol/Phospholipid Ratio		Beta-Lipoproteins %		Beta-Lipoprotein Cholesterol mg.%		Average Nitrite Tablets/Week	
			T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
9	78	M	721	756	283	271	260	282	378	383	1·09	·97	67	70	214	212	5	2
10	52	M	1,082	1,058	280	277	325	305	688	683	·86	·91	79	79	237	235	0	0
11[c]	44	M	754	813	234	257	258	239	440	467	·92	1·09	69	74	185	202	24	15
12[a]	52	M	963	910	387	345	319	334	512	483	1·18	1·04	78	76	338	297	18	10
13[a]	44	M	793	852	259	281	293	290	288	472	·89	·97	66	72	190	230	5	3
14[a]	66	M	696	765	224	261	284	293	367	407	·79	·89	67	68	179	205	12	5
15[a,b,c]	66	F	768	945	227	287	266	333	390	549	·83	·86	69	72	189	239	27	20
16	57	M	650	681	239	261	295	277	309	338	·84	·95	68	69	181	205	29	28
Mean			803	848	269	279	288	294	422	473	·93	·96	70	73	214	228	15	10

T=Mean treatment value. C=Mean control value. a=Previous Myocardial infarction. b=Myxoedema. c=Hypertension. d=Diabetes mellitus.

sulphate first, another set of tables was prepared. In these the blood value obtained before the magnesium sulphate injections was compared with the blood value obtained at the end of one month's magnesium sulphate treatment. Again no obvious trends were discernible.

DISCUSSION

The principal criterion by which subjects were selected for this trial was the presence of repeated typical angina of effort due to atherosclerosis. Although this selection makes the assessment of subjective effects easier it renders assessment of blood lipid studies more difficult.

Thus the series included 3 cases with myxoedema, 1 with diabetes mellitus, and 3 with some degree of hypertension. The initial cholesterol, lipid and lipoprotein values were not grossly abnormal in all cases and were strictly normal in every respect in one (case 8). The percentage beta-lipoprotein was elevated above 75 in only 4 cases. This contrasts with the series of Malkiel-Shapiro and Bersohn in which all cases without an elevation of the percentage beta-lipoprotein were excluded. The results of the 2 series are therefore not comparable. In our series there was a reduction of more than 25 mg.% in the level of beta-cholesterol in 5 patients (cases 4, 7, 13, 14, 15). If a reduction of 50 mg.% or more is taken, only 2 patients (cases 4 and 15) can be included. However, consideration of the group means shows that there were no very striking trends in any of the values examined as a result of treatment with magnesium sulphate.

The injections of magnesium sulphate were no more painful than the saline, and the subjects were in no instance aware of the change from one to the other.

As regards subjective improvement, it is well known that the institution of *any* active treatment produces apparent subjective benefit in patients with chronic illness. This placebo-induced improvement renders any attempt at assessment of drug therapy most difficult. Because of this a large number of subjects must be studied to show significant differences, and a blind or preferably a double-blind technique, as was employed here, is essential. One can only conclude that this series was too small to disprove the possibility of subjective benefit. There was, however, no difference in the frequency and degree of subjective improvement following each of the 2 substances given. Brigden[14] summarizes the situation neatly when he says:

'It is not always realized that myocardial ischaemia shows an

inherent tendency to improve over long periods of time, especially in patients who are able to adjust their minds and life situation to the disease. Many observers have noted that when a patient is started on any new form of treatment improvement is almost invariably the rule. The conclusion cannot be escaped that psychological factors as well as many physical ones are of importance. An understanding doctor-patient relationship is as important in this disease as in any condition in the whole field of medical practice.'

SUMMARY

Sixteen patients suffering from coronary artery disease and typical angina of effort received courses of magnesium sulphate and a placebo using a double-blind technique. No very striking trends were observable in the pattern of blood lipids or lipoproteins though 5 individual cases showed reductions of beta-cholesterol which were possibly significant. Subjective improvement was very great with magnesium sulphate but just as great with the placebo. The results of this series do not conflict with those of Malkiel-Shapiro and Bersohn, who used different criteria for the selection of cases.

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