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PILOT STUDY OF METHYLCYSTEINE (VISCLAIR)

EFFECT ON LIPOPROTEIN (a)

Report to Sinclair Pharmaceuticals Ltd, Borough Road, Godalming, Surrey, England

The enclosed protocol (appendix 1 previously sbmitted) has been carried out on five male subjects and in one female subject who had an excellent lipoprotein (a) [Lp(a)] response to hormone replacement therapy which she was currently receiving but which had to be terminated. The question arose therefore whether methylcysteine was capable of preventing the return of her previous high Lp(a) levels. There is increasing evidence that Lp(a) will be improved substantially by hormone replacement therapy in the perimenopausal and post-menopausal female [1]. This will almost certainly be the treatment of choice for this group in the future. However, there is no satisfactory treatment for males or the pre-menopausal female with raised Lp(a) levels, although some reducing effect has been found using fish oil and a combination of neomycin and niacin treatment [2,3]. Evidence for N-acetylcysteine effect on Lp(a) has raised the question as to whether it acts by cleavage of low density lipoprotein and apoprotein (a) at the disulphide linkage, or whether it could be an effect of reduced liver production of lipoprotein (a) [4]. A further study has only shown a minor reduction in Lp(a) using oral N-acetylcysteine [5].

Methylcysteine hydrochloride (Visclair) belongs to the same family of thiol containing drugs, which is used as a mucolytic agent, able to splice disulphide bonds between mucous macromolecules [6]. However, one drawback to the study was the fact that we have given it in a reduced dosage, that is the recommended dosage, of 200mg t.d.s., whereas N-acetylcysteine was given in doses of up to 2 grams. Thus we are dealing with less than a third of the dose by weight but there may be different biological activities as well.

PATIENTS AND METHODS

Five male patients and one female patient were studied and a short history of each of these patients is given:

N.H. - Male aged 66

Coronary heart disease diagnosed 1991 and bypass surgery completed in early December 1991. Known to have high total cholesterol of 8mmol/L with a raised LDL cholesterol of 6mmol/L. Lp(a) measurement 0.67 g/L. Current treatment before entering the trial was aspirin 150mg daily.

P.M. - Male aged 37

Asymptomatic patient with no clinical evidence of significant vascular disease but family history with mother having a heart attack at the age of 62. Previous cholesterol testing was within the normal range as was the LDL cholesterol but Lp(a) was raised at 0.49g/L. He was on no current medication.

B.S. - Male aged 37

First suffered heart attack in April 1986 at the age of 32 and a coronary artery bypass graft was done in August 1991. Current treatment was aspirin 75mg daily. Previous lipid testing for cholesterol and LDL cholesterol were normal. Lp(a) was 0.79g/L. He was currently asymptomatic.

M.B. - Male aged 56

Long history of ischaemic heart disease and obesity resulting in coronary artery bypass graft in November 1991. Current treatment was aspirin 300mg on alternate days and Zocor 20mg t.d.s. Current total cholesterol was normal. Lp(a) was raised at 0.3g/L.

J.V.W. - Male aged 52

Ischaemic heart disease since 1983 and coronary artery bypass graft done at that time. Recurrence of angina recently. Current treatment aspirin 75mg but not regular. Lipid profile normal and Lp(a) raised at 0.31g/L.

I.D. - Female aged 54

Very obese woman with normal total and LDL cholesterol but initial Lp(a) 0.8g/L (see table). She then began hormone replacement therapy in the form of Estradiol Valerate 2mg and norethisterone 0.7mg daily and level was reduced to 0.29g/L, (see table) just above the normal range. Hormone replacement therapy was

discontinued because of other complications and the question arose as to whether Lp(a) would continue to be suppressed by methylcysteine.

LIPOPROTEIN (a) METHODOLOGY

Lp(a) is a plasma fraction which contains LDL and one or possibly two copies of a highly glycosylated antigen apoprotein (a) which is linked with apoprotein B 100 by disulphide bridges. It shows inter and intra individual heterogeneity in its lipid and protein composition. At least 8 polymorphic forms of the apo (a) antigen are known.

The estimations were carried out by JS Pathology Services, a national quality control laboratory, based on the method of Molinari. The normal range for this method is <0.2g/L. (See enclosed copy of methodology.)

Blood was drawn from patients after 12 hour fasts at -2 weeks and 0 time, methylcysteine in a dose of 200mg t.d.s. before meals with water was then given. Blood for Lp(a) was then drawn fasting at +2 weeks and +4 weeks. Methylcysteine was then discontinued.

RESULTS

Lp(a) levels (g/L) are shown in the Table. Mean level at 10 readings before treatment = 0.49 g/L. Mean level of 5 readings at the end of treatment = 0.51 g/L. Thus by inspection no significant change. I.D. was not included in this analysis as her levels had responded dramatically to hormone replacement therapy. However, during methylcysteine therapy the level rose again and thus was not suppressed on withdrawal of H.R.T. (see Table).

No adverse reactions or side effects were reported by the patients during methylcysteine therapy.

DISCUSSION

These results have failed to show a response by Lp(a) to methylcysteine in a dose of 600mg daily in divided doses over four weeks. In view of the response to N-acetylcysteine at the 2g level, the most likely explanation is that the current dosage is too low or the biological activity of N-acetylcysteine is more specific for breaking disulphide linkages or inhibiting metabolism of Lp(a). Lp(a) variation intra individually is small. Thus, any change by drug intervention should be easily observed. Even when levels had been previously suppressed as in

I.D., this was unable to be maintained with methylcysteine at this particular dosage. The dosage of 600mg was chosen as this is the standard dose as a mucolytic agent. We do not have clinical information on much larger doses, for example the 2g used in the case of N-acetylcysteine which showed a significant effect on Lp(a) [4]. Additonally the small effect observed in a further study [5] (7% reduction as opposed to 50-75% reduction [4]) has thrown doubt on initial expectations. It is possible that the different polymorphic forms of apoprotein (a) measured in the assay may respond differently to these drugs. For example MB showed a reduction in Lp(a) level, the only one of the five subjects studied (see table).

RECOMMENDATIONS

1. To determine whether a further small study using a 2 to 3 gram dosage of methylcysteine daily for a period of 2 to 3 months, would be feasible. N-acetylcysteine is well tolerated in very high oral doses [6] and thus side effects would be unlikely.

2. To publish the present information in the form of a letter to the Lancet to see whether any further contributory ideas may be suggested.

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TABLE

Patient	-2 weeks	0	+ 2 weeks	+4 weeks
NH	0.67	0.57	0.69	0.62
PM	0.49	0.65	0.54	0.45
BS	0.41	0.79	0.67	0.65
MB	0.38	0.30	0.34	0.26
JVW	0.31	0.34	0.44	0.58
ID	0.80	0.29	0.66	0.50

NB: ID pre-treatment level 6 months earlier (0.80), 0.29 at end of HRT treatment, subsequent readings on methylcysteine alone.