Clinical observations on treatment of alkylmercury poisoning in hospital patients

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Twenty-six patients suffering from methylmercury poisoning were treated by different therapeutic regimes. Seven received penicillamine or N-acetyl-d-L-penicillamine, 10 were treated with dimercaprol sulfonate and 9, who could not be treated, were given a placebo and were used as controls. Penicillamine, N-acetyl-d-L-penicillamine, and dimercaprol sulfonate reduced the blood level of mercury and increased its urinary excretion. No appreciable clinical improvement was noticed among the severe or very severe cases, while mild or moderate cases improved clinically irrespective of the treatment given.

During the outbreak of mercury poisoning in Iraq many patients were admitted to various hospitals early in 1972. The outbreak was unpredicted. There were only a few scattered reports in the literature on the drug therapy of this condition. Some time elapsed before chemotherapeutic agents were available and even these were available only for some cases. Patients in the Medical City, Karama, and Kadhimain Hospitals were put on a therapeutic programme. The period of exposure to organomercury varied from 30 to 60 days; 2 patients had exceptionally long exposure periods of 90 and 110 days, respectively. The latent period between ingestion and the appearance of symptoms was in the range of 1-2 months.

It was impossible to choose control cases matching in age, sex, and severity the patients treated. The ethical situation was a strong factor in this difficulty, in case any therapeutic agents should prove to be beneficial. Therefore only 9 controls were included, for the reasons set out below.

METHOD

This is a preliminary report on 26 patients. Seventeen were placed on different therapeutic regimens while 9 received no specific treatment and were given a placebo, these are referred to as controls.

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Cases were classified into 4 grades according to the severity of their condition; this classification was a purely clinical one made on the first physical examination and evaluation. The grades are defined in detail in the paper on clinical aspects of the outbreak (see page 65).

For purposes of therapy, patients were divided into 3 groups. Group 1 included 7 patients; 3 were placed on N-acetyl-d-L-penicillamine and 4 were given penicillamine. Their age, sex, clinical grade and the result of treatment are listed in Table 1.

TABLE 1. GROUP 1: PATIENTS TREATED WITH D-PENICILLAMINE AND N-ACETYL-d-L-PENICILLAMINE

Serial No.	Age	Sex	Clinical grade	Treatment	Result	Initial blood mercury level ng/ml	% reduction of level
14	40	F	very severe	n-acetyl penicillamine	died	4 078	8
15	10	M	severe	n-acetyl penicillamine	no change	3 400	48[a]
61	20	F	very severe	n-acetyl penicillamine	died	3 320	19
48	43	M	mild	penicillamine	asymptomatic	2 744	9[b]
49	14	M	very severe	penicillamine	improved	4 020	13[b]
50	15	M	moderate	penicillamine	improved	4 200	21[b]
79	20	F	severe	penicillamine	no change	-	-

[a] Patient received 2 courses of treatment.

[b] Patient received 3 courses of treatment at double dose.

The period of treatment was 10-14 days, the dose was 1 g per day, by mouth. One patient received 2 courses of treatment and 3 received 3 courses. The dose was doubled in each course subsequent to the first.

Group 2 comprised 10 patients who were treated with 2,3-dimercaptopropanesulfonate (dimercaprol sulfonate) (Table 2). An antagonist of sulfydride, this was given intramuscularly at a dosage rate of 50 mg (1 ml) per 10 kg of body weight, three times on the first day, twice on the second day, and once daily thereafter until the seventh day. Three of these patients received 2 courses each.

Group 3 was made up of the 9 patients who received no treatment (Table 3).

RESULTS

It was unfortunate that mercury excretion estimations were not made for all patients and that faecal excretion estimations were not performed at all, owing to the large number of patients in hospital. However, urinary excretion of mercury was found to be increased during the period of treatment with penicillamine, N-acetyl-d-L-penicillamine (Group 1) and dimercaprol sulfonate (Group 2) as shown in Tables 1 and 2.

TABLE 2. GROUP 2: PATIENTS TREATED WITH DIMERCAPROL SULFONATE

Serial No.	Age	Sex	Clinical grade	Result	Initial blood mercury level ng/ml	% reduction of level
80	20	F	very severe	died	4 232	21
95	8	M	very severe	no change	679	-[a]
56	18	F	severe	no change	3 725	20
57	14	F	severe	no change	3 572	20
74	15	F	severe	improved	1 871	30[a]
75	54	F	severe	deteriorated	302	4
76	8	F	moderate	improved	1 544	26
96	6	M	moderate	improved	604	-[a]
97	32	F	mild	improved	12	-
139	23	M	mild	improved	835	no reduction

[a] Patient received 2 courses of treatment.

TABLE 3. GROUP 3: PATIENTS RECEIVING NO TREATMENT

Serial No.	Age	Sex	Clinical grade	Blood mercury level ng/ml	Results
45	15	F	severe	2 710	no change
77	45	F	severe	1 901	no change
82	16	M	severe	2 318	no change
53	-	F	severe	1 418	improved
40	33	M	mild	356	improved
98	5	F	mild	12[a]	improved
99	10	F	mild	140	improved
100	8	M	mild	20	improved
120	18	M	mild	512	improved

[a] Blood mercury level was estimated very late after exposure.

An attempt was made to compare the effects of treatment on the blood mercury level and on the urinary excretion of mercury during the period of treatment. The results of these analyses were not constant, nor did they parallel clinical progress. Thus, in Group 1, case 15 (Table 1) showed a reduction of 48% in the blood level but no appreciable clinical change was seen, while case 49 (Table 1) improved, although the blood mercury level was reduced by only 13%.

The percentage reduction of mercury level of the blood in the course of therapy varied a great deal, the range being 8-48%. One explanation for the high reduction of 48% is that the patient concerned was only 10 years old and received the same dose as the other patients, hence he could easily have received double the dose per kg of body weight.

In the Group 1 patients who received a second course of double the dose of penicillamine blood mercury levels were slightly lower at the end of the second course of treatment than at the end of the first. It is reasonable to think that this was due to the increase in the dose; however, this effect was not seen after a third course of therapy. On the contrary, the blood mercury level was elevated.

Of the 3 very severe cases, 2 died and the third showed some improvement after 162 days of hospitalization; 2 cases, classed as severe, showed no essential change or improvement after 42 days of hospitalization; 1 was a moderate case, who improved; the last was a mild case who had no signs which could be evaluated but who showed a reduction of about 9% in blood mercury level as the result of treatment.

Details of cases in Group 2 are shown in Table 2. In one mild and 2 moderate cases improvement was reported after their period in hospital, which varied from 26 to 51 days. Four of the cases were classified as severe; 1 patient deteriorated in spite of treatment, 1 was reported to have improved, and the other 2 showed no change. The remaining 2 cases in the group were classed as very severe; 1 patient died and the other showed no change after 162 days of hospitalization. Both of them had 2 courses of treatment.

There was less variation in the percentage reduction of blood mercury level than was induced by penicillamine or N-acetyl-penicillamine: about 20-30% reduction in the level at the end of treatment period. Excretion of mercury in the urine increased simultaneously in the same period. It was observed in most cases that the mercury level started to rise again after cessation of treatment.

All drugs were well tolerated and there no side effects were observed.

In both Groups 1 and 2, no appreciable lowering in blood mercury level was noted during the third course of therapy. In those who showed a low blood mercury level initially, the estimation was often made some time after exposure.

DISCUSSION

It is obvious that the grouping of patients into clinical grades is not very accurate and there may be an overlap between one group and another. Other ways of helping the patients were sought, and in addition to the therapeutic regimens reported here, trials were carried out on other patients to assess the effect of haemodialysis and of administering a resin by mouth; the results of these trials are described elsewhere.[a]

The majority of the patients admitted to hospital had been exposed to organomercury ingestion for a long time and had a heavy body burden of mercury. Changes in the severity of poisoning are dose-dependent most of the time but there is no strict or parallel relationship. By the time they had been admitted to hospital, all the moderate, severe and very severe cases had an already established clinical picture with clear positive objective findings. Most of them were subsequently observed for a long time.

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[a] KOSTYNIAK, P. J. ET AL. An extracorporeal complexing hemodialysis system for the treatment of methylmercury poisoning. I. In-vitro studies of the effects of four complexing agents in the distribution and dialyzability of methylmercury in human blood. J. Pharm. exp. Ther., 192(2): 268-269 (1975).

To summarize the results in 7 Group 1 patients treated with D-penicillamine and N-acetyl penicillamine, there were 2 deaths, 2 patients with severe symptoms showed no appreciable change, while 1 very severe case and the moderately severe case showed improvement. The 4 patients who received N-acetyl penicillamine for a longer period (25 days) showed no appreciable clinical changes.

In Group 2, 4 cases were mild or moderate and improved in similar fashion to those in the control group; 2 of the 4 severe cases showed no change, 1 deteriorated and 1 improved. Of the 2 very severe cases, 1 patient showed no change and the other died; this was in spite of a lowering of the blood mercury level by about 21%. Of the 3 patients who received 2 doses, one showed no change and the other improved; the third, a mild case, improved.

Of the 9 Group 3 cases who received no treatment, 5 were mild and showed some improvement while in hospital. Of the 4 severe cases, 3 showed no change and 1 improved. This seems to demonstrate clearly that in mild cases, whether treated or not, there is some improvement with time. This may be due to natural progress and probably no great structural damage had been caused by mercury.

It is our belief that when there was severe structural damage after a long period of heavy exposure, little could be achieved by the drugs tested; improvement tended to be inversely proportional to the amount of damage.

Table 4 confirms the impression that no good result was obtained among the severely or very severely affected patients, irrespective of the type of treatment given, while all the mild or moderate cases in all 3 groups improved.

The lowering of the blood mercury level had a rather weak relation to clinical improvement because, firstly, the damage had already been done; secondly, there was a mild actual rise in the blood mercury level in the first few days of treatment; and, thirdly, often the post-therapeutic level returned to the pre-treatment value. The last two points may indicate the presence of large deposits of mercury in the body.

TABLE 4. SUMMARY OF RESULTS BY CLINICAL GRADE AND TREATMENT GROUP

Result	Clinical grade														
	Very severe			Severe			Moderate			Mild			Total		
	1[a]	2[b]	3[c]	1[a]	2[b]	3[c]	1[a]	2[b]	3[c]	1[a]	2[b]	3[c]	1[a]	2[b]	3[c]
Died	2	1	-	-	-	-	-	-	-	-	-	-	2	1	-
Deteriorated	-	-	-	-	1	-	-	-	-	-	-	-	-	1	-
No change	-	1	-	2	2	3	-	-	-	-	-	-	2	3	3
Improved	1	-	-	-	1	1	1	2	-	-	2	5	2	5	6
Asymptomatic	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-
Total	3	2	-	2	4	4	1	2	-	1	2	5	7	10	9

[a] Treatment Group 1: penicillamine and n-acetyl-d-L-penicillamine.

[b] Treatment Group 2: Unithiol.

[c] Group 3: placebo.

RESUME

OBSERVATIONS CLINIQUES SUR LE TRAITEMENT EN HÔPITAL DE L'INTOXICATION PAR LES COMPOSES METHYLMERCURIELS

Vingt-six malades souffrant d'intoxication par des composés méthylmercuriels ont été soumis à différents régimes thérapeutiques. Sept d'entre eux ont été traités par la pénicillamine ou la N-acétyl-d-L-pénicillamine, 10 par le sulfonate de dimercaprol et 9 sujets, qu'il était impossible de traiter, ont reçu un placebo et ont servi de témoins. La pénicillamine, la N-acétyl-d-L-pénicillamine et la sulfonate de dimercaprol ont réduit la concentration de mercure dans le sang et augmenté son excrétion dans les urines. On n'a pas constaté d'amélioration clinique appréciable dans les cas graves ou très graves, tandis que les cas bénins ou modérés s'amélioraient, quel que fût le traitement administré.