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Effect of a Single Oral Dose of Metrifonate on Human Plasma Cholinesterase Levels

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Clinically, metrifonate or trichlorfon 2,2,2 - trichloroethyl dimethyl phosphate), or Dipterex is an organophosphorus compound. Consequently metrifonate exhibits most of the pharmacological and toxicological characteristics of the organophosphorus group of compounds, i.e.characteristically it inhibits the activity of acetylcholinesterase. Significant exposure to metrifonate results in the well known and well studied signs and symptoms of organophoshate poisoning (Goulding, 1981).

While occupational exposure to organophosphates is common, (mostly in agriculture as insecticides), (Lu, 1984), exposure to metrifonate is mostly through its therapeutic use in the control and treatment of schistosoma haematobium infection, (el Kholy, 1984; Snellen, 1981). In Zimbabwe, metrifonate is used to treat bilharzia. It is administered as a single oral dose of 7.5 - 10mg per kilogram body weight (Ministry of Health, 1989). The present study was carried out to measure the duration of inhibition and significance of recovery of plasma cholinesterase activity in Schistosoma haematobium infected school children after a single oral dose of metrifonate.

METHODS AND MATERIALS

The study was carried out at a primary school in an area that is endemic with Schistosoma haematobium, in the north - east part of the country. A single oral (tablets) dose of metrifonate, 10mg/kg body weight was administered to grade 3 school children, (24 girls and 25 boys, with an average age of 11.4 $\pm$ 0.5 years, average weight of 24.4 $\pm$ 3.3 kilograms). Blood plasma cholinesterase levels were assayed immediately before administration of the drug and 3 times i.e. 2 days,

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5 days and 30 days after treatment, using the method of Edison, 1955.

Exposure to organophosphates can be determined by observing the levels of normal cholinesterase activity in the blood. In the present study, measurement of blood cholinesterase activity was used as a quick and accurate way of screening school children for possible metrifonate exposure.

The standard lovibond comparator disc 5.30 (Limperas and Rama), uses normal enzyme activity in steps of 12.5 per cent and is calibrated for use with 2.5 mm cells. Further discrimination of $\pm$ 5 per cent can be achieved by assessing the direction of the colour difference between the most closely matching colours. The reagents were tested by mixing 0.5 ml of indicator (Bromo Thymol Blue), 0.1 ml of fingerprick blood form an unexposed 'control' subject, and 0.5 ml of substrate (actylcholine perchlorate) solution in a test tube. The well-mixed contents were placed in a 2.5 mm cell in the right-hand compartment of the comparator and compared with a test solution by revolving the disc until a close colour match with the test solution is obtained.

Control blood was obtained from the researchers. These researchers had no history of exposure to organophosphates. From each subject, 0.1 ml of blood (finger-prick) was pipetted into a reaction tube with the indicator. Temperature, taken in the shade was noted and 0.5 ml of substrate was added to the reaction tube. Each tube was allowed to stand for exactly the time corresponding to the shade temperature shown in the Time - Temperature Table provided with the kit. The reaction tube contents were then immediately transferred to the 2.5 mm sample cell, which was placed in the right-hand compartment of the comparator and matched against the standards in the disc. The results are consistent with those obtained by the electrometric method of Michel (1949). The cholinesterase activity is expressed as a percentage of the activity in normal blood and less than 75 percent of the normal activity was taken as a significant decrease (Edson, 1955).

RESULTS AND DISCUSSION

The use of a single oral dose of metrifonate in the treatment of Schistosoma haematobium infection is efficacous and widely used, (Aden-Abdi et al, 1987; Feldmeier et al, 1982; druilhe et al 1981; Ministry of Health, 1989).

The results of our study confirm the efficacy of

Table 1. Effect of a single oral dose of metrifonate on Cholinestarase levels in Primary school children.

Cholinestarase levels Activity as % of Baseline Line Activity	Number of Subjects			
	Pretreatment "Controls" 0 Days	2 Days after treat-ment	5 Days after treat-ment	30 Days after treat ment
30 - 40	0	0	1 (2%)	0
41 - 50	0	5 (10%)	3 (6%)	0
51 - 60	0	0 0	0	0
61 - 70	0	18 (37%)	17(35%)	0
71 - 80	19 (39%)	18 (37%)	19(39%)	0
81 - 90	16 (33%)	8 (16%)	7 (14%)	21(42.1%)
91 -100	14 (28%)	2 (4%)	2 (4%)	28(57.9%)

Total number of students N = 49

Table 2. Relationship between the number of subjects with cholinesterase levels activity significantly inhibited and the number of days after treatment.

	Pretreatment 'O' Days treatment	2 Days after treat-ment	5 Days after treat-ment	30 Days after treat-ment
Number of subjects with cholinesterase activity < 70% of controls	0	23	21	0
% of subjects with < 70% choli-nesterase acti-vity	0	47%	43%	0

Where N = 49

metrifonate in inhibiting cholinesterase activity, (table 1 and 2). Cholinesterase activity of 43% of the subjects was determined to be less than 70% of normal for a period of at least 5 days. The last

cholinesterase assay was done 30 days after treatment, to reduce the frequency of the trauma of finger-prick. However our results indicated that at most, by the end of month, cholinesterase activity had recovered back to normal levels in all the subjects. Similar results have been shown by Aden-Abdi et al 1987.

In view of the fact that metrifonate may be toxic, (Csik et al, 1986; Hu et al, 1986), and based on the results from this study, we recommend that after therapeutic treatment with metrifonate subjects should avoid occupational exposure to organophosphates since this might exacebate the toxic effects of these compounds.

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