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Clinical experience with metrifonate

Review with emphasis on its use in endemic areas

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Summary

Metrifonate is an excellent drug for the treatment of urinary schistosomiasis in areas with *S. haematobium* monoinfection. Toxicity apparently is negligible. Side effects due to the inhibition of acetylcholinesterase are usually scarce, light and transient in nature. At the recommended dosage of 3 times 10 mg/kg the chemotherapeutic potential of metrifonate to cure can be expected to range between 60 and 90%. Each dose of metrifonate reduces egg excretion by almost 90%. Treatment with metrifonate clearly reverses lower and upper renal tract pathology. An intermittent course of metrifonate may be administered by minimally trained health personnel. When appropriately timed with regards to local transmission dynamics the minimal requirement to achieve 99% reduction of egg excretion may be as low as three or four doses spaced over a period of two years.

Key words: metrifonate; *S. haematobium; S. mansoni;* renal tract pathology; control measures.

Introduction

In the early fifties an organophorous compound named Dipterex was widely used in Africa as an insecticide for crop protection and farm animals. Its insecticidal action was known to depend on the inhibition of cholinesterases in ganglionar synapses and neuromuscular transmission junctions. While working in the Congo in the sector of public health, a group of Belgian workers headed by Dr. Jacques Cerf considered the extension of the cholinesterase inhibiting

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property to intestinal nematodes and trematodes (Lebrun and Cerf, 1960). Cerf et al. (1962) later showed the efficacy of the compound against *S. haematobium*, and Beheyt et al. (1961) demonstrated its rather low toxicity in humans. With these publications began the highly unconventional evolution of an insecticide to a useful chemotherapeutic agent. The drug was first named trichlorfon and later metrifonate. As of 1967 metrifonate has been commercialized under the trade mark of Bilarcil by Bayer AG, Leverkusen, Federal Republic of Germany. For human use the drug is formulated in tablets of 100 mg of active substance for oral administration.

Many dose finding and clinical studies have been carried out in the sixties (for review see Wegner, 1970; Gönnert and Wegner, 1973). Later clinical experiences have been recently summarized (Wegner, 1984). Despite the development of antischistosomal agents with higher efficacy and a broader antiparasitic spectrum metrifonate has been kept in use for the treatment of urinary schistosomiasis especially in areas with *S. haematobium* monoinfection. This review aims to summarize the recent experiences with metrifonate under endemic conditions and to show its prospects for reducing prevalence and intensity of disease in community based chemotherapeutic programs.

Tolerability and side-effects

Metrifonate is very well tolerated if administered in a dose of 7.5 to 10 mg/kg bodyweight (Table 1). In most field studies the frequency of side-effects was less than 1%. However, in earlier studies, when metrifonate was given in doses of 15 mg/kg and higher, adverse reactions were observed in about 40% of the patients (Wegner, 1984). These symptoms consisted of abdominal pain, nausea, vomiting, diarrhea, malaise, asthenia, dizziness, vertigo and cephalgia. Hence, these side-effects appear to be typical cholinergic symptoms related to the inhibition of acetylcholinesterase (Maxwell et al., 1981). They were usually mild and disappeared within a few hours. This is in contrast to the comparatively long-lasting decrease of enzyme activity in vivo after administration of a single dose of 10 mg/kg metrifonate (Plestina et al., 1972).

For symptomatic relief atropine sulfate (1 mg every 6 h) is effective. There is no report in the literature of severe acetylcholinesterase depression after metrifonate treatment, which would have urged the use of an enzyme reactivator, such as pralidoximine iodide.

However, attention should be drawn to the problem that in rural tropical areas persons may be chronically exposed to organophosphorous compounds used as insecticides. These individuals are expected to have low levels of cholinesterase, and if treated with metrifonate may be very sensitive for further inhibition of their acetylcholinesterase. Indeed, in a recent study from Zimbabwe (Creasey et al., 1982) it was demonstrated that chronic occupational contact with organophosphorous compounds decreased cholinesterase activity

Table 1. Frequency of side effects

Authors	Area	Number of side effects/ administration	%
Forsyth and Rashid, 1967	Zanzibar	0/228	0
Davis and Bailey, 1969	Tanzania	0/135	0
Diallo and Druilhe, 1973	Senegal	13/345	4
Gentilini et al., 1973	Paris	12/150	8
Reddy et al., 1975	Nigeria	6/138	4
Jewsbury et al., 1977	Zimbabwe	0/500	0
Arap Siongok et al., 1978	Kenya	0/072	0
Rugemalia and Eyakuze, 1981	Tanzania	7/3723	0.2
Druilhe et al., 1981	Upper Volta	1/1382	0.1

to 50% of its normal value. This probably applies to other insecticides known to inhibit cholinesterase activity such as carbamates. Hence, special care must be taken, if chemotherapeutic programs will include occupational groups at risk for prolonged contact with such compounds, e.g. spraymen and workers in insecticides producing plants. In these situations, pretreatment estimation of blood cholinesterase in individuals at risk would be mandatory.

Toxicity and metabolism

Data available on the toxicity of metrifonate have extensively be summarized by Holmstedt et al. (1978). It can be derived from many clinical studies that there is virtually no short-term toxicity affecting heart, liver and renal functions, as well as hematopoesis when metrifonate is administered at the recommended dose of 7.5 to 10 mg/kg. In a study from Ghana no adverse effects were detected in patients suffering from G-6-PD deficiency or hemoglobinopathies (Wegner, 1984). Chronic toxicity studies demonstrated no evidence for carcinogenicity (Machemer, 1981). There was no indication that metrifonate had a clinically significant cumulative toxic effect. Furthermore, animal experiments as well as observation of female patients unaware of their pregnancy when treated with metrifonate did not reveal any embryotoxic or teratogenic potential (Wegner, 1984). A case report mentioned delivery of a baby with meningomyelocele after treatment with metrifonate during pregnancy (Monson and Alexander, 1984). A causal relationship, though, could not be established.

Until recently all efforts to demonstrate biodegradation products of metrifonate had failed. Using a highly sensitive technique Nordgren et al. (1978) established the nonenzymatic biotransformation of metrifonate into a compound named 2,2 dichlorovinyldimethyl-phosphate or dichlorvos (DDVP). This conversion occurs in vitro and in vivo.

In man the ratio of plasma metrifonate and dichlorvos is almost 100 to 1 (Nordgren et al., 1981). Both compounds reach peak levels in blood within two

hours after drug intake, half-life being less than two hours. Current views are that dichlorvos derived from metrifonate is the active compound, which reacts with the acetylcholinesterase to produce a dimethylphosphorylated enzyme. Thus metrifonate has been described as an intrinsic slow release formulation for dichlorvos (WHO, 1984).

Pharmacology and mode of action

Despite many pharmacological and parasitological investigations undertaken, the reason for the monospecific activity of metrifonate against *S. haematobium* in human infections and its mode of action remain obscure (Andrews, 1984). Two hypotheses have been formulated to explain the monospecific action of metrifonate. One hypothesis suggests that the susceptibility of cholinesterases to inhibition by metrifonate and/or its degradation product dichlorvos could differ between schistosome species (Nordgren et al., 1978; Bueding et al., 1972). However, the pharmacological studies provided either controversial or inconclusive results concerning the kinetic characteristics of cholinesterases of *S. mansoni* and *S. haematobium* worms, on the degree of inhibition of these enzymes by metrifonate and dichlorvos as well as their effect on worm motility (Bueding et al., 1972; Gear and Fripp, 1974; Denham and Holdsworth, 1971). Investigations in hamsters infected with *S. mansoni* or *S. haematobium* demonstrated that a reduction of the parasites' cholinesterase to less than 20% of normal values did not result in paralysis of adult worms (Bloom, 1981).

Hence, the hypothesis proposed by Forsyth and Rashid (1967) needs a critical reappraisal. They postulated that worms located in the perivesical plexus undergo an irreversible shift to the lungs after damage by metrifonate. In contrast, a hepatic shift would be reversible since the worms could return to their original sites in the mesenteric plexus. On anatomical grounds this appears reasonable as worms shifted to the lungs via the inferior vena cava pass on their way some valves whereas no valves exist in the mesenteric venae. Unfortunately, experimental studies performed in hamsters and baboons infected with *S. haematobium* to support the lung shift theory (James et al., 1972; James and Webbe, 1974), cannot be directly extrapolated to humans, since the vascular anatomy of these animals and the topographic distribution of worms do not parallel the human situation (Davis, 1982; Bloom, 1981). Recently, however, results from a clinical study performed in the Sudan provided strong support for the lung shift theory.

Patients with a mixed *S. haematobium* and *S. mansoni* infection and egg excretion of both parasitic species in urine *and* stool were treated with metrifonate and followed-up for a period of 5 months (Doehring et al., 1986). The application of metrifonate resulted in a quantitatively similar reduction of *S. haematobium* and *S. mansoni* eggs in the urine, whereas no effect of egg excretion was observed in the stool irrespective of the parasite species. These

results confirmed previous observations (Omer and Teesdale, 1978; Feldmeier et al., 1982b) that metrifonate eliminates *S. haematobium* and *S. mansoni* worms dwelling in the perivesical plexus.

"Cure-rate" versus reduction of worm load

The therapeutic efficacy of metrifonate has been reported in a wide range of clinical trials, in which, 7.5 or 10.0 mg/kg metrifonate was given twice fortnightly or monthly (Table 2). Such a treatment schedule resulted in a parasitological cure in 44 to 100% of patients. As metrifonate is formulated in tablets of 100 mg for sake of convenience a dose of 10 mg/kg is recommended. It is interesting to note that studies performed before 1975 consistently obtained higher cure rates than those reported more recently. This discrepancy may be attributed to differences in patient or parasite populations as well as to a different technical methodology. Indeed, difference in susceptibility to metrifonate of *S. haematobium* strains has been claimed to explain the divergence between results of clinical trials in East and West Africa (Wilkins and Moore, 1980). On the other hand, in the elder studies miracidia hatching was more frequently used to assess the efficacy of treatment with metrifonate, whereas filtration techniques were applied rather recently (Peters et al., 1976; Feldmeier et al., 1979).

From studies in which quantitative parasitological methods were used surprisingly homogeneous results were obtained when data are compared with respect to reduction of egg excretion rather than to presence or absence of eggs. Application of a single dose of metrifonate (7.5 or 10.0 mg/kg) reduced ova output by more than 80% in 4 out of 6 studies, in which quantitative data were provided (Table 3).

It appears that the percent reduction of egg excretion is independent of the number of parasites present before initiation of chemotherapy. Indeed, when patients from different endemic areas with heavy and light intensity of infection are compared it was observed that the first dose reduced median egg output by about 90%, the second dose by 99% and the third dose by 100% (Table 4). Using the arithmetic mean as statistics, reduction after the third dose was about 98%. Consequently, it can be assumed that in a diseased population with a typical negative binomial distribution of urinary egg counts 50% of patients or more will cease to excrete eggs after three doses of metrifonate. Moreover, persons with the highest urinary egg counts before treatment will tend to have persistent egg excretion. This hypothesis is supported by data from field studies. Davis and Bailey (1969) demonstrated conclusively that the number of doses required for a complete cure depended significantly on the intensity of infection. Their data clearly indicated that the greater the mean pretreatment urinary miracidial count, the more doses were requested to cure. Arap Siongok et al. (1978) showed that 36% of patients excreting 50 eggs per 10 ml were cured after one single dose of metrifonate. In contrast, only 10% of those with heavy

Table 2. Cure-rates of metrifonate in clinical trials from different endemic areas

Authors	Area	Dosage (mg/kg)	Follow-up (months)	Cure-rate[a] (%)
Forsyth and Rashid, 1967	Zanzibar	3×7.5 fortnightly	6	100
		3×10 fortnightly	6	92
Davis and Bailey, 1969	Tanzania	3×7.5 monthly	6	71
		3×10 monthly	6	58
		3×15 monthly	6	66
Gentilini et al., 1973	Paris	3×10 monthly	6	92
Reddy et al., 1975	Nigeria	3×7.5 monthly	4	44
Jewsbury and Cooke, 1976	Zimbabwe	3×7.5 fortnightly	3	57
Feldmeier et al., 1982c	Hamburg	3×10 fortnightly	6	59
McMahon, 1983	Tanzania	3×10 fortnightly	4	59

[a] at the last month of follow-up

Table 3. Percent reduction of egg excretion after a single dose of metrifonate (7.5 or 10.0 mg/kg)

Authors	Area	Pretreatment intensity of infection	Statistics used	% reduction
Davis and Bailey, 1969 ...	Tanzania	94 miracidia/10 ml	median	94[a]
Reddy et al., 1975	Nigeria	1195 ova/10 ml	arithm. mean	78
Arap Siongok et al., 1978	Kenya	374 ova/10 ml	arithm. mean	97
Wilkins and Moore, 1980	Gambia	541 ova/10 ml	arithm. mean	75
Feldmeier et al., 1982c ...	Hamburg	5 ova/10 ml	median	96
Feldmeier et al., 1982c ...	Sudan	100 ova/10 ml	median	86

[a] reduction in non-cured only

Table 4. Reduction of egg excretion after one, two and three doses of metrifonate

	Studies performed in:		
	Hamburg[a]	Sudan[a]	Nigeria[b]
Egg excretion before treatment (ova/10 ml)	5.1	100.3	1195
Percent reduction after			
1. treatment	96.3[c]	85.9[c]	78[c]
2. treatment	99.8[c]	98.8[c]	89[c]
3. treatment	100.0[c]	100.0[c]	95[c]

[a] Feldmeier et al. (1982c)
[b] Reddy et al. (1975)
[c] calculated using the median as statistics
[d] calculated using the arithmetic mean as statistcs

intensity of infection (>400 eggs per 10 ml) ceased to excrete ova after one dose of metrifonate. These observations have recently been confirmed by Rey et al. (1984).

In only a few studies interest has been focused in the analysis of drug failure after the recommended regimen of three doses. Studies in patients from various West African countries, the Gambia and the Sudan demonstrated that failure of metrifonate was quantitatively and qualitatively similar in patients from different endemic areas and occurred independently of the pretreatment level of intensity of infection (Wilkins and Moore, 1980; Feldmeier et al., 1982c). Our own observations indicated that, if patients failed to respond appropriately after the first two doses of metrifonate, a third, a fourth or even fifth had no further effect on egg excretion (Feldmeier et al., 1982c).

Reduction of morbidity

Until very recently little attention has been paid to the question how treatment with metrifonate will effect the morbidity associated with *S. haematobium* infection. Proteinuria, haematuria and leukocyturia are indicators of lower renal tract pathology which are significantly related to the intensity of this infection (Feldmeier et al., 1982a; Mott et al., 1983).

A three-year longitudinal study clearly evidenced, that only three doses of metrifonate spaced over a period of 16 months, significantly reduced lower renal tract pathology (Doehring et al., 1984). Moreover, a statistical relationship was observed between decrease of individual egg counts and reduction of proteinuria, hematuria and leukocyturia. Recently, improvement of abnormal renographic findings after treatment with metrifonate has been reported (Wilkins et al., 1985). A longitudinal study from Kenya (Stephenson et al., 1985b) demonstrated that treatment with metrifonate produced significant rises in hemoglobin level which were positively correlated with the reduction in the intensity of *S. haematobium* infection. As in these patients treatment was also paralleled by a decrease in splenomegaly (Stephenson et al., 1985a) and as increased red cell hemolysis by the enlarged spleen is considered to contribute to the anaemia in schistosome infection (Mahmoud and Woodruff, 1972) the positive effect of metrifonate treatment may be more than a simple decrease in urinary iron loss.

In addition, a standard three-dose course can produce hookworm cure-rates on the order of 20% and egg reduction rates of about 80% (Stephenson et al., 1982; Kurz et al., 1986). Hence, mass-treatment with metrifonate in areas where hookworm infection is prevalent may have the additional benefit to reduce hookworm associated anaemia. Such an additional benefit is not to be expected after treatment with praziquantel, as this drug acts only against trematodes and cestodes. However, it should be made clear, that metrifonate cannot be recommended as a primary treatment for hookworm infection.

Table 5. Single dose of metrifonate

Authors	Area	Number of patients	Follow-up time	Reduction of egg excretion[a]	Cure-rate
Arap Siongok et al., 1978	Kenya	72	3 months	97%	22%
Wilkins and Moore, 1980	Gambia	49	3 months	75%	28%
Pugh and Teesdale, 1984	Malawi	48	24 months	54%	–
Pugh and Teesdale, 1984	Malawi	97	6 months	87%	–
Mason and Tswana, 1984	Zimbabwe	280	4 months	75%[b]	41%
Tswana and Mason, 1985	Zimbabwe	256	18 months	–[c]	24%

[a] calculated using the arithmetic mean as statistics
[b] 65% of patients showed a reduction of 90% or more
[c] 50% of patients showed a reduction of 90% or more

Single dose treatment

The recommended 3 doses of metrifonate at 10 mg/kg administered at 14 days intervals increase logistic requirements and costs in population based chemotherapy programs. Based on the epidemiological knowledge of the highly clumped nature of the distribution of adult schistosomes in the human host (Anderson and May, 1982) and on clinical evidence for a causal relationship between intensity of infection and disease a new concept has been put forward by Kloetzel (1967) and later on by Warren and Mahmoud (1976). The aim of targeted treatment being not to eradicate parasites from each infected host but rather to substantially reduce the intensity of infection in the individual patient and the number of eggs excreted in the environment. A single dose of 10 mg/kg metrifonate should be a cost-effective means for such a targeted mass treatment (El Kholy et al., 1984). It would be expected from results previously shown that a single dose of metrifonate would reduce egg excretion by almost 90%. Indeed five studies from different endemic areas with continuing transmission of *S. haematobium* showed a reduction of egg excretion between 97 and 54%, three to 24 months after chemotherapy, respectively (Table 5). This contrasts favorably with cure-rates between 41 and 22% during the same period of follow-up. As most of these studies have been done on small populations longitudinal studies in larger populations using the single dose approach are required before it can be recommended on a large scale.

Intermittent chemotherapy

In 1976 Jewsbury and Cooke formulated the concept that metrifonate given at regular intervals to inhabitants of endemic areas should a) maintain egg excretion at a low level and b) protect still non-infected individuals against infection. Their results from studies performed in Zimbabwe (Jewsbury et al., 1977; Jewsbury, 1981) clearly demonstrated that metrifonate given monthly or four-monthly (7.5 mg/kg) reduced egg-excretion by almost 100% for a period of

18 months and prevented the development of significant egg excretion in children negative at the beginning of the study. Moreover, Druilhe et al. (1981) demonstrated that the aministration of two consecutive doses repeated three times a year had a similar effect. Interestingly, it has recently be shown that the minimal requirements to obtain significant reduction in intensity of infection in diseased individuals can be lowered to three doses of metrifonate spaced over a period of two years (Doehring et al., 1984). Intermittent chemotherapy with metrifonate could therefore be of value if directed at selected segments of a population to be at risk for perpetuating infection and the development of disease.

Conclusion

Metrifonate is an excellent drug for the treatment of urinary schistosomiasis in areas with *S. haematobium* monoinfection. The most interesting features of this drug are the following: The mode of action remains obscure. Inhibition of cholinesterase alone does not explicate the failure of metrifonate in infections with *S. mansoni* or *S. japonicum*. Data recently published support the hypothesis that a shift of adult worms to the liver or the lungs plays a significant role. However, it is conceivable that the mechanistic explication of a simple shift to liver or lungs (Forsyth, 1965) is not adequate to explain the paradox of effective elimination of worms dwelling in the perivesical plexus and the lack of effect, if worms are located in mesenteric plexus. It may also be possible that in the presence of a high number of immunocompetent cells in the lungs such as eosinophils or alveolar macrophages pharmacologically damaged worms could be killed in the lungs, but not in the liver. Toxicity apparently is negligible. Side effects due to the inhibition of acetylcholinesterase are usuallay scarce, light and transient in nature. The recommended 3 doses of metrifonate at 10 mg/kg can be expected to achieve cure rates ranging between 60 and 90%. Cure rates with metrifonate are inversely related to the intensity of infection. On the other hand the reduction in egg count is surprisingly consistent: each dose eliminates almost 90% of the existing worm population. Considering the typical binomial distribution of egg output in an endemic area, it is predictable that 50% or more of a population will cease to excrete ova after three doses of metrifonate.

An intermittent course of metrifonate may be administered by minimally trained health personal. When appropriately timed with regard to local transmission dynamics the minimal requirement to achieve 99% reduction of egg excretion may be as low as three or four doses spaced over a period of two years. Such a minimal regimen should be feasible even for widescale programs and its costs should be less than 20 cents per child (Jordan, 1985).

It is clear that metrifonate is not the drug of choice, if radical cure is the objective of treatment. However, the drug meets an important objective of schistosomiasis control, i.e. reduction of morbidity. This is achieved by a

constant quantitative decrease in the parasite load after each administration of metrifonate. Moreover, mass treatment with metrifonate in areas with a high prevalence of hookworm infection would reduce hookworm associated anaemia.

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