Metrifonate

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202 Metrifonate

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1. DESCRIPTION

Metrifonate (trichloforon; Bilarcil®) is an organophosphate compound that was first developed as an insecticide and later used for the treatment of *Schistosoma haematobium* infection.

Metrifonate is a prodrug that is converted nonenzymatically at physiologic pH to the potent cholinesterase (ChE) inhibitor dichlorvos (2,2-dichlorovinyl dimethyl phosphate, DDVP). DDVP-inhibition of rat erythrocyte ChE is not reversible by repeated washing (Holmstedt *et al.*, 1978; Nordgren *et al.*, 1978). The chemical formula is $C_4H_8Cl_3O_4P$ and the structure of metrifonate is shown in Figure 202.1.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

In vitro, dichlorvos is an equally potent inhibitor of both *S. mansoni* and *S. haematobium* acetylcholinesterases (Holmstedt *et al.*, 1978). However, metrifonate shows clinical efficacy only against *S. haematobium* (Talaat, 1964a; Forsyth and Rashid, 1967; Holmstedt *et al.*, 1978).

3. MECHANISM OF DRUG ACTION

The molecular basis of metrifonate's action remains incompletely understood. Metrifonate has anticholinesterase activity, but this does not completely explain the drug's mechanism of action.

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

The standard dose of metrifonate for *S. haematobium* is 7.5–10 mg/kg on three occasions at 14-day intervals (Danso-Appiah *et al.*, 2008).

Table 202.1 summarizes the doses used in early trials of metrifonate therapy for *S. haematobium* infection.

4b. Newborn infants and children

There are few data available regarding the use of metrifonate in children and infants.

4c. Altered dosages

There are minimal data available regarding whether dosage adjustments are required in patients with renal or hepatic impairment.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

5a. Bioavailability

The drug is administered orally, with peak plasma concentrations of the parent drug, metrifonate, and its active metabolite, dichlorvos, attaining ~30 µmol and 0.3 µmol/l, respectively, within 1 hour of a single dose of 10 mg/kg (Holmstedt *et al.*, 1978). The plasma elimination half-life of both compounds is 1.5–2.0 hours. The bioavailability of metrifonate is unaffected by taking the drug with or without food (Heinig and Sachse, 1999).

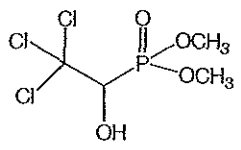

Figure 202.1 Chemical structure of metrifonate.

5b. Drug distribution

There are no large studies of the pharmacokinetics or pharmacodynamics of metrifonate in healthy volunteers. Data have been extrapolated from early field trials and recent studies in patients with Alzheimer's disease (AD) (Pettigrew *et al.*, 1998). The standard dose for *S. haematobium* is 7.5–10 mg/kg on three occasions at 14-day intervals (Danso-Appiah *et al.*, 2008). Data from the field are not directly comparable with the dose regimens trialled in AD, which ranged up to 80 mg daily for 26 weeks (Gélinas *et al.*, 2000). This

Table 202.1 Early trials of metrifonate therapy for *S. haematobium* infection

Oral dose (mg/kg)	Schedule	Reference
5	Daily for 12 days	Abdalla *et al.*, 1965
5	Daily for 12 days	Hanna *et al.*, 1966
5	Daily for 23 days	Talaat, 1964a
10	Daily for 6 days	Talaat, 1964b
20	Every 48 hours, three doses	Talaat, 1964a
7.5	Every 2 weeks, five doses	Katz *et al.*, 1968
10	Every 2 weeks, three doses	Forsyth and Rashid, 1967
7.5	Every 2 weeks, three doses	Davis and Bailey, 1969b
7.5	Every month, three doses	Reddy *et al.*, 1975
7.5	Every 2 weeks, three doses	Jewsbury *et al.*, 1977

Adapted with permission from Holmstedt *et al.*, 1978.

dose-ranging study in AD patients compared four treatment doses after a loading dose. All metrifonate doses were well tolerated. Mean area under the concentration–time curve (AUC) and maximum concentration (C_{max}) for both metrifonate and DDVP increased in relation to dose (Pettigrew *et al.*, 1998). Metrifonate and DDVP had similar, largely dose-independent mean values for time to C_{max} (t_{max}) and half-life ($t_{\frac{1}{2}}$). Accumulation of either metrifonate or DDVP was minimal after long-term administration. After 21 days of treatment, mean percentage erythrocyte ChE inhibition was 14% for the placebo group, and ranged in a dose-dependent fashion from 35% to 82% for the four treatment groups (Pettigrew *et al.*, 1998).

There are no data on the excretion of metrifonate in breast milk.

5c. Clinically important pharmacokinetic and pharmacodynamic features

There are minimal data linking the clinical efficacy of metrifonate to its pharmacokinetic and pharmacodynamic parameters.

5d. Excretion

Less than 1% of the drug is excreted unchanged in the urine. Disruption of the phosphonate bond is the major catabolic pathway of metrifonate, with 65% of administered drug recovered as a trichloroethylglucuronide conjugate from the urine (Holmstedt *et al.*, 1978). O-Demethylation followed by phosphonate cleavage is the other major catabolic pathway and has been described in rat brain homogenates (Holmstedt *et al.*, 1978). DDVP is demethylated to dimethyl DDVP, with concurrent methylation of glutathione catalysed by glutathione S-methyltransferase in the cytosol of the liver and lung. The major pathway of metrifonate catabolism that is observed in the rat also occurs in pigs, mice, hamsters, and humans (Holmstedt *et al.*, 1978; Nordgren *et al.*, 1978).

5e. Drug interactions

There are few data available regarding co-administration of metrifonate with other agents.

6. TOXICITY

Most adverse events associated with metrifonate are restricted to gastrointestinal toxicity and are usually mild and transient.

Extensive monitoring in early clinical trials demonstrated an expected fall in plasma and erythrocyte ChE, but no other biochemical, haematologic, or cardiovascular problems. The decreased ChE activity could be reversed with pralidoxime, and cholinergic symptoms were relieved with atropine (Holmstedt *et al.*, 1978).

Human cases of neurotoxicity – predominantly presenting as a late peripheral neuropathy – have been reported in overdose suicide attempts in the Former Soviet Union (Johnson, 1981). No other similar reports have been reported. Animal studies suggest that neurotoxicity only arises from doses many times above the LD_{50}.

The largest reported single oral dose administered was 72 mg/kg (Talaat, 1964a; Holmstedt *et al.*, 1978), which led to significant side-effects, including severe vomiting, colicky abdominal pain, and muscular weakness that resolved over 3 days with atropine sulfate administered 6-hourly for the first 2 days. The same paper reported that 33 mg/kg caused similar symptoms that resolved over 3 hours with 2 mg of i.m. atropine. A dose of 15 mg/kg produced intestinal colic in three of six male volunteers (Forsyth and Rashid, 1967), which settled within 24 hours. Some cholinergic side-effects have been observed in histosomiasis patients given 5 mg/kg daily for 12 days (Hanna *et al.*, 1966).

a. Animal studies

The LD_{50} for metrifonate in rats ranges from 250 mg/kg when given by intraperitoneal administration to 650 mg/kg when administered orally. Similar values have been obtained for mice and guinea-pigs (Holmstedt *et al.*, 1978). The acute toxicity of metrifonate, expressed as LD_{50} in rats, is low compared with other organophosphate insecticides, such as parathion (3–6 mg/kg) or methylparathion (12–15 mg/kg). Metrifonate has a very low dermal toxicity (LD_{50} > 2800 mg/kg) compared with DDVP (LD_{50} 75–900 mg/kg) (Holmstedt *et al.*, 1978). This is probably explained by differences in lipid solubility between the two compounds.

The acute toxic effects of high doses in mammals result in clinical findings typical of cholinergic drug effects. Complete recovery usually occurs within a few hours. Maximum inhibition of brain ChE after i.p. administration of metrifonate to rats occurred within 15 minutes (Nordgren *et al.*, 1978). The rate of recovery is dose dependent, with 100% of brain ChE recovery 1 hour after 25 mg/kg compared with 75% 5 hours after 125 mg/kg (Nordgren *et al.*, 1978).

Subacute and chronic organ toxicity has been reported in livestock after use of the commercial insecticide preparation, trichlorfon (Holmstedt *et al.*, 1978). These initial reports describe cardiac and liver necrosis, interstitial nephritis, and hemorrhagic infarction of the adrenal glands. Longer-term studies, in which 500–1000 ppm of metrifonate was fed to rats and dogs for up to two years, failed to demonstrate significant clinical, biochemical, hematologic, or histopathologic abnormalities, apart from a 20% reduction in whole-blood ChE activity (Holmstedt *et al.*, 1978). When given to rats (p.o., i.m., or i.p.) at doses of 15–30 mg/kg two to three times per week for the lifespan of the animals, an excess of malignant tumors (mostly sarcomas of the liver and spleen) was observed, compared with controls given saline injections (Holmstedt *et al.*, 1978; Nordgren *et al.*, 1978). Myeloproliferative changes were also observed. Such toxicities have not been reported in humans to date.

6b. Mutagenicity and embryotoxicity

Embryotoxicity and teratogenicity has been evaluated in laboratory animals with mixed results. It is associated with embryotoxicity in rats and hamsters after administration on days 7–11 of gestation at 400 mg/kg/day by gavage feeding (Staples and Goulding, 1979). Mice, however, appeared relatively resistant to the embryotoxic effects, but

a significant increase in the incidence of cleft palates was observed from exposure on days 10–14. More recent work suggests that the mouse preimplantation and pregestation embryos are able to recover from metrifonate toxicity (Tian *et al.*, 2000) to produce normal term fetuses. However, guinea-pig pups and piglets demonstrate cerebellar hypoplasia following *in utero* exposure to Dipterex (Knox *et al.*, 1978; Hjelde *et al.*, 1998; Mehl *et al.*, 2000). Cerebellar DNA alkylation and inhibition of DNA repair by trichlorfon is believed to be the mechanism of this hypoplasia (Mehl *et al.*, 2000).

6c. Pregnancy and lactation

There is a paucity of data regarding the safety of metrifonate in pregnancy (Monson and Alexander, 1984). There is one published case report of a Liberian infant born with hydrocephalus and meningomyelocele after the mother was treated with 450 mg of metrifonate at week 5 and then again at week 8 of pregnancy (Monson and Alexander, 1984). Another report documents a cluster of 11 (of 15) live births from a Hungarian village in 1989–90 with various congenital abnormalities including Down syndrome (Czeizel *et al.*, 1993; Czeizel, 1996). A subsequent case–control study demonstrated a significant association between Down syndrome and the consumption of fish with high levels (100 mg/kg) of triclorfon contamination. All mothers of Down syndrome-affected offspring had measurable blood levels of triclorfon (Czeizel *et al.*, 1993; Czeizel, 1996). There are no data on the excretion of metrifonate in breast milk. Metrifonate should therefore not be used in either pregnancy or lactation.

7. CLINICAL USES OF THE DRUG

The use of metrifonate has now greatly diminished because it has been demonstrated to be inferior clinically, economically, and operationally to praziquantel for the treatment of schistosomiasis (see Chapter 200, Praziquantel) (Feldmeier and Chitsulo, 1999) – particularly the requirement for multiple doses, the risk of poor compliance with second and third doses, and the potential for overdose. Subsequently, metrifonate was withdrawn from the WHO Model List of Essential Medicines (Cioli, 2000; Utzinger and Keiser, 2004). Praziquantel remains the mainstay drug for the treatment of schistosomiasis throughout the world, and metrifonate is currently unavailable for the treatment of schistosomiasis (Danso-Appiah *et al.*, 2008).

7a. *Schistosoma haematobium* infection

Metrifonate was initially used as an insecticide, which then led to the treatment of the ectoparasites of farm animals. Initial *in vitro* studies suggested activity against schistosomes, hookworm, *Ascaris* spp., and *Trichuris* spp. (Holmstedt *et al.*, 1978). The vast majority of information obtained on the human use of metrifonate comes from the treatment of schistosomiasis – in particular, *S. haematobium* infection.

Many of the early trials (see Table 202.1) were conducted using the commercial insecticide form, Dipterex (Talaat, 1964a; Talaat, 1964b; Abdalla *et al.*, 1965; Hsiao *et al.*, 1975; Holmstedt *et al.*, 1978). The standard dose of 7.5–10 mg/kg given three times at 14-day intervals has been used extensively and is mostly well tolerated (Forsyth and Rashid, 1967; Davis and Bailey, 1969a; Rugemalila and Eyakuze, 1981; Feldmeier and Doehring, 1987). Adverse effects are mainly as a result of cholinergic stimulation and include fatigue, muscular weakness, tremor, sweating, salivation, fainting, abdominal colic, diarrhea, nausea, vomiting, and bronchospasm.

More recent field trials with the recommended dose of 7.5–10 mg/kg for three doses at 14-day intervals have demonstrated cure rates (cessation of urinary egg shedding) ranging from 20% to 60% (Feldmeier *et al.*, 1982; Pugh and Teesdale, 1983; Wilkins and Moore, 1987; Aden Abdi and Gustafsson, 1989). Reduction in egg burdens of over 95% at one month were also reported in all trial subjects not cured. These reductions in egg shedding appear to be maintained for at least six months (Aden Abdi and Gustafsson, 1989) and are accompanied by reductions in hematuria from 50–75% of study populations to less than 20% (King *et al.*, 1988; King *et al.*, 1990). Proteinuria rates fall by similar percentages, and ultrasound-determined bladder wall thickening is also substantially reduced (King *et al.*, 1988; King *et al.*, 1990). Nutritional indices including hemoglobin measurements improve (Stephenson *et al.*, 1985a; Stephenson *et al.*, 1985b) after metrifonate treatment, independently of the presence of either hookworm or malaria. Infection intensity at baseline does not appear to influence response to metrifonate (Feldmeier *et al.*, 1982). One group has demonstrated equivalent responses of *S. haematobium* and *S. mansoni* infections in infection exclusively restricted to the urinary tract (Doehring *et al.*, 1986), suggesting that the antihelminthic effect of metrifonate is confined to the vesical plexus. This hypothesis remains to be confirmed.

As noted above, the use of metrifonate greatly diminished after it was demonstrated to be inferior operationally to praziquantel (see Chapter 200, Praziquantel) (Feldmeier and Chitsulo, 1999) and the drug has subsequently been withdrawn from the WHO Model List of Essential Medicines (Cioli, 2000; Utzinger and Keiser, 2004).

A review of the limited comparative data available demonstrates that metrifonate (10 mg/kg every 2 weeks for three doses) is of equivalent efficacy to praziquantel (40 mg/kg as a single dose) for *S. haematobium* infection (Danso-Appiah *et al.*, 2008), despite its more complex dosing schedule and potential for reduced adherence. This has resulted in calls for metrifonate to be made available as an option for the treatment of patients with *S. haematobium* infection (Danso-Appiah *et al.*, 2008). Metrifonate should not be used in communities or individuals with recent exposure to either organophosphate insecticides or within 48 hours of receiving a nondepolarizing neuromuscular blocking agent.

7b. Alzheimer's disease

In recent years, metrifonate has been trialled in patients with AD. However, the report to the US FDA that approximately 20 of the 3000 patients with AD in clinical studies of metrifonate in AD developed "asthenia, myasthenia, and malaise" and that "four patients with muscular weakness received respiratory support" led to the cessation of clinical development of metrifonate for this indication (AlzForum, 2005; Lopez-Arrieta and Schneider, 2006).

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