Oxamniquine

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201 Oxamniquine

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1. DESCRIPTION

Oxamniquine (Mansil® and Vansil® from Pfizer) – developed as UK 4271 – was first described in 1969 (Richards and Foster, 1969) as a metabolite of a compound then known as UK 3883 (2-isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline). Oxamniquine is 1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolylmethanol. It is a derivative of hycanthone (Richards and Foster, 1969). The chemical structure is shown in Figure 201.1.

The drug has been used for the treatment of *Schistosoma mansoni*, but has now been largely replaced by praziquantel in most regions (see Chapter 200, Praziquantel).

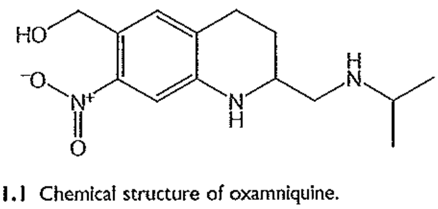

Figure 201.1 Chemical structure of oxamniquine.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

Oxamniquine is a narrow-spectrum drug that is active only against *Schistosoma mansoni*. It is ineffective against *S. japonicum* in animal models, and early human studies demonstrated no efficacy against either *S. haematobium* or *S. matthei* (Pitchford and Lewis, 1978). Animal studies suggest that male worms are preferentially killed by oxamniquine. Surviving single female worms then cease laying eggs, effectively halting the pathogenesis of schistosomiasis.

2b. Emerging resistance and cross-resistance

Strains of *S. mansoni* were identified as early as 1986 in Brazil, Puerto Rico, and Kenya that were resistant to oxamniquine – and in some cases also hycanthone and niridazole (Bruce *et al.*, 1987). These strains do not appear to lack replication fitness and can be maintained in the laboratory (Bruce *et al.*, 1987). Some strains isolated from patients who had failed multiple oxamniquine courses have been studied in laboratory animals (Conceicao *et al.*, 2000), and have shown a relative excess of male worm survival following drug exposure. Recent work has demonstrated that the schistosome-encoded 32-kDa sulfotransferase responsible for the esterification and activation of oxamniquine is absent from oxamniquine-resistant strains of *S. mansoni* (Pica-Mattoccia *et al.*, 2006). This sulfotransferase is not detectable in either *S. haematobium* or *S. japonicum* – both species being intrinsically oxamniquine resistant (Pica-Mattoccia *et al.*, 2006). Cross-breeding experiments have demonstrated that vertical transmission of oxamniquine resistance occurs in an autosomal recessive fashion (Geerts and Gryseels, 2000). In resistance that has been observed, it tends to occur in individual cases rather than affecting whole communities (Geerts and Gryseels, 2000).

3. MECHANISM OF DRUG ACTION

In susceptible *S. mansoni* strains, oxamniquine is believed to require activation by a parasite-encoded sulfotransferase to an electrophilic ester that alkylates parasite DNA (Pica-Mattoccia *et al.*, 1997; Pica-Mattoccia *et al.*, 2006), resulting in contraction and paralysis of the worms and eventual detachment from terminal venules in the mesentery, and subsequent death. It is also hypothesized that its mechanism of action is related to an anticholinergic effect that increases the parasite's motility, as well as inhibition of synthesis of nucleic acids. Immature worms (<28 days post infection) are relatively refractory to the effect of oxamniquine – with an ED_{50} 30 times greater than that of 7-week-old parasites (Pica-Mattoccia and Cioli, 2004). The drug is also more effective in bisexual infections than in single-sex infections (Pica-Mattoccia and Cioli, 2004). Tetanic contractions were observed with *in vitro* incubation of adult worms of all ages – even with sublethal oxamniquine concentrations (Pica-Mattoccia and Cioli, 2004). Although oxamniquine acts mainly on male worms, it also induces small changes in a small proportion of females. Like praziquantel, it promotes more severe damage of the dorsal tegument than the ventral surface. The drug causes the male worms to shift from the mesenteric circulation to the liver, where host cellular host responses cause its final elimination (Pica-Mattoccia and Cioli, 2004). It is believed that changes caused to female worms are reversible and are due primarily to discontinued male stimulation rather than to any direct drug effect. Passive serum transfer experiments in mice suggest that immune serum augments the schistosomicidal activity of oxamniquine (Doenhoff, 1989).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

Oxamniquine is available as either a 250-mg capsule or 50 -mg/ml syrup. It is marketed as Mansil® in South America (deVClarke *et al.*, 1976) and Vansil® in Africa (Pitchford and Lewis, 1978). The shelf-life of the capsules and syrup is five and three years, respectively (Foster, 1987). Both preparations need to be stored in closed containers away from light. It has been recommended that the drug be taken on an empty stomach (deVClarke *et al.*, 1976), although this point has not been the subject of rigorous study.

Oxamniquine is used mostly in Brazil. It is no longer marketed in Africa because of the commercial predominance of praziquantel (Geerts and Gryseels, 2000).

Oxamniquine is generally used in an oral dose of 15 mg/kg body weight twice daily for 1 day in adults, although regimens vary (see below under 7. Clinical uses of the drug) (Katz *et al.*, 1976; Foster, 1987). Overall, oxamniquine appears to be as effective as praziquantel for the treatment of only *S. mansoni* infection provided a total dose of 30 mg/kg is used (Saconato and Atallah, 2000). Doses of 20 or 40 mg/kg/day have been used in children in Africa; with the latter dose being preferred by some authors (Abdel Rahim *et al.*, 1988).

5. PHARMACOKINETICS AND PHARMACODYNAMICS

5a. Bioavailability

In healthy volunteers, peak plasma concentrations (1–4.3 mg/l) are achieved in 1–4 hours after oral administration (Kokwaro and Taylor, 1991). The plasma elimination half-life is 1–2.5 hours (Kokwaro and Taylor, 1991). Daneshmend and Homeida (1987) demonstrated that schistosomiasis patients have similar mean AUC, elimination $t_{1/2}$, and t_{max} as healthy control subjects. However, infected patients had a significantly reduced C_{max} (p=0.04). There was no correlation between disease severity and oxamniquine pharmacokinetic values (Daneshmend and Homeida, 1987).

5b. Drug distribution

Animal models have demonstrated that oxamniquine is widely distributed throughout the body, with a steady-state volume of distribution of 7.9 ± 4.5 and 2.1 ± 0.5 l/kg in rabbits and rats, respectively (Kokwaro *et al.*, 1996). Oxamniquine pharmacokinetics was studied following oral administration of 750, 1000, or 1250 mg (equivalent to approximately 15 mg/kg) to five healthy Kenyan African volunteers (Kokwaro and Taylor, 1991).

5c. Clinically important pharmacokinetic and pharmacodynamic features

There are no data to correlate the clinical activity of oxamniquine with its pharmacokinetic and pharmacodynamic parameters.

5d. Excretion

The metabolism of oxamniquine has been studied in the mouse, rat, hamster, rabbit, rhesus monkey, dog, and man (Kaye and Woolhouse, 1976; Daneshmend and Homeida, 1987; Kokwaro *et al.*, 1996). Urinary excretion is a major route of elimination in man. Two major metabolites are formed in the liver, the major one arising from oxidation of the 6-hydroxymethyl group to a carboxyl group, and the other by oxidation of the side chain to give the 2-carboxylic acid (Kaye and Woolhouse, 1976). The 2-carboxylic acid metabolite is detectable only in trace amounts in human urine (Kaye and Woolhouse, 1976).

5e. Drug interactions

There are few data regarding drug–drug interactions given the current limited use of this agent.

6. TOXICITY

In general, oxamniquine is well tolerated. Dizziness, drowsiness, and headache have been infrequently reported; those affected should not drive or operate heavy machinery for 24 hours after treatment. A brief fever in the 24 hours following treatment is not uncommon. In Egypt only, a sustained fever of 38–39 °C for 2–5 days has been reported (Foster, 1987). No explanation for this observation has been proffered and the fever appears to occur in the absence of aberrant pharmacokinetics or excessive immune complex production (Foster, 1987).

Drowsiness and euphoria are rare side-effects at conventional doses, but are frequent at higher doses (over 60% of patients given 15 mg/kg as a single dose) (Katz *et al.*, 1976). Vomiting and abdominal discomfort also appear to occur in a dose-dependent relationship (Katz *et al.*, 1976). Although some patient groups may need close monitoring, there are few contraindications. There are infrequent reports of generalized seizures in patients with a history of epilepsy, with 14 cases reported from 9 million patients treated up to 1987 (Foster, 1987). Monitoring is recommended for 48 hours after treatment. Hallucinations and significant psychiatric complications occur at a frequency of approximately 0.4% (Foster, 1987). A peripheral blood eosinophilia is a common consequence and peaks at about 7–10 days post treatment. It may occur in conjunction with scattered pulmonary infiltrates, elevated serum aminotransferases, and increased circulating immune complexes – consistent with the hypothesis that this is a response to debris released from dead or injured schistosomes.

An early parenteral form of oxamniquine given by intramuscular injection was associated with significant pain at the injection site (Katz *et al.*, 1973; Rees *et al.*, 1975) and is no longer available. There are no data on the safety of oxamniquine for the treatment of schistosomiasis in pregnancy.

7. CLINICAL USES OF THE DRUG

7a. *Schistosoma mansoni* infection

Oxamniquine was first used for schistosomiasis in clinical trials in Africa and Brazil as a parenteral formulation. Small clinical studies demonstrated some clinical efficacy in immunologically naive patients with acute schistosomiasis (Katayama fever) – consistent with *in vitro* activity against juvenile schistosomes (de Clarke, 1980; Foster, 1987).

In a small Brazilian study a single dose of 7.5 mg/kg i.m. was well tolerated and all subjects were cured, as defined by cessation of fecal egg shedding (Katz *et al.*, 1973). Katz *et al.* (1976) later undertook extensive dose-ranging studies in both adults and children in Brazil. Single-dose therapy ranged from 10 to 15 mg/kg in adults and children, while two split doses ranged from 7.5 to 10 mg/kg were trialed only in children. In the single-dose study, cure rates in adults ranged from 79% to 94% at 15 mg/kg, while they rose to around 86% in all split dose regimens. Cure rates in children with single-dose therapy in that study were disappointing at 30–60% (Katz *et al.*, 1976). Similar results were reported from Africa (deVClarke *et al.*, 1976), where cure rates of 82% were associated with a dose of 15 mg/kg twice daily for 2 days (total dose, 60 mg/kg). In agreement with the Brazilian study, the investigators reported that the majority of treatment failures occurred in children weighing less than 30 kg (deVClarke *et al.*, 1976). Two potential explanations for treatment failure in African pediatric populations are relative underdosing and incorrect diagnosis. In other studies where oxamniquine was dosed at 800 mg/m^2 body surface area (Axton and Garnett, 1976), cure rates of 66% among children were reported. One group (deVClarke *et al.*, 1976) suggested that inadequate speciation led to missed diagnoses of mixed *S. mansoni* and *S. haematobium* infections, therefore confounding some of the early African pediatric data. Also, children appear to have a greater component of their worm burden from recent infections which are more likely to be oxamniquine refractory (Pica-Mattoccia and Cioli, 2004).

When treated with 40–60 mg/kg over 2 days, cure rates of over 80% can be expected. In those not cured, fecal egg shedding can be reduced by over 90% (Foster, 1987). It is likely that cure is not related to infection intensity (Foster, 1987). In patients with late-stage hepatosplenic disease who have confirmed parasitologic cure, over half have significant but not complete regression of hepatosplenomegaly (de Clarke, 1980; Foster, 1987). Patients with established schistosomal glomerulopathy do not have an improvement in renal function following parasitologic cure despite a reduction in circulating immune complexes (Foster, 1987).

In more recent clinical trials oxamniquine dosage at 15 mg/kg daily for 2 days has been compared with praziquantel – usually at a single dose of 40 mg/kg (de Rezende, 1985; Creasey *et al.*, 1986; da Cunha and Pedrosa, 1986; da Silva *et al.*, 1986; Gryseels *et al.*, 1987; Zwingenberger *et al.*, 1987; Taddese and Zein, 1988; Gryseels and Nkulikyinka, 1989; Butterworth *et al.*, 1991; Ferrari *et al.*, 2003). Cure rates in groups treated with oxamniquine are generally not significantly different from those in patients treated with praziquantel when the endpoint is clearance of fecal egg shedding. Oxamniquine, administered in appropriate divided doses administered to a total of 40 mg/kg, results in cure of 86% of children and 97% of adults at 6 weeks (Gryseels *et al.*, 1987; Taddese and Zein, 1988). However, neurotoxicity was observed frequently in such patients, and single-dose therapy is logistically easier in field settings (Taddese and Zein, 1988; Gryseels and Nkulikyinka, 1989). If the clearance of eggs from rectal biopsy specimens (the more sensitive parasitologic technique) is used as the determinant of cure, praziquantel cure rates remain at up to 96% (equivalent to fecal microscopy results), whereas the apparent oxamniquine cure rate falls from 90% (fecal microscopy) to 42% (da Cunha and Pedrosa, 1986; Ferrari *et al.*, 2003).

Overall in routine field and clinical settings, oxamniquine is as effective as praziquantel for the treatment of only *S. mansoni* infection provided a total dose of 30 mg/kg is used (Saconato and Atallah, 2000).

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