**ANTISCHISTOSOMAL DRUGS**

**Schistosomiasis** is a group of diseases (as paragonimiasis,clonorchiasis) which is effect millions of people around the world. The Middle East area is still suffering from this disease.

1. **The tremetodes (flukes)** which cause this disease are

*1. S.haematobium*

*2. S.mansoni*

*3. S.japonicum*

**Antischistosomal drugs:**

1. Praziquantel

2. Metrifonate

3. Oxamniquine

**1- Praziquantel**

It is **broad spectrum anthelmintic drug**

It is *effective* *in the treatment of schistosome infections of all species* and *most other trematodes and cestode* but **nematodes are unaffected.**

**Anthelmintic action:**

* The drug **increases cell membrane permeability to calcium** resulting in *vacuolization , marked contraction* (death of parasite) *Paralysis , dislodgement* from *blood vessel walls* and *rapid shift* from *mensentric veins to liver and death of a parasite.*

At *lowest effective concentration* ,it causes *increase in muscular activity followed by contraction and paralysis* . At *higher doses* it *damages the capsule of the worm* by influx of calcium across tegument.

It is *effective* against adult worms and also against immature stages.

 It also possess **prophylactic effect** against **cercarial infections**.

**Pharmacokinetics:**

It is **a synthetic isoquinoline pyrazine derivative**

It is *rapidly absorbed* after **oral administration**

Its *maximum plasma concentration reaches* in *1-2 hours*

It has large distribution volume It **can cross BBB**

*Highly bound* to plasma proteins (80%)

*Metabolized* **extensively** **in liver** to *inactive metabolites* and excerted in **urine.**

It has a half life of **0.8 to 3 hours**( which **increases in** **liver diseases**)

Carbohydrate diet and cimetidine (enzyme inhibitors) **increases** its *bioavailability*

* Corticosteroids and antiepileptics( *phenytoin and carbamazepine*) **reduces** its *bioavailability*

It is taken *after meals with liquids without chewing.*

The interval between the doses should *not be less than 4 hours* and *not more than 6 hours (taken more than once daily)*

**Clinical uses:**

**1. Schistosomiasis: ( drug of choice for all trematodes infections)**

* For *S.Japonicum infections*, 20 mg/kg at intervals 4-6 hours for a total of 3 doses.
* For *S.mansoni and S.hamatobium* 40 mg /kg in two divided doses.

The drug is *effective in children* ***as well as*** in *adults* and is well tolerated.

It is ***not clear*** whether the drug can safely be used during acute stage of disease (Katayama fever),*because release of antigens from dying of immature worm* may exacerbate the symptoms.

Effectiveness of the drug for *chemoprophylaxis has* ***not*** *been established.*

**2. Use in other infestation (infections):**

*Clonorchiasis, opisthorchiasis and paragonimiasis.*

*Taeniasis and diphyllobothriasis.*

*Neurocysticercosis ( albendazole is preferred)*

*H.nana ( the drug of choice)*

*Hydated cyst and others.(echinococcosis)*

**Adverse reactions:**

1. **Most frequent** are *headache, dizziness, drowsiness , and lassitude.*

2. GIT disturbances

3. Pruritus, urticaria ,arthralgia, myalgia ,low grade fever

4. *Minimal to mild* transient elevation *of liver enzymes*.

5. *Skin rashes ,augmented eosinophilia* , may appear several days after starting the medication *due to release of foreign protein from dying worm* rather than direct toxicity.

* adverse effects may be more severe , especially in ***S.mansoni infections***

**Contraindications and precautions :**

**Mainly in ocular cysticercosis** for fear of destruction of parasite in eye.

The drug can be used in liver impairment but the dose should be **reduced.**

It is **not safe** to be used for **children below 4 years of age**.

*Driving or work which require alertness and physical coordination* **should be prohibited.( the drug induce dizziness and drowsiness)**

It **should not** be used during **pregnancy.**

In case of *nursing mother ,feeding* should be **stopped for 3 days.**

Patient should be informed regarding **chewing the drug** because it has a **bitter taste** that can induce **drug regurgitation**.

**2- METRIFONATE (TRICHLORFON)**

It is *safe, low cost alternate* for treatment of **S.haematobium infections**. (NOT active against S.mansoni and S.japonicum)

**Pharmacokinetics**

It is **organophosphate compound.**

It is *rapidly absorbed* after **oral admininstration** andgets **widely distributed** to tissues.

It has a half life of *1-5 hours*

*Metabolized to active metabolites*

**Anthelmintic action:**

* It is effective against both the ***mature and immature*** stages of ***S.haematobium*** .It is thought it produces this effect by **inhibition of cholinestrase.**

It *temporarily paralysis* the adult worm which leads to **their shift** *from the bladder venous plexus*(is the primary site of infection by S.H)*to a small arterioles of the lungs* ,where they are **trapped** by the immune system and killed.

It is **not effective** *against S.haematobium eggs* , live eggs continue to pass in the urine for several months after all adult worms have been killed.(USED IN DIGNOSIS)

**Clinical uses:**

* A single dose of 7.5-10mg/kg is *given orally three times* at 14 days intervals.
* It is also effective as **prophylactic** when give monthly to children in a highly endemic area.
* *In mixed infection with S.H and S.M* , metrifonate is successfully combined with oxamniquine.

**Adverse Reactions:**

**Mild and transient cholinergic symptoms** including ,*nausea , vomiting, diarrhea, abdominal pain, bronchospasm , headache, sweating , fatigue, weakness, dizziness, and vertigo ,* that may start after 30 min and persist up to 12 hours.

The drug is tolerated by patients in the *advanced hepatosplenic stage.*

**Contraindications and cautions:**

It **should not** be used ***after recent exposure to insecticides*** *(organophosphate compound)*or ***drugs that potenciate cholinestrase inhibition.***

The *use of muscle relaxants* ***should be avoided for 48 hours after administration of the drug***

It is contraindicated **in pregnancy.**

**3- OXAMNIQUINE**

It can be used **as alternative to Praziquantel for treatment of S.mansoni infections.**

**Pharmacokinetics:**

* It is administered **orally**
* It has a half life of **2.5 hours**
* It is **extensively** **metabolized** and excreted **via kidney**.

**Anthelmintic actions:**

It is *effective against* mature and immature stages of S.mansoni but it is *not effective* against cercaricidal form.

Its mechanism of action is **unknown.**

It **may cause** *contraction and paralysis of worms* which leads to its *detachment from the terminal venules in the mesentery (*is the primary site of infection by S.M*)*and **shift** *to the liver where worm may die*, surviving females may return to the mesenteric vessels but cease to lay eggs.

**Clinical uses:**

It is **less effective in children** (not used because of severe GI disturbance)

It is *better tolerated if given with food and at the end of the day* and in divided doses separated by 6-8 hours.

15 mg /kg twice daily for 2 days

1. In mixed infection with *S.haematobium and S.mansoni*, oxamniquine and metrifonate are given in combination.

**Adverse Effects:**

Dizziness , headache ,and drowsiness (CNS symptoms)\*

GIT disturbance \*

* Pruritus and urticaria \*
* low grade fever, Transient leucocytosis

Orange to red discoloration of urine

Protein urea

Convulsion and seizures

Increase in liver enzymes

Eosinophilia , urticaria (allergic manifestation due to the death of parasites and release of antigen.

**Contraindications:**

**Not for use** with activities requires **mental alertness**.

**Epilepsy.**

**Pregnancy.**