SAFETY REVIEW OF NICLOSAMIDE, PYRANTEL, TRICLABENDAZOLE and OXAMNIQUINE


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Executive Summary
The WHO Model List of Essential Medicines (2003) includes intestinal anthelminthics (pyrantel and niclosamide) and antischistosomal and antitrematodes (oxamniquine and triclabendazole). The continued inclusion of oxamniquine, triclabendazole, pyrantel and niclosamide on the EML has been questioned on the basis of their public health relevance and/or efficacy and/or safety. These four medicines among others will be reviewed at the next meeting of the Expert Committee (March 2005).

A detailed review of the safety of these four medicines (oxamniquine, triclabendazole, niclosamide and pyrantel) is reported here. The review was carried out using publications in journals and major reference sources combined with the assessment of adverse drug reaction (ADR) reports in the database of the WHO Collaborating Centre for International Drug Monitoring in Sweden (Uppsala Monitoring Centre).

The data from the published literature, though not as many as would be expected, provide evidence in support of the overall safety of these medicines with no publication citing an unfavourable safety assessment of any of the drugs. Whilst there have been concerns about the risk of seizures with oxamniquine, these concerns appear not to have diminished the extent to which the medicine has been used in several countries. All four medicines appear to be safe and well tolerated even when used in mass treatment campaigns. Adverse reactions reported to the UMC are relatively few, although in general they do not differ much from the published literature. This situation may be due to the absence of established pharmacovigilance systems in those settings where these drugs are largely used.

The current safety review indicates that oxamniquine, triclabendazole, niclosamide and pyrantel are safe for use in humans. In addition, the comments from CDS (as posted at the EDM website) are very relevant in considering the retention of these medicines on the Model List of Essential Medicines.

In order to enhance the evidence base to determine safety issues in relation to medicines that are likely to be used in settings with poor or non-existent pharmacovigilance systems, WHO should push its current efforts in the setting up of such systems.
**Introduction**
Parasitic infections are a major cause of disease burden, particularly in many countries in the tropics and sub-tropics. Several millions of people suffer because of diseases caused by schistosomes and other trematodes, and soil transmitted helminths. The importance of schistosomiasis and soil-transmitted helminthic infections have been recognised as priority health problems and through guidelines and technical assistance WHO has encouraged member countries to set up control programmes (Savioli et al., 1992). At the 54th World Health Assembly a resolution expressing concern about the global impact of soil-transmitted helminthiasis and schistosomiasis was adopted.

Periodic drug administration is one of the three principal strategies for reducing the burden of these diseases. The others are health education and information campaigns and the augmentation of knowledge and skills with regard to infections in the public health system at central and peripheral levels.

The WHO since 1997 has produced the Model List of Essential Drugs (now Medicines) for member countries. The list is made up of Core and Complimentary medicines. According to the Explanatory Notes of the 2003 Model List, “The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings”.

In the 2003 review of the Model List of Essential Medicines several drugs were flagged for consideration, by the Expert Committee at its next meeting, of their continued inclusion on the Model List on the basis of their public health relevance and/or efficacy and/or safety.

This report examines the safety of oxamniquine, triclabendazole, niclosamide and pyrantel as used in humans. It must be noted that these drugs have been used extensively in veterinary practice.

**Data Sources**
A search was made on PUBMED and “Google Scholar” (http://scholar.google.com) for all four drugs with emphasis on publications with the keywords “safety”, “adverse reactions” “adverse drug reactions”, “drug effect”, “adverse effects” or “clinical trials”. The Cochrane database was also searched for reviews on any of the four medicines. Following the electronic web searches, copies of available texts were obtained from the local library or electronically through HINARI for free and/or preferential access to...
selected online journals. In addition, through HINARI, specific high profile journals on infectious diseases and parasitology were searched for publications on the four medicines.

The search of the primary literature was complemented with review of textbooks and reference material including the WHO Model Formulary 2004, the British National Formulary (47, 2004), USP DI (2004), Martindale – the Extra Pharmacopoeia (31st Edition, 1996), Meyler’s Side Effects of Drugs (12th edition, 1992) and Stockley’s Drug Interactions (4th edition 1996). Adverse events information received from this desk review was added to those retrieved from the UMC database and reviewed together.

All the information retrieved were reviewed and summarised by a clinician and pharmacist (with interest in pharmacovigilance).

**Limitations**

This review was limited by the number of reports that contains information on adverse events for most of the anthelminthics. Although the burden of the diseases lies predominantly with developing countries, there were very few reports from this source except for countries in South America. Most of the reports were dated before the availability of electronic versions of the publications on databases and hard copies were therefore not easy to obtain. Furthermore, since most of the countries where these drugs are widely deployed do not have any formal pharmacovigilance systems, they do contribute to the global database of adverse drug reactions maintained at the Uppsala Monitoring Centre. Hence, any analysis of adverse events reported to the WHO database on these drugs gives only a partial picture.

It was also not possible to get access to International Medical Statistics (IMS) data to determine the extent of current consumption of these products (if available).

**Main Outcome**

The safety profile of each of the four medicines (niclosamide, oxamniquine, pyrantel and Triclabendazole) in humans.

**Results**

The safety assessment of each of the four medications is presented below. Very few studies were found that provided detailed information on safety of the medicines. Many of the studies made general statements regarding adverse/side effects.
NICLOSAMIDE

Niclosamide (2', 5-Dichloro-4'-nitrosalicylanilide; 5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide) is a nitrosalicylanilide introduced in early 1960s as an anticestodal drug. The drug has been used extensively since then and is listed on the WHO Model List of Essential Medicines 2003 and the WHO Model Formulary 2004.

Indication

An anthelmintic which is active against most tapeworms, including the beef tapeworm (Taenia saginata), the pork tapeworm (T. solium), the fish tapeworm (Diphyllobothrium latum), the dwarf tapeworm (Hymenolepis nana), and the dog tapeworm (Dipylidium caninum).

Cochrane Review

None cited

Adverse Effects

The WHO Model Formulary 2004 lists the adverse effects of niclosamide as follows: nausea, retching, abdominal pain; light-headedness, pruritus. Although there were several publications on the use of niclosamide in taeniasis, few provided enough information about adverse effects.

Since 1975, there have been 84 reports of suspected adverse drug reactions to niclosamide in the WHO database. These 84 reports involve 173 reactions from 16 countries (figures 1 and 2). The most common adverse reactions are those involving the skin and appendages (41), gastrointestinal tract (37) and cardiovascular system (28). There were 9 reports of anaphylactic shock and anaphylactoid reactions.

![Figure 1: ADRs on niclosamide in the UMC database](image-url)
A recent review of adverse events to anthelmintics in the French national pharmacovigilance database revealed that adverse drug reactions in 9 subjects were reported between 1985 and 1999 (Bagheri et al., 2004). The majority of the reports related to the use of the drug in tapeworm infection. The ADRs occurring during treatment for taeniasis were abdominal pain and vomiting – 3; dizziness – 2 and one each of polymorph erythema, sweating and anaphylactoid reaction (requiring hospitalization).

**Figure 2: Yearly ADR reports involving niclosamide**

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<tbody>
<tr>
<td>Total</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>13</td>
<td>12</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>13</td>
<td>13</td>
<td>15</td>
</tr>
</tbody>
</table>

**Safety in children and pregnancy**
According to Martindale, The Extra Pharmacopoeia, there is no contra-indication for the use of niclosamide in both small children and pregnant women.

**Pregnancy**
FDA Pregnancy Category B. According to Martindale, The Extra Pharmacopoeia, there is no contra-indication for the use of niclosamide in pregnant women.

**Breast Feeding**
No data on distribution into milk. No effects in humans documented.

**Paediatrics**: No paediatric specific problems documented and niclosamide is not contra-indicated in small children.

**Geriatrics**: No information available

**Carcinogenicity**: No human studies and animal data to suggest carcinogenicity

**Mutagenicity**: No studies available

**Medical considerations**: None known except hypersensitivity to niclosamide
**Drug Interactions**
Niclosamide is soluble in alcohol which enhances its absorption raising the possibility of dose related adverse effects. Alcohol intake is therefore restricted during treatment with niclosamide.

**Discussion**
Niclosamide is a well established drug which has been used in several countries since 1960. Whilst the absence of formal pharmacovigilance systems in most of the countries where the drug has been widely deployed limits the safety data available for analysis, anecdotal evidence and the published literature points to a dearth of adverse events in its usage. If there are substantial safety concerns associated with the use of niclosamide, these will have been noted during its 40+ years of usage.

**Conclusions**
The current review supports the continuous use of niclosamide as no major safety concerns have been raised. Its safety in children and pregnant women and efficacy and safety in treating *T. solium* carriers even in the presence of (neuro)cysticercosis is an advantage over praziquantel.
**OXAMNIQUINE**

Oxamniqueine (1, 2, 3, 4-Tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolylmethanol) is a tetrahydroquinoline derivative used in the treatment of schistosomiasis caused by *Schistosoma mansoni* but not by other species of *Schistosoma*. Oxamniqueine is listed as a complementary drug in the WHO Model Formulary 2004.

**Indication**

Intestinal schistosomiasis due to *Schistosoma mansoni* (acute stage and chronic hepatosplenic disease)

**Cochrane Review:**

A recent Cochrane review (Saconato and Atallah, 2004) indicates no deaths associated with oxamniqueine use in the treatment of schistosomiasis caused by *S. mansoni*. Two cases of seizures were noted out of 372 patients evaluated. Diarrhoea occurred in 17% of patients while abdominal pain occurred in 20% of patients. The review compared oxamniqueine with praziquantel and indicated important differences in some of the side effects as shown in Table 1.

**Table 1: Side effects of Oxamniqueine compared to Praziquantel**

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Oxamniqueine</th>
<th>Praziquantel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>38/544 (7%)</td>
<td>74/536 (14%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>115/571 (20%)</td>
<td>240/563 (42%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7/352 (2%)</td>
<td>0/327 (0%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>2/372 (0.5%)</td>
<td></td>
</tr>
</tbody>
</table>

There was no difference in reports of asthenia, skin rash, nausea or vomiting. Both oxamniqueine and praziquantel appear to be similarly safe except for the occurrence of seizures in two patients treated with oxamniqueine.

**Adverse Effects**

Side effects to oxamniqueine listed in both the WHO Model Formulary and Meyler’s Side Effects of Drugs include commonly dizziness, drowsiness, headache, nausea, vomiting and diarrhea. These reportedly occur in up to a third of patients. The drug causes intense reddish discolouration of urine (Lefrock and Smith 1985). Rare adverse events include urticaria, hallucinations, epileptiform convulsions, raised liver enzyme values; transient fever, eosinophilia and scattered pulmonary infiltrates (Loeffler syndrome) – after 3 day course in patients in Egypt and Eastern Mediterranean. It may also cause pruritic skin rashes.

In the WHO database 15 suspected adverse events have been reported since 1979. These come from 8 reports and include convulsions (6), allergic reaction (1), dizziness (1), headache (1), glossitis (1), anorexia (1), agitation (1), confusion (1), somnolence (1) and blindness (1).
The effective dose for oxamniquine varies geographically and there have been reports of resistance to oxamniquine (Foster, 1987). The 8 reports in the WHO database were received from four countries – Great Britain, Netherlands, Norway and USA.

In the survey of the literature, several adverse effects were reported (Table 2). The study designs employed varied tremendously and there was very little indication on how safety data was collected. While the incidence of adverse events appears quite high, most of them (especially the gastrointestinal tract symptoms) appear to be mild. The reports of epileptic seizures or convulsions, however, indicate the need for caution in the use of the drug in susceptible patients. The high incidence of seizures means that the performance of skilled tasks e.g. driving and operating machinery, after intake of oxamniquine may be impaired.

Table 2: Reported incidence of side-effects to oxamniquine

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>40</td>
<td>Foster 1987; Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.1</td>
<td>Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>14.7</td>
<td>Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Abdominal Pain or discomfort</td>
<td>41.1</td>
<td>Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Epileptic Seizure</td>
<td>2.4</td>
<td>Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Reversible abnormal electroencephalograph</td>
<td>20 (after 2\textsuperscript{nd} dose)</td>
<td>Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Auditory and visual hallucinations</td>
<td>0.4-0.8</td>
<td>Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Headache or burning sensation</td>
<td>3.2</td>
<td>Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Itching</td>
<td>7.4</td>
<td>Taddese and Zein, 1988</td>
</tr>
<tr>
<td>High pulse pressure and sweating</td>
<td>6</td>
<td>Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Seizure</td>
<td>2.4</td>
<td>Foster 1987; Taddese and Zein, 1988</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Approx 14 out of 9 million</td>
<td>Foster 1987</td>
</tr>
</tbody>
</table>

**Pregnancy**
FDA Pregnancy Category C

**Breast Feeding**
No data on distribution into milk. No effects in humans documented.

**Paediatrics:**
No paediatric specific problems documented.

**Geriatrics:**
No information available

**Carcinogenicity:**
No carcinogenicity, maternal toxicity and teratogenicity was found in mice and rabbits. There was slight embrotoxicity after high doses (Chedoff et al., 1984).

**Medical considerations:**
- Epilepsy
- Hypersensitivity to oxamniquine

**Drug Interactions**
None reported

**Discussion**
Oxamniquine is a useful alternative to praziquantel in areas where the latter is ineffective. It has a long period of use. Several studies have been carried out on the drug, especially on regional variations of effective dosages. Whilst resistance to the oxamniquine has been reported (Cioli et al., 1993) there is no evidence that its utility is waning. It has been used in mass campaigns and though the side effects are frequent, they appear not to have been a barrier to widespread use in all age groups and populations (Foster, 1987). With increasing discussions on development of resistance (or tolerance) to praziquantel (Coles GC., 2002; Coles et al., 1987; Danso-Appiah A and De Vlas SJ, 2002; Doenhoff MJ et al., 2002; Stelma et al., 1997; Katz N et al., 1991) its usefulness as an alternative to praziquantel should remain paramount.

**Conclusion**
Oxamniquine administration is accompanied by a relatively high incidence of minor gastrointestinal and central nervous system side effects. These are often mild and have not limited the widespread use of the drug. The drug is very effective in treating *S. mansoni* infections. It is also a useful alternative in areas where praziquantel have failed. In view of this and the long experience with its use and side effect profile, it is recommended that the drug be kept on the Model List of Essential Medicines.
TRICLABENDAZOLE
Triclabendazole (5-Chloro-6-(2,3-dichlorophenoxy)-2-(methylthio) benzimidazole) is a benzimidazole anthelmintic.

Indications
Triclabendazole is used as the primary agent in fascioliasis (*Fasciola hepatica* and *Fasciola gigantica*) and is the primary or alternate agent to praziquantel in paragonimiasis. It has no action against nematodes as do other benzimidazoles in clinical use.

Cochrane Review:
None cited

Adverse Effects
Frequently, studies simply report that the drug is well tolerated without providing specific information on side or adverse effects (e.g. Ripert et al 1992; Apt et al 1995). Gastrointestinal discomfort and headache have been mentioned as side effects. In a study on the use of triclabendazole in paragonimiasis (in comparison with praziquantel), the main side effects noted were dizziness, headache and abdominal pain. These occurred more frequently in those receiving praziquantel (Calvopina et al 1998). Nausea and vomiting occurred only in the group receiving praziquantel. No important changes in blood biochemistry were noted in the two groups.

In a study comparing two dosage regimens for fascioliasis in Cuba involving 82 patients, a total of 74 adverse events possibly related to therapy was reported by 54 patients. The most important adverse event was colic-like abdominal pain in 40 (49%) patients. This was related to the expulsion of the parasite through the bile duct. Most adverse events (53) were graded as mild, 20 as moderate, and only 1 as severe (a biliary colic), which responded to treatment with a spasmolytic within two hours (Millan C et al., 2000).

Chills, fever, leukopenia and upper abdominal colic have been described in Meyler’s Side Effects of Drugs though the incidence rate is not given.

In the WHO Drug Safety Database, there are 2 reports of adverse reactions to triclabendazole. These were reported from Spain and Germany in 2001-2002. The 2 reports contained four adverse reactions – vomiting, jaundice, raised hepatic enzymes and psychosis.

The low incidence of adverse reactions to triclabendazole were also confirmed in the literature survey (Table 3).

Table 3: Reported incidence of adverse events to triclabendazole

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>5.5</td>
<td>Calvopina et al., 1998; Calvopina et al., 2003</td>
</tr>
<tr>
<td>Headache</td>
<td>0.5</td>
<td>Calvopina et al., 1998; Calvopina et al., 2003</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.0</td>
<td>Calvopina et al., 1998; Calvopina et al., 2003</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Incidence (%)</td>
<td>References</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Fever</td>
<td>2.0</td>
<td>Calvopina et al., 1998; Calvopina et al., 2003</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.0</td>
<td>Calvopina et al., 1998; Calvopina et al., 2003</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0.7</td>
<td>El-Morshedy et al., 1999</td>
</tr>
</tbody>
</table>

**Mutagenicity**

Not demonstrated

**Pregnancy** – No human studies reported but animal studies show no evidence of teratogenicity or embryocidal effects (Yoshimura H, 1986).

**Breast Feeding**

The drug is distributed in breast milk.

**Paediatrics**

No paediatric specific problem documented

**Geriatrics**

No specific geriatric problem documented

**Drug Interactions**

None documented

**Discussion**

Triclabendazole appears to be a very well tolerated drug. The low number of reports in the WHO database could be a reflection of its safety though lack of pharmacovigilance systems in several of the countries where the drug is used may also be a factor. There are reports of the successful use of triclabendazole in treating praziquantel-ineffective fascioliasis (Ishii et al., 2002; Merino et al., 1998). It is the drug of choice for both fascioliasis and paragonimiasis. Fewer side effects were recorded with its use in comparison with praziquantel (Calvopina et al 1998)

**Conclusion**

Triclabendazole is a well tolerated drug with minimal safety concerns and should remain on the Model List for fasciolisis and paragonimiasis.
PYRANTEL

Pyrantel (1, 4, 5, 6-Tetrahydro-1-methyl-2-[(E)-2-(2-thienyl) vinyl]pyrimidine 4,4' -methylenebis(3-hydroxy-2-naphthoate) is a pyridine derivative anthelmintic which appears to act by paralysing susceptible worms which are then dislodged by peristaltic activity.

**Indications**

Pyrantel is effective against intestinal nematodes including roundworms (*Ascaris lumbricoides*), threadworms (*Enterobius vermicularis*), and Trichostrongylus spp., the tissue nematode *Trichinella spiralis*, and hookworms. It is also used in treating mixed helmintic infections. Pyrantel may not be effective against all strains of a particular helminth.

**Cochrane Review**

None cited

**Adverse effects**

Side effects associated with Pyrantel are generally mild and include gastrointestinal disturbances, headache, dizziness, drowsiness, insomnia, rash and elevated liver enzymes. Vomiting may occur in up to 20% of cases.

A review of the French Pharmacovigilance Database revealed 10 ADRs during treatment for ascariasis (4), pinworm (5) and an unspecified helmint infection (Bagheri et al., 2004). The ADRs reported were four cases of nausea, vomiting and flatulence; pruritus and urticaria (2 cases); and a case each of dizziness, headache and hypotonia. One case of paraesthesia associated with ataxia and weakness in a 32 year old man had a positive rechallenge and a child who suffered gastrointestinal symptoms required hospitalization.

There have been 431 adverse reactions (188) reports from 17 countries in the WHO Database since 1974. Majority of the reports originate from Australia and this may be a reflection of active pharmacovigilance system in operation in the country. The main organs and systems affected are shown on Table 4

**Table 4: Adverse reactions to pyrantel in the WHO Database**

<table>
<thead>
<tr>
<th>System-Organ Class</th>
<th>Number of reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>12</td>
</tr>
<tr>
<td>Other body as a whole - general disorders</td>
<td>50</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>3</td>
</tr>
<tr>
<td>Central and peripheral nervous systems disorders</td>
<td>58</td>
</tr>
<tr>
<td>Foetal disorders</td>
<td>6</td>
</tr>
<tr>
<td>GIT disorders</td>
<td>162</td>
</tr>
<tr>
<td>Hearing and Vestibular Disorders</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate and rhythm disorders</td>
<td>4</td>
</tr>
<tr>
<td>Liver and biliary system disorders</td>
<td>9</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td>3</td>
</tr>
<tr>
<td>System-Organ Class</td>
<td>Number of reactions</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Muscolo-skeletal system disorders</td>
<td>6</td>
</tr>
<tr>
<td>Platelet, bleeding and clotting disorders</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>21</td>
</tr>
<tr>
<td>Red blood cell disorders</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory system disorders</td>
<td>6</td>
</tr>
<tr>
<td>Skin and Appendages disorders</td>
<td>50</td>
</tr>
<tr>
<td>Urinary System Disorders</td>
<td>6</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>3</td>
</tr>
<tr>
<td>Vision disorders</td>
<td>21</td>
</tr>
<tr>
<td>White cell and red cell disorders</td>
<td>3</td>
</tr>
</tbody>
</table>

In the main, GIT disorders (152) dominated followed by CNS (58), skin and appendages (50) and general body as whole disorders (50).

The range of adverse reactions reported in the literature mirror the range in the WHO database as shown on Table 5.

Table 5: Adverse reactions to pyrantel

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>3.5</td>
<td>Rim and Lim, 1972; Farahmanidian et al., 1972; Pits and Migliardi, 1974; Kale et al 1987; Urbani and Albonico, 2003</td>
</tr>
<tr>
<td>Abdominal pain/colic</td>
<td>9.6</td>
<td>Rim and Lim, 1972; Farahmanidian et al., 1972; Pits and Migliardi, 1974; Kale et al 1987; Urbani and Albonico, 2003</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.3</td>
<td>Rim and Lim, 1972; Farahmanidian et al., 1972; Pits and Migliardi, 1974; Kale et al 1987; Urbani and Albonico, 2003</td>
</tr>
<tr>
<td>Vomitting</td>
<td>2.1</td>
<td>Rim and Lim, 1972; Farahmanidian et al., 1972; Pits and Migliardi, 1974; Kale et al 1987; Urbani and Albonico, 2003</td>
</tr>
<tr>
<td>Headache</td>
<td>4.9</td>
<td>Rim and Lim, 1972; Farahmanidian et al., 1972; Pits and Migliardi, 1974; Kale et al 1987; Urbani and Albonico, 2003</td>
</tr>
<tr>
<td>Skin rash</td>
<td>1.1</td>
<td>Kale et al 1987;</td>
</tr>
<tr>
<td>Weakness</td>
<td>3.8</td>
<td>Kale et al 1987;</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3.2</td>
<td>Kale et al 1987;</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>3.6</td>
<td>Kale et al 1987;</td>
</tr>
<tr>
<td>Feverishness</td>
<td>0.5</td>
<td>Kale et al 1987;</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>3.6</td>
<td>Bell and Gould 1971</td>
</tr>
</tbody>
</table>

Pyrantel is very well studied drug with millions of doses supplied. The huge number of cases reported seems to reflect the widespread usage of the drug and the actual proportion of reactions may be low though the absence of consumption data makes it impossible to prove this.
**Pregnancy**
Not recommended during pregnancy

**Breast Feeding**
Pyrantel is poorly absorbed from the gastrointestinal tract and low levels detected in breast milk. No problems in humans have been recorded.

**Paediatrics**
No paediatric specific problems documented. It is not contraindicated for use in children under 1 year of age.

**Geriatrics**
No information available

**Drug Interactions**
Piperazine may counteract the anthelmintic effect of pyrantel (Aubury et al., 1970). There has also been a single report of an interaction between pyrantel and theophylline leading to increase serum theophylline levels (Hecht et al., 1989).

**Discussion**
There is extensive and established safety experience with pyrantel in several countries. The drug has been well studied and adverse reaction profiles documented. Majority of reactions to pyrantel relate to the gastrointestinal system and are mild. There is no information to suggest an unfavorable safety profile of the drug under current conditions of use.

**Conclusion**
Pyrantel remains a safe and useful anthelmintic drug that has a place in the management of nematode infections.
REFERENCES


