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FREQUENTLY ASKED QUESTIONS ON THE USE OF MEDICINES IN CHILDREN

-  Many medicines used in children, have not undergone extensive evaluation in children
-  It is recommended that a recognised source of information is used for prescribing unauthorised/unlicensed medicines in children such as the British National Formulary for Children
-  The National Medicines Information Centre, through its enquiry answering service, can provide specific information on the use of medicines in children

As described in the previous bulletin (Use of Medicines in Children Vol 15 No 2, 2009) many medicines which are used to treat the paediatric population have not been investigated in children in the same way as in adults, and are used outside the terms of the marketing authorisation (product licence). It is suggested that the extent of unlicensed medicinal preparations being used in children varies from 11-90%.¹ The Summary of Product Characteristics (SmPC) contains full prescribing information for each medicine when licensed for paediatric use, and should be consulted; additional information on adverse effects, drug interactions etc., contained therein may also be useful even when the medicine is not licensed for paediatric use.

The NMIC receives many queries in relation to the use of medicines in children, including those which are unlicensed. This bulletin reviews some of the frequently asked questions which are received by the NMIC.

HOW SHOULD THREADWORMS BE MANAGED IN CHILDREN?

Threadworms (*Enterobius vermicularis*) are parasites that infest human intestines. The eggs are ingested, and after a period of maturation of between 2-6 weeks travel to the large intestine where they have a lifespan of approximately 6 weeks. The female worm, which is approximately 8-13mm long, lays eggs in the perianal area usually at night. In addition, mucous is secreted which causes the person to scratch the area. Eggs then become stuck under fingernails and can be transferred to the mouth to cause re-infestation.^{2,3} Threadworms are more common in small children as they are less likely to be aware of the importance of hygiene. They are also difficult to see because of their size and colour, and infestation is frequently asymptomatic.^{2,3}

An antihelminthic is generally recommended for the person infested with threadworms and for all household members (unless contraindicated). **Mebendazole is the drug of choice for children aged over 6 months,² however it is only licensed in Ireland for use in children over 2 years.⁴** A single 100mg dose is recommended, which can be repeated in 2 weeks if infestation persists.⁵ In addition, **strict hygiene measures should be adopted.** Environmental hygiene measures should be undertaken on the first day of treatment including washing of sleepwear, bed linen, towels, thoroughly vacuuming, dusting and thorough cleaning of the bathroom. Personal hygiene measures should be continued for 2 weeks if combined with drug treatment or for 6 weeks if used alone and includes wearing close fitting underwear at night and changing them every morning, bathing/showering immediately on rising, washing hands and scrubbing under nails first thing in the morning, after using the toilet, changing nappies, and before eating or preparing food.^{2,3,5} If there are frequent recurrences consider seeking advice from a paediatrician/consultant in infectious diseases. For children under six months, treatment options are limited. **Children over 3 months can be given piperazine with sennosides,** at a dose of one level 2.5ml spoonful as a single dose in the morning, repeated after 14 days.^{2,5} However there is no preparation of piperazine with sennosides, either licensed or readily available in Ireland. For children under 3 months, infestation should be managed by physical removal of eggs, combined with hygiene measures for 6 weeks.²

CAN MELATONIN BE USED FOR SLEEP DISORDERS IN CHILDREN?

Melatonin is a pineal hormone, which may affect sleep pattern. Clinical experience suggests that it may be of value for treating sleep onset insomnia and delayed sleep phase syndrome in **children with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder (ADHD), autism, and learning difficulties**. It is also sometimes used before magnetic resonance imaging (MRI), computed tomography (CT), or EEG investigations.⁶

Treatment with melatonin should be initiated and supervised by a specialist. Melatonin is not licensed for use in children and the dose has not yet been firmly established. It is available as immediate release capsules and tablets, sustained release capsules and tablets, and as a liquid formulation⁷ [all unlicensed]. A dose in children from 1 month–18 years of melatonin 2-3mg initially, increased if necessary after 1-2 weeks to 4-6mg, max 10mg has been recommended.⁶ Melatonin is usually given 30-60 minutes before bedtime.⁸ A prolonged release formulation of melatonin was licensed recently in Ireland as monotherapy for the short-term treatment of primary insomnia characterised by poor sleep quality, but only in patients aged 55 years or over.⁹ This preparation has not been evaluated in children and its use in this age group is therefore unlicensed.^{7,10}

There are concerns that melatonin may **adversely affect seizure control and asthma**^{7,11} and at present there are no robust data available to support or refute these concerns.⁷ Until more is known melatonin should be used with caution in these groups.⁷ Other reported adverse effects include headache, depression, restlessness, confusion, nausea, tachycardia and pruritus.^{7,11} Little is known about its long-term effects in children, but there is a theoretical basis for an effect on sexual development.^{6,7} The need for continuing melatonin therapy should be reviewed every 6 months.⁶

WHICH SYSTEMIC ANTIFUNGAL DRUGS CAN BE USED IN CHILDREN TO TREAT SCALP AND NAIL INFECTIONS?

In general mild localised fungal infections of the skin usually respond to topical therapy. Systemic therapy however is appropriate in certain circumstances, e.g. where the site of infection is difficult to treat, such as infection of the scalp (tinea capitis) and of the nails (onychomycosis).¹² **Although not licensed for the treatment of fungal infections in children**, evidence indicates that the newer antifungals, including itraconazole and terbinafine, are as well tolerated as griseofulvin,^{13,14} and are used more frequently than griseofulvin, which is no longer licensed in Ireland.¹⁵ They have a broader spectrum of activity and require a shorter duration of treatment.¹² Itraconazole oral solution is only licensed for the treatment of oropharyngeal and oesophageal candidiasis in severely immunocompromised patients including children, if the potential benefits outweigh the risks.¹⁶

Tinea capitis which is mainly caused by *Trichophyton tonsurans* in African children and *Microsporum Canis* in Irish children¹⁷, requires systemic treatment, and additional topical application of an antifungal may reduce transmission.¹² **Specialist advice is recommended**, particularly if the diagnosis is in doubt and if mycological investigation is not available.^{13,18} Evidence suggests that terbinafine, itraconazole and fluconazole (all unlicensed) are as effective as griseofulvin for tinea capitis caused by *Trichophyton* infections.^{13,14} They may not be as effective as griseofulvin against *Microsporum* species.¹⁹ The recommended dosage regimen for **terbinafine** is: child over 1 year (10–20kg) 62.5mg once daily, 20–40kg 125mg once daily, over 40kg 250mg once daily generally for **4 weeks**.¹² Treatment with **itraconazole**, which has been shown to be effective in over 80% of children with tinea capitis due to *Trichophyton tonsurans*, is generally given at a dose of 3–5 mg/kg per day for **4 to 6 weeks**.²⁰ Standard dosing information for fluconazole is limited in this setting.²⁰ There is no preparation of griseofulvin, either licensed or readily available in Ireland. The dose is 15-20mg/kg/day¹², taken in one dose after a meal containing fat (e.g. ice cream), for **6 weeks**¹³.

Onychomycosis is uncommon in children under 18 years of age, hence **specialist advice is recommended**.^{21,22} If treatment is necessary, a systemic antifungal is more effective than topical therapy, which is only of proven benefit in superficial white onychomycosis.¹⁷ Terbinafine and itraconazole have largely replaced griseofulvin for the systemic treatment of onychomycosis, particularly of the toenail.¹² Neither is licensed for this indication and must be used under specialist advice; current evidence suggests that terbinafine has higher cure rates than itraconazole.²² Treatment with **terbinafine** (same dosage as for tinea capitis) is usually for **6 weeks – 3 months**. Treatment with **itraconazole** is usually give as **intermittent “pulse”** therapy as follows: child 1 - 12 years course (‘pulse’) of 5mg/kg (max 200mg) daily for 7 days;

subsequent courses repeated after 21 day intervals; fingernails - 2 courses, toenails - 3 courses. Child 12 – 18 years *either* 200mg once daily for 3 months or course ('pulse') of itraconazole 200mg twice daily for 7 days; subsequent courses repeated after 21 day intervals; fingernails - 2 courses, toenails - 3 courses.¹²

Adverse effects – most commonly include gastrointestinal symptoms (e.g. abdominal pain, dyspepsia, nausea and diarrhoea) and skin reactions.²¹ Liver toxicity has been reported rarely with terbinafine and other adverse reactions include serious skin reactions including Stevens-Johnson syndrome and drug-induced lupus.¹² Potentially life-threatening hepatotoxicity has been reported very rarely with itraconazole, and there have been rare reports of heart failure:¹² monitoring of liver function is required if treatment duration is >1 month or the patient is receiving other hepatotoxic drugs and caution is advised in patients at risk of heart failure.¹² The SmPC should be consulted for further information on adverse effects.

Formulation issues - Terbinafine is only available as a scored 250mg tablet which can be halved or quartered; this can be crushed and mixed with a little water before immediate administration (unlicensed).²³ Itraconazole is available as a 100mg capsule and as a 10mg/ml oral solution; bioavailability between the two formulations varies depending on whether taken before or after food.^{16,24}

HOW IS PRIMARY HERPES SIMPLEX IN CHILDREN MANAGED?

Primary herpetic gingivostomatitis (PHG), which occurs in up to 10% of children,²⁵ is the most common clinical presentation of primary herpes simplex (HSV) infection in children.²⁶ The peak period of PHG incidence in children, of which HSV type 1 (HSV-1) is almost always the cause,²⁶ is between the ages of 6 months and 5 years.²⁵ Primary HSV-1 infection in immunocompetent patients is usually asymptomatic or associated with non-specific upper respiratory tract symptoms,^{25,26} however those who are immunocompromised are at increased risk of severe infection.²⁷ The infection, which is very contagious, has an incubation period ranging from 2-12 days.^{26,27} Most patients acquire the infection through direct contact, which can spread rapidly in community settings including crèches. Patients usually present with painful vesicles on the buccal and gingival mucosa and tongue; the vesicles rupture to become ulcers, which last approximately 12 days causing eating and drinking difficulties. Most children have a fever of >38°C, enlarged cervical lymph nodes and two-thirds of children will have extraoral skin lesions around the mouth. Many children refuse to eat or drink due to the discomfort and pain from the lesions and consequently become dehydrated, with up to **8% of children requiring hospitalisation**.²⁶ Complications while rare do occur and include ocular herpes, infections of the digits (herpetic whitlow)²⁵ and encephalitis.²⁷ Diagnosis, which is usually based on clinical presentation and history, can be confirmed by laboratory tests including: serological assays and culture of the virus.

Patients with symptoms such as pain, fever and dehydration require treatment including rehydration, analgesics and oral lavage. There have been a number of studies, which evaluated the efficacy of antiviral drugs for treatment of PHG.^{25,26,28-31} Antiviral drugs including aciclovir, are thought to shorten the acute phase of the illness, relieve symptoms, stop the virus from going into the latent phase and possibly prevent future recurrence.²⁵ Evidence suggests that antivirals may be effective in reducing the duration of symptoms of PHG, however **antivirals are not routinely indicated for the treatment of PHG in immunocompetent patients**.^{32,33} Antiviral drugs may be indicated in severe infection, neonates or immunocompromised people, when specialist advice should also be sought.^{32,33} The maximum clinical benefit is gained when treatment is started early because most viral replication occurs in the first 48 hours.³² Aciclovir is authorised for use in children with HSV infections; - the dose for children <2 years is 100mg five times daily usually for 5 days and for children ≥ 2 years 200mg 5 times daily usually for 5 days.³⁴ Higher doses are required in immunocompromised patients.³⁵ Aciclovir causes a range of adverse effects including: nausea, vomiting, diarrhoea and headaches.^{28,34}

WHAT OPTIONS ARE AVAILABLE TO TREAT GASTRO-OESOPHAGEAL REFLUX IN CHILDREN?

Gastro-oesophageal reflux (GOR) is common in infancy, especially in preterm babies, younger infants and those with neurodevelopmental disorders.^{36,37} It results from an inappropriate relaxation of the lower oesophageal sphincter allowing stomach contents to pass into the oesophagus.³⁷ It is usually manifest by effortless and non-distressing regurgitation of stomach contents.^{36,38} **GOR resolves without intervention in the majority of these cases by 12-18 months of age.**³⁶⁻³⁸ When troublesome symptoms associated with

GOR occur the condition is referred to as **gastro-oesophageal reflux disease (GORD)**. In the younger paediatric population these symptoms range from regurgitation, vomiting, abdominal pain, arching and irritability, feeding refusal and poor growth to respiratory symptoms.³⁶⁻³⁸ Older children may complain of heartburn, acid regurgitation and dysphagia.³⁸ The incidence of GORD in infants and children has been found to be between 0.47-0.9 per 1,000 person years.³³ Heartburn occurring a few times per week has been reported by 3.3% of adolescents.³³ Children with GORD that is secondary to or associated with underlying disease (e.g. cerebral palsy with neurodevelopmental delay or congenital abnormalities) are more prone to severe and chronic forms of GORD with complications.^{33,36}

The diagnosis of GOR / GORD is usually clinical. The principal hospital-based tests, undertaken under specialist supervision, include intraluminal oesophageal pH monitoring and endoscopy with biopsy to confirm oesophagitis.^{36,37} Although widely used, oesophageal acid exposure as measured by pH monitoring is a poor marker of GORD in infants.³³ Rather than relying on arbitrary acid exposure criteria, the ability to demonstrate a temporal association between individual reflux events and symptomatic episodes is more diagnostically useful.³³ Frequent milk feeding and resultant gastric pH buffering renders most reflux episodes 'non acidic' (pH>4) and therefore undetectable using standard pH-based reflux detection criteria.³³ Intra luminal impedance monitoring is a diagnostic modality which allows detection of reflux independently of pH. By combining impedance monitoring with pH sensing, all reflux (acidic & non-acidic) can be detected and correlated with symptomatic events.³³

The main aims of treatment are to alleviate symptoms, promote normal growth and prevent complications.³⁷ For infants with GOR, **the parents should be reassured that most cases resolve spontaneously.** An increase in the frequency and a decrease in the volume of feeds may reduce symptoms.³⁸ Use of a **feed thickener** or pre-thickened formula feed may be considered; a recent meta-analysis showed that such an intervention is only moderately effective in treating GOR in healthy infants.³⁹ Advice from a dietician is recommended with such usage.³⁸ **Alginate preparations** act by reacting with the acidic gastric contents to form a viscous gel that stabilises stomach activity and reduces the incidence of gastro-oesophageal reflux.⁴⁰ These can be used in place of thickened feeds.³⁸ One such preparation (Gaviscon Infant®) is authorised for use from birth for infants (breast-fed and bottle-fed babies) and young children. It should only be used under the supervision of a healthcare professional. It is contraindicated in infants with known or suspected impairment of renal function or in situations where excessive water loss is likely (e.g. diarrhoea). Full prescribing details are available in the SmPC.⁴⁰ An alginate-containing antacid may be used in older children to relieve symptoms and lifestyle changes such as weight loss may also be necessary.³⁸ Gaviscon® oral liquid should not be used in young children (less than 6 years).^{33,41,42}

For those infants and children who do not respond to these therapies or where GORD complications are suspected, **specialist referral is warranted for further investigation and possibly pharmacotherapy to reduce gastric acid secretion** (H2 receptor antagonists (H2A) and proton-pump inhibitors (PPI)).^{33,37,38}

The use of these medicines in GOR and GORD is unlicensed and therefore there is a paucity of evidence-based guidance on appropriate dosing levels and efficacy of these therapies to reduce reflux-related symptoms.^{33,37} H2A therapy (e.g. ranitidine)³⁸ may be used to relieve the symptoms of GORD, promote mucosal healing and permit reduction in antacid consumption. Treatment should be carefully monitored and reassessed if symptoms persist despite 4-6 weeks' therapy. Use of a PPI may be considered by the paediatrician if the patient has failed to respond to H2A therapy.³⁷ Therapy should be closely tailored to the individual patient's needs as there is limited clinical trial experience with such usage. The following side effects have been reported: gastrointestinal upset, agitation, irritability, headache with H2As and headache and gastrointestinal upset with PPIs. In addition, studies have suggested that use of gastric acid inhibitors in children may be associated with an increased risk of acute gastroenteritis and respiratory tract infections.⁴³

Current best practice does not recommend any other drugs to treat GOR / GORD. Surgery is reserved for those with severe refractory or life-threatening symptoms as success is uncertain and complications high.³⁷

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