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Dr Sue Hill
Department of Medicines Policy and Standards (PSM)
Health Technology & Pharmaceuticals
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Dear Dr Hill,

RE: Expert Consultation on Essential Medicines for Children

I would like to respond to your call for comments on the first draft of a model EML for children in relation to a number of medications.

1. Antipyretics: as a class should be removed.
   There is a strong argument that there is no need for antipyretic in the vast majority of childhood illnesses. Fever forms an important part of the bodies defences against infection and thus we should not be attempting to decrease it with medications. If the section on antipyretics is to remain, only one medication should be included on the list to prevent the temptation for polypharmacy As paracetamol and ibuprofen have been shown to be equally effective and paracetamol is already on the list it would seem reasonable to leave it as the single agent. (See appendix 1)

2. Simple Analgesics:
   Ibuprofen are of similar efficacy when used as single agents. (See Appendix 1) There is some evidence that they may be some advantages to there combined use in treatment of minor trauma and post operatively. Very few paediatric studies have looked at the question of the effectiveness of these agents in combination. Morton and O'Brien found that there was no increase in pain relief with the combination of paracetamol and diclofenac over diclofenac alone, in children 5-13 years post appendicectomy.[1] Pickering found that there was a benefit of adding ibuprofen to paracetamol as measured by need for early postoperative pain relief, 72% vs 38% (34% diff; 95% CI 4-46%).[2]

3. Antiemetics:
   Metoclopramide: - there is little indication for this medication in children in light of its side effects - ie. extrapyramidal effects such as Acute Dystonic Reactions which children (especially girls, young women, and those under 10 kg) are particularly susceptible), hyperprolactinaemia, occasionally tardive dyskinesia on prolonged administration; also reported, drowsiness, restlessness, diarrhoea, depression, neuroleptic malignant syndrome, rashes, pruritus, oedema; cardiac conduction abnormalities reported following intravenous administration; rarely methaemoglobinaemia. [3] It is not indicated for infective gastroenteritis as it does not decrease vomiting and increases diarrhoea.[4] It may be indicated in

post operative vomiting, but an oral form is not need for this indication, and as for post chemotherapy vomiting there are more effective and safer medications available.

Yours sincerely,

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General Paediatrician
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Appendix 1: Comments on 1st Model EML for Children

Evidence for use of simple antipyretics and analgesics

The Role of Fever

It has been accepted for decades now that fever plays and important role in the bodies' defences against infection. Despite this knowledge, unfounded concerns about brain damage, febrile convulsions and death from mild to moderate fever persist.[1] Several guidelines on the topic exist but, many are not evidence-based.[2] Normal body temperature is defined as 37.0°C (98.6°F) orally,[3] and fever as a body temperature above the normal range.[4] Fever is part of the body's normal response to infections, and it plays an important role in fighting such infections.[4] At most elevated temperatures the immunological system is enhanced; for example the lymphocyte transformation response is initiated, production of interferon is increased and the bactericidal activity of polymorph nuclear lymphocytes is increased.[5] These beneficial effects indicate that mild to moderate fever should not be suppressed — hence fever *per se* does not generally need to be treated.

Febrile convulsions occur in 2-5% of children with fever.[6] Controlling fever with antipyretics does no prevent either an initial or recurrent febrile convulsion.[7-10] However, temperature reduction is recommended if the child is placed 'at risk' by the debilitating effects of an increased metabolic rate in the absence of adequate protein, fluid and electrolytes[11-14] or has a pre-existing significant cardiac, respiratory, neurological, metabolic, renal or hepatic condition.[15;16]

Most young children with fever present with a self limiting viral illness that does not need any treatment and disappears without sequelae. Nevertheless, febrile infants and young children pose a challenge to primary care physicians because the clinical appearance of children who present with fever related to a viral illness may be similar to the appearance of those with occult bacteraemia.[17] How unwell a child is can not be reliably predicted by the height of the fever and it should be borne in mind that a response to an antipyretic does not exclude a serious illness and may in fact even mask it. As such, one of the most important aspects of treating children with acute illness is identifying a child at risk of serious infection. All febrile children under 3 years of age who have toxic manifestations should be medically assessed to discount a serious infection.[18;19]

The currently recommended doses of paracetamol and ibuprofen products for paediatric use listed in Table 1.[20]

Comparative efficacy of paracetamol and ibuprofen in fever

A search identified 23 randomised controlled trials that directly compare the antipyretic efficacy of paracetamol to that of ibuprofen in the paediatric setting.[21-43] The inclusion criteria, definition of fever and outcome measures vary greatly between these studies. The challenge therefore is to determine whether the data can show clinically meaningful differences among these two treatments.

Nine studies reported that ibuprofen was significantly more effective than paracetamol in reducing fever.[22;23;25;31;32;34;36;37;39] However, all of these studies used lower than currently recommended doses of paracetamol (i.e. less than 15 mg/kg per dose). Only three of the 23

studies identified in our search evaluated a paracetamol dose of 15mg/kg,[27;33;35] all of which showed no statistically significant difference in efficacy (rate or extent of temperature reduction) between this dose of paracetamol and 5-10mg/kg doses of ibuprofen.

It has been suggested that the effects of multiple doses of antipyretics are probably more important than temperature decreases produced by single doses, particularly from the point of view of possible drug accumulation and side effects.[44] More than half (14/23) of the studies we identified were single dose studies. Of the nine multiple dose studies,[21;24;28;29;31-33;37;43] only one used the recommended paracetamol dose of 15mg/kg.[33] In this study 64 children aged 6 months to 12 years with a fever higher than 39°C were randomised to receive ibuprofen (2.5, 5 or 10 mg/kg) or paracetamol (15 mg/kg) given as an oral dose every 6 hours for 24 to 48 hours. There were no statistically significant differences between 10mg/kg ibuprofen and 15 mg/kg paracetamol.

In addition to the 23 original studies cited above, four recently published reviews were identified in which the authors evaluated the relative antipyretic efficacy of paracetamol and ibuprofen.[45-48] All support the conclusion that the efficacy and clinical effectiveness of paracetamol and ibuprofen are similar when used at the recommended dosages, with ibuprofen tending to have a longer lasting effect (up to 6 hours after a single dose). However, as with this analysis, it should be borne in mind that these conclusions have been based on a review of several studies in which the dose of paracetamol was lower than the recommended 15mg/kg/dose. Only one of these stusies[45] analysed multiple dose trials separately from single dose trials, with the authors concluding that although some studies show ibuprofen to be more effective than paracetamol after single lower than recommended doses, studies with multiple doses have failed to show that one drug is better than the other.

Comparative efficacy of paracetamol and ibuprofen in pain

This search identified 10 randomised controlled trials that directly compare the analgesic efficacy of paracetamol to that of ibuprofen in children with pain.[29;49-57] Three of the studies compared the recommended dosages of paracetamol (15mg/kg) and ibuprofen (5-10 mg/kg) — all were single dose studies, with one in migraine pain[52], one in sore throat pain[55] and one assessing the analgesic effects of preoperatively administered paracetamol and ibuprofen.[51] Although this latter study showed no statistically significant differences between paracetamol and ibuprofen, it is of limited relevance with regard to the management of childhood pain in the community setting. The remaining two studies both demonstrate that when used at the recommended dose paracetamol is as effective as ibuprofen in relieving the pain of migraine and sore throats.

A recent study in children with musculoskeletal injuries suggests that ibuprofen 10mg/kg is more effective than paracetamol 15mg/kg.[49] However, 48% of the children in the paracetamol group received a maximum dose of 650mg (less than 15mg/kg based on body weight) whereas 22% of the patients in the ibuprofen group received a maximum dose of 600mg. Moreover, superior efficacy with ibuprofen was only statistically significant for patients with fractures and there was no difference in efficacy for patients with soft tissue injuries.[49]

Comparative safety of paracetamol and ibuprofen in the paediatric population

The majority of clinical studies directly comparing paracetamol and ibuprofen in pain and fever suggest that both drugs are remarkably well tolerated with no statistically significant differences between them in terms of the number of adverse events. In addition, data derived from the Boston University Fever Study[58-60] show that the risk of hospitalsation for serious adverse events (gastrointestinal bleeding, renal failure, or anaphylaxis) was not increased following short-term use of ibuprofen in children.

However, there is a need to consider the potential for adverse effects with paracetamol and ibuprofen outside of the constraints of controlled environment of clinical trials. Such data has recently been provided through work conducted at the Royal Children's Hospital, Melbourne, which involved a review of all adverse drug reactions (ADRs) reported with the use of NSAIDs, coxibs and paracetamol in the hospital's database.[61] Over a 5-year period (January 1999 - December 2003), 25 ADRs to these agents were found (representing 3.3% of the total database of 754 reports). Of these, 19 reports implicated coxib or NSAID usage and 6 implicated paracetamol usage, despite the fact that in this hospital over 4 times more paracetamol is used than NSAIDs or coxibs. Over one-third (36%) of the ADRs identified were preventable - for example, there was one case of acute renal failure probably due to ibuprofen use in a 10 year old being treated at home for a viral infection.

The use of ibuprofen is potentially dangerous in situations with even moderate volume depletion.[62] Acute renal failure has previously been reported in seven children who presented with diarrhoea and/or vomiting and fever were treated with therapeutic doses (11.5-32 mg/kg per day) of ibuprofen for 1 to 3 days.[62] After stopping the ibuprofen and rehydrating the children, all recovered completely (creatinine levels normalised after 3 to 9 days).

Aspirin induced asthma (AIA) is a distinct clinical syndrome in which some patients with asthma will experience a worsening of symptoms or an acute asthma attack after taking aspirin or NSAIDs.[63;64] It is not a hypersensitivity reaction — a single NSAID exposure may elicit a response in a susceptible individual.[65] Whilst more often associated with adults, this condition should not be overlooked in children. A meta-analysis of the available studies in children has indicated a prevalence of 5% (95% CI: 0-14%).[63] More recently, a prevalence of 2% (95% CI: 0.2%-7%) for ibuprofen-sensitive asthma has been reported, despite the fact that children were specifically excluded from the study if they had known aspirin or ibuprofen sensitivity or allergy.[65] The possibility of ibuprofen-induced asthma should be considered before recommending ibuprofen or another NSAID to children with asthma.

From a physiological standpoint, acute paracetamol hepatotoxicity at therapeutic doses is extremely unlikely.[66] Most reports of paracetamol-induced hepatotoxicity have resulted from either deliberate self-poisoning or cases of accidental overdoses in a therapeutic setting.[67] Moreover, a comprehensive review of reported cases of hepatotoxicity after therapeutic doses of paracetamol has demonstrated that liver damage occurring with therapeutic use is usually associated with administration of excessive doses.[68]

Due to its ubiquity, paracetamol is involved in large proportion of accidental paediatric exposures. Subsequent hepatic failure and death are both uncommon outcomes.[69] Published data evaluating sequalae in children exposed to paracetamol doses of up to 200mg/kg have shown that these children can be successfully treated with home monitoring and that when this is done, they do not develop signs or symptoms of hepatic injury.[70] Ibuprofen overdose has also been reported in the literature.[71] In most cases the clinical features are mild and

confined to the gastrointestinal and central nervous systems,[72] however, serious drug toxicity, including death from the complications of over dosage, may occasionally occur.[73]

Is there a role for combining or alternating antipyretics?

Alternating antipyretics is reported to be an increasingly common intervention to attempt to control fever amongst carers.[1] This practice is also being used amongst a surprisingly high number of physicians. In their study to assess the place of ibuprofen in the treatment of fever in children, Charkaluk et al[74] found that antipyretic bi-therapy (predominantly paracetamol and ibuprofen) was received by over one-third of children (35%). There is concern that whilst widespread, this practice is not supported by any evidence,[75] and may be associated with an increased risk of adverse effects.[76] Moreover, the promotion of this practice has the potential for further negative outcomes — it places an unnecessary emphasis upon the degree of fever (with the result that it may perpetuate fever phobia) and may introduce additional safety issues resulting from confusion over which product to give, when to give it, and in what dose.[77] Australian research shows that when alternating antipyretics ibuprofen and paracetamol are given too frequently by 32% and 4% of parents, respectively.

This search revealed 54 citations on the use of alternative or combing therapy, of which only four studies were of direct relevance (Table 6).[78-81] Erlewyn-Lajeunesse showed that the combined use of paracetamol (15 mg/kg) and ibuprofen (5 mg/kg) reduced fever more after 1 hour than did paracetamol alone.[78] Similarly, in a randomised, double-blind and placebo-controlled trial significantly more children became afebrile at 6 hours after receiving alternating therapy (a single 10 mg/kg dose of ibuprofen followed 4 hours later by a single 15 mg/kg dose of paracetamol) than after receiving ibuprofen followed 4 hours later by a placebo (83.3% vs. 57.6%; P = 0.018).[79] Despite these results, larger trials are needed to confirm the efficacy and safety of this type of regimen.[78;79] In another randomised, double-blind, parallel-group trial children received either paracetamol (12.5 mg/kg per dose every 6 hours) or ibuprofen (5 mg/kg per dose every 8 hours) or alternating paracetamol and ibuprofen (every 4 hours) for 3 days after a loading dose of ibuprofen. The alternating regimen was more effective than monotherapy in lowering fever ($P<0.001$).[80] In contrast to the above results, in a randomised, double blind, parallel group, multicenter study, in which children with respiratory tract infections received either nimesulide (1.5 mg/kg/dose), paracetamol (10.0 mg/kg/dose) or an ibuprofen-paracetamol combination (10.0 mg/kg/dose) three times daily for 5 days, significant reduction in temperature was seen in all three treatment groups as compared to their respective basal values ($p < 0.001$) and there was no significant difference between the treatment groups.[81]

Conclusion

Pain and fever are common symptoms associated with various childhood illnesses and daily living. While both paracetamol and ibuprofen may be appropriate for use in children, we need to encourage the quality use of all medicines. This means discouraging their use simply to lower temperature and primarily considering them for the treatment of pain or discomfort. Paracetamol has a long history of use; it is effective and well tolerated. Ibuprofen is also generally well tolerated, but as the above data indicate there can be some additional iatrogenic risks associated with its use. Given that there is no obvious efficacy advantage to using ibuprofen, paracetamol should be the first-line treatment of choice in paediatric patients. There is no role for the combined use of these products, either simultaneously or alternating in fever. There may be an indication for there combined use in pain but that was not the focus of this review.

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Table 1. Recommended doses of paediatric paracetamol and ibuprofen.[20]

Paracetamol	Ibuprofen
Community setting: 15 mg/kg every 4-6 hours. Maximum 4 doses (60mg/kg) per day for up to 48 hours *Other settings* Up to 90 mg/kg per day can be used under medical supervision with review after 48 hours. Single doses of 30mg/kg may be used for night-time dosing.	*Community setting:* 5-10mg/kg every 6-8 hours. Maximum 4 doses (40mg/kg) per day for up to 48 hours *Other settings* For juvenile rheumatoid arthritis 10mg/kg/dose 3 or 4 times a day.