

## Comments from a German perspective via HW Seyberth (May 31 07) to the first draft: WHO Model List of Essential Medicines for Children

### 1. ANAESTHETICS

#### 1.1 General anaesthetics

Halothane should not be used for dental procedure outside hospital in children. This might be too dangerous. There are alternatives(see below).

Ketamine should not be used intramuscularly. In an emergency situation the rectal , intranasal or even transdermal administration might be worthwhile considering as an alternative. There are quite a few data in the literature on this topic (Kronenberg RH, J Pain Palliat Caree Pharmacother 2002, Ozdemir D et al J Trop Pediatr 2004, Heinrich M Eur J Pediatr Surg 2004). However, ketamine is not licensed for children < 12 yrs in Europe! More data on PK, efficacy and safety particularly in the younger children are urgently needed (see EMEA assessment of paediatric needs: anaesthesiology).

Thiopental is authorised with a dose of 4 mg/kg in children > 1 month in EU (EMEA assessment). There are a lot of published data on PK in infants and children (e.g. Russo H and Bressolle F Clin. Pharmacokinet 1998). However, etomidate might become a true alternative as a short acting anaesthetic particularly in rapid sequence intubation in children (Zelicof-Paul A et al. Curr Opin Pediatr 2005).

#### 1.3 Preoperative medication and sedation for short-term procedures

Atropine is hardly anymore used in children during anaesthesia (personal communication from the chief pediatric anaesthesiologist from the Medical School of Hannover).

Diazepam ought to be substituted by midazolam, which has a much better PK and is nowadays probably better evaluated in children except in infants < 6 month (e.g. Tobias JD Pediatr Ann 2005). However, additional age and route appropriate formulations are still needed (EMEA assessment). Apparently midazolam is also quite popular in the clinics of paediatric dentists ( statement from the German Society for Pediatric Dentistry)).

Is fentanyl not worthwhile to be considered as a major analgesic during surgery besides morphine?

### 2. ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIDs), MEDICINES USED TO TREAT GOUT AND DISEASE MODIFYING AGENTS IN RHEUMATOID DISORDERS (DMARDs)

#### 2.1 Non-opioids and NSAIDs

Acetylsalicylic acid is also not anymore needed for juvenile idiopathic arthritis (JIA) in the Developed World because of its high intestinal intolerance and relative weak inflammatory activity. One needs almost toxic blood levels to see an anti-rheumatic effect. One of the more potent and older NSAIDs with a lot of paediatric experience and high acceptability in children - in contrast to adults - is indomethacin in the dose range of 1-4 mg/kg/d (d. or t.i.d.) (e.g. Cassidy-Petty Textbook of Pediatric Rheumatology 5<sup>th</sup> edition 2005). In addition a variety of age appropriate formulations (supp., suspension, iv., slow release tabs, etc.) are available. Unfortunately not authorisation for children < 6 years for this indication (EMEA assessment: Rheumatology).

Ibuprofen is certainly an effective minor analgesic for children in all age groups and available in almost all age appropriate formulations. However, aseptic meningitis is possible, particularly in SLE . Moreover there is abundant experimental evidence that ibuprofen is a much weaker prostaglandin synthesis inhibitor (Mitchell JA et al Proc

Natl Acad Sci UAS 1994, Frölich JC TiPS 1997, FitzGerald GA and Patrono C N Engl J Med 2001) and is by no means as effective as indomethacin in JIA (see Cassidy-Petty, personal experience and recommendation from the German Working Group of Pediatric Rheumatology). The study of Clark et al. in Pediatrics 2007, which compared the analgesic power in acute pain of ibuprofen with that of paracetamol/acetaminophen and codeine, is not so conclusive as the selected single dose of paracetamol has been only 15 mg/kg instead of up to 40 mg/kg for this indication and age group (see also BNF for children).

## 2.2 Opioid analgesics

Codeine may not anymore be qualified to remain on the list. Its major pharmacologically active metabolite morphine is too much dependent on the different CYP2D6 genotypes leading to treatment failure in slow metabolizer or intoxication in ultrarapid metabolizer (e.g. Tseng CY et al Clin Pharmacol Ther 1996, Eckardt K et al. Pain 1998, Williams DG et al. Br J Anaesth 2002, Koren G et al. Lancet 2006). Moreover there is a fair potential of drug interaction by medicines metabolized via CYP2D6.

On the European continent - despite the threat of agranulocytosis - metamizol/dipyrone remains a very popular alternative for more severe pain and fever in children of almost all age groups except the neonates now already for decades (e.g. Zernikow B et al. Eur J Pain 2006, Ramacciotti A et al. Cochrane Database Syst Rev 2007, Andersohn F et al. Ann Intern Med 2007). In addition all needed age appropriated formulations of metamizol, such as supp., various forms of tabs, droplets, and i.v.-solutions are available and in part licensed for children (Deutsche "Rote Liste"). Reanalysis of the benefit-risk of this very popular analgesic in children on the base of existing data is absolutely recommended by the Paediatric Working Party at the EMEA.

Morphine remains the medicine of choice in that group, however PK, efficacy and safety studies/data are urgently needed in infant <6 months and more age and route appropriated formulations for all age groups (EMEA assessment: Pain).

## 2.3 Medicines used to treat gout

Allopurinol is needed in paediatric oncology.

## 2.4 Disease modifying agents used in rheumatoid disorders (DMARDs) are certainly relevant (see EMEA assessment: Rheumatology and Hashkes PJ and Laxer RM JAMA 2005). However these disorders may be considered as orphan diseases in children.

Hydroxchloroquine is used in JIA and SLE.

Azathioprine is still used in paediatric rheumatology, particularly in dermatomyositis and SLE.

Methotrexate is the first choice DMARD (the gold standard) in paediatric rheumatology.

Penicillamine is out of use in paediatric rheumatology, including scleroderma.

Sulfasalazine might be indicated in enthesitis related arthritis and in Crohn's disease. However, sulfasalazine is more often associated with ADRs as compared with other anti-rheumatic medicines in children, such as macrophage activating syndrome (MAS) and liver failure.

Prednisone/-olone (not mentioned here) is considered as the "standard"-corticosteroid because of its favourable cost-effectiveness.

Triamcinolone-hexacetonide (not mentioned here) is highly effective as intra-articular injection. However it is not licensed for children <16 yrs in the EU.

Colchicine (not mentioned here) might be considered as an essential and payable medicine in familial Mediterranean fever (FMF).

### 3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

Chlorophenamine appears to be quite popular in the UK, while it is completely unknown in Germany and is only in a strange combination in flu-medication from Stada on the market. In contrast, if the additional sedative effect of an older antihistamine is appreciated, dimetindene (Fenestil) is of widespread use on the Continent for decade, licensed for children >1 yr and available in most age appropriated formulation incl. droplets, otherwise cetirizidine is preferred as antiallergic agent. There are only a few more recent publication available about dimetindene (Englisch W and Bauer CP Arzneimittelforschung 1997, Bauer CP and Unkauf M Arzneimittelforschung 2001).

Prednisolone or prednisone (trade name: Rectodelt) 100 mg suppositories are very popular in German-speaking countries to overcome painful intra-muscular administration and/or to avoid not palatable formulation for oral administration in usually non-cooperative infants and small children (Reinhardt`s Textbook: Therapie der Krankheiten im Kindes- und Jugendalter, 7<sup>th</sup> ed. 2004, p.858). This is also true for mild to moderate viral croup. However, assuming a large variable bioavailability ranging from 20-80% and an effective systemic (p.o. or iv.) dose of 1 mg/kg, a single rectal dose of 100 mg appears to be rather high. Unfortunately appropriate dose ranging studies as well randomised controlled trials have not been conducted. Nevertheless these corticosteroids are licensed for viral croup and obstructive laryngo-tracheitis and bronchitis in Germany for decades.

## 6. ANTI-INFECTIVE MEDICINES

### 6.2 Antibacterials

#### *Complementary List*

Ceftriaxone should be considered for inclusion in the Core List. However, a warning for the development of bacterial resistance with more frequent use - as has been seen in the developed world in the last decade - should be included. In this situation chloramphenicol with tight TDM has been reintroduced as a successful rescue intervention in patients with bacterial meningitis associated with emerging bacterial resistance of a third generation cephalosporin (personal experience). Moreover intravenous ceftriaxone administration is contraindicated in preterm infants and in term infants with hyperbilirubinemia or requiring calcium supplementation in France, Switzerland and soon probably in Germany. The reason is the observation of serious and lethal reactions due to the formation of crystalline precipitate in the tubing and/or in the pulmonary and renal parenchyma of these infants in France (see the Dear-Doctor-letters from *afssaps* and *Swissmedic*).

Chloramphenicol can indeed only be titrated into the therapeutic window (10-25 microgram/ml) by close therapeutic drug level monitoring (TDM) particularly in the very sick and small infant on polypharmacotherapy because of unpredictable and rapid changing drug disposition. When considering a 1% topical formulation of chloramphenicol for neonatal conjunctivitis, one should mention that there had been at least a report of aplastic anemia (type B and not dose dependent ADR) after administration of chloramphenicol containing eye drops (Daum et al. J Pediatr 1979). Are eye drops containing neomycin not a better alternative?

## 6.4 Antiviral medicines

Aciclovir is needed for life threatening herpes simplex infection, e.g. encephalitis.

Ribavirin is indicated in children with life-threatening RSV, parainfluenza virus and adenovirus infection in immunocompromised children as well as in children with chronic hepatitis C in combination with interferon alfa-2b.

## 7. ANTIMIGRAINE MEDICINES

### 7.1 For treatment of acute attack

As migraine is a common disorder in children and adolescents with prevalence of 5 and 10%, respectively (Hamalainen ML CNS Drugs 2006), these medicines should not be deleted from the list.

Acetylsalicylic acid has a long tradition as an antimigraine medicine also in adolescent medicine, although there are truly alternatives (see for ibuprofen: Hamalainen ML CNS Drugs 2005 and Balottin U et al. Expert Opin Pharmacother 2007 and for dipyrrone: Ramacciotti A et al Cochrane Database Syst Rev 2007).

Paracetamol remains the first drug of choice, although conclusive dose finding and safety studies in the paediatric populations are missing (EMEA assessment: Migraine). This holds also true for ibuprofen.

### 7.2 For prophylaxis

Propranolol should certainly remain for this indication on the list, although age and disease appropriate formulations are also not available (EMEA assessment).

## 8. ANTINEOPLASTIC, IMMUNOSUPPRESSIVES AND MEDICINE USED IN PALLIATIVE CARE

General comment: One can not agree more that this entire section needs a specific review.

### 8.1 Immunosuppressive medicines are essential, if organ transplantation in children, such as the kidney, is considered essential.

Prednisolone (not mentioned here) is indicated for transplantation and immunological disorders and licensed without any age limit; however age appropriate oral formulation should be made available. The present prednisolone solution has a very bitter taste and is hard to swallow for children.

Azathioprine has an authorised indication for organ transplantation and various autoimmune diseases in children without identification of a specified age group. In view of the cost, azathioprine should remain in the standard triple therapy (ciclosporin, azathioprine and steroid regimen (CAS)) for immunosuppression after kidney transplantation, despite newer immunosuppressive medicines, such as tacrolimus and mycophenolate (Remuzzi G et al. J Am Soc Nephrol 2007, Yao G et al. Health Technol Assess 2006).

Ciclosporin is licensed with no specified paediatric age group, although there is a need for PK data in children < 1 year. It has a broad authorized spectrum of indications such as solid organ transplantation, bone marrow transplantation, nephrotic syndrome, endogenous uveitis, minimal change nephropathy, focal and segmental glomerulosclerosis, membranous glomerulonephritis, rheumatoid arthritis, psoriasis, severe dermatitis (see EMEA assessment: Nephrology).

## 10. MEDICINES AFFECTING THE BLOOD

### 10.2 Medicines affecting coagulation

Heparin sodium Warning: Some heparin solutions on the market do contain for sterility reasons benzyl alcohol, which is rather toxic for neonates and small infants.

Moreover lower strength solutions are urgently needed, e.g. for flushing the tubing to keep it open for prolonged needed intravenous infusion in paediatric intensive care. Protamine sulfat should remain in the list, although it is only licensed for adults. Warfarin should remain in the paediatric list, although no dose recommendation is available for children in the age range from 12 months to 10 yrs (<12 months: 0.32 mg/kg/d and for 11-18 yrs: 0.09 mg/kg/d) and there is a need for age appropriate formulation (EMEA assessment: Cardiology). Acetylsalicylic acid in low dose (1 mg/kg/d) should be included in the context for prevention of arterial thrombosis and for Kawasaki disease. Age and route appropriate formulation is needed (EMEA assessment).

## 12. CARDIOVASCULAR MEDICINE

**12.2 Antiarrhythmic medicines** is quite relevant in paediatric cardiology. However the child with cardiac arrhythmias may be considered as an orphan patient. Here also a specific review is highly recommended.

Atenolol's labelling needs to be extended to all paediatric age groups. Efficacy, safety data and dose recommendation are needed including age appropriate formulations.

Epinephrine (adrenaline) is not used as an antiarrhythmic agent in paediatrics but is indicated for cardiac arrest with an authorised dose of 0.01-0.03 mg/kg.

Lidocaine is indicated for treatment of ventricular fibrillation and tachycardia.

However this antiarrhythmic medicine is only licensed for adults (with the exception in Spain?), so efficacy and safety data, dose recommendation and age appropriate formulation are missing.

Verampamil is authorised for children (undefined age groupe) in Germany with a starting dose of 0.05-0.1 mg/kg/h, which can be titrate up to an effective dose with ECG and blood-pressure monitoring. The average daily dose should not exceed 1.5 mg/kg/d. Verampamil is authorised for youngest age group (<0 yrs) in Sweden. Age and

route (iv.) appropriated formulations are needed. The stock solution of 5 mg/2 ml is too concentrated for exact dose-titration in small infants.

### 12.3 Antihypertensive medicines

Atenolol as an antihypertensive medicine needs the extention of the paediatric indication, that means efficacy and safety data, dose recommendation and age appropriate formulation.

Enalapril as all other ACE-inhibitors are purely studied in neonatal hypertension (e.g. renal vein thrombosis). In addition effective renal filtration and function in the neonates is heavily dependent on an intact renin-angiotensin-system, thus you need an ACE-inhibitor with an short half-life, such as captopril, for careful dose-titration. The same holds true in hypertensive children with renal failure or heart failure (Momma K Paediatr Drugs 2006, Dutta S and Narang A Pediatr Nephrol 2003).

Both ACE-inhibitors are apparently licensed for all paediatric age groups in Spain with the exception of enalapril being not authorised for the use in neonates. Both medicines need extemporaneous formulations for age appropriate administration. The liquid formulation for enalapril is obviously particularly challenging. For both medicines reanalyse of benefit/risk in children from existing data are needed as well as the definition of the age limit for both major indications, hypertension and heart failure (see below).

Hydrochlorothiazide is not licensed for the use in all paediatric age groups irrespective of its indication, thus efficacy and safety data, dose recommendation and age appropriated formulation are needed. At least at the age of school-children hydrochlorothiazide might be an appropriate antihypertensive medicine except for

those with a GFR < 40 ml/m<sup>2</sup>/min. In this situation furosemide is the diuretic of choice.

Sodium nitroprusside should not be deleted from the list as it has a clear paediatric indication for managing a hypertensive crisis. However, again there is not paediatric labelling with all its consequences.

#### **12.4 Medicines used in heart failure**

Furosemide The square box is probably not needed here, as furosemide is the loop-diuretic, of which we have by far the most extensive paediatric experience in the treatment of arterial hypertension and heart failure as well.

Hydrochlorothiazide (see above)

#### **12.5 Antithrombotic medicines**

Acetylsalicylic acid (see above) Here again age appropriate dosage recommendation and formulation is needed.

**12.6 Lipid lowering agents** do probably belong nowadays to the class of essential paediatric medicines. We should not only consider the children with familial dyslipidaemias but also all children with end-stage renal failure, who are on chronic dialysis. They are at high risk of premature death related to secondary dyslipidaemia and hypertension.

### **13. DERMATOLOGICAL MEDICINES**

This list needs to be reviewed by an international group of paediatric dermatologists.

### **16. DIURETICS**

Furosemide is as oral solution (10mg/ml) on the market.

Hydrochlorothiazide (see above)

Spirolactone is authorised for the paediatric use (undefined age limit) and available as tabs and oral suspension (5mg/ml).

### **17. GASTROINTESTINAL MEDICINES**

#### **17.1 Antacids and other antiulcer medicines**

Ranitidin should be exchanged by an off-patent proton pump inhibitor.

**17.2 Antiemetic medicines** are usually given as symptomatic therapy. Normally we are focused to treat the primary cause, such as an infection, thus the benefit/risk of antiemetic therapy needs careful consideration. Vomiting induced by chemotherapy, motion sickness and migraine belong to these conditions.

Metoclopramide might be worthwhile considering. However extrapyramidal effects, such as torticollis, have been reported to be more often in children and may need pharmacotherapeutic intervention with the muscarin receptor antagonist biperiden (personal experience and Leavy PM Drug Saf 1991, Allen JC et al J Clin Oncol 1985).

Promethazine is an old antihistamine with strong sedative effect. It is labelled for paediatric use, however, as it is with all old remedies, they have never been evaluated in a proper way as we would do it today. If promethazine is deleted from the list, we would probably need another antihistamine (see above).

#### **17.3 Anti-inflammatory medicines**

Crohn's disease and colitis ulcerosa are by no means uncommon chronic inflammatory diseases in the paediatric population, starting in school-child age. Here I would suggest to consult the upcoming list with the assessment of the paediatric needs in gastroenterology from the collaboration of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) with the Paediatric Working Party (PEG) at the EMEA.

#### **17.4 Laxatives**

Lactulose and liquid paraffin are generally preferred.

- 17.5.3 Antidiarrhoeal (symptomatic) medicines in children** need to be considered.  
Loperamide is licensed for children >4 yrs in UK for symptomatic treatment of acute and chronic diarrhoea.

**18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES**  
need to be considered. Check with paediatric endocrinologist and gynaecologist.

- 18.1 Adrenal hormones and synthetic substitutes** are apparently missing.  
Fludrocortisone acetate (100 micrograms tabs) for mineralocorticoid replacement  
Hydrocortisone (10 mg tabs) for congenital adrenal hyperplasia and chronic maintenance and replacement therapy (BNF for children and German Working Group of Paediatric Endocrinology)

**18.5 Insulins and other antidiabetic agents**

Insulin injection (soluble) PK, PD, efficacy and safety data are needed for children <2 years.

Intermediate-acting insulin PK, PD, efficacy and safety data are missing in all paediatric age groups.

Metformin is licensed and needed for children with diabetes type II ( licensed for children > 10 yrs in France).

**20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS**

Suxamethonium is licensed for paediatric with no specific age limit in France.

Authorised dose is 1-2 mg/kg in Finland. There is a need for PK data in infants and an age appropriate formulation. 50 mg/ml stock solution is too strong.

Vecuronium is licensed in all paediatric age groups (Finland). As an extremely low test dose of 0.001- 0.002 mg/kg for infants < 4 months is recommended, an age appropriated iv-solution is needed.

**25. MEDICINES ACTING ON THE RESPIRATORY TRACT**

All what has been suggested for change in this section is well appreciated, except:

What is the indication of caffeine citrate in this context? Do you mean for obstructive apnoea of the preterm infant?

**ADDENDUM**

The Society of Neonatology and Paediatric Intensive Care Medicine (GNPI stands for Gesellschaft für Neonatologie und Pädiatrischer Intensivmedizin) including German-speaking colleagues from Austria, Germany and Switzerland would like to propose a separate EML for neonates for the following reasons:

- (1) Term and even more preterm neonates are too different from all other maturation phases later in childhood and adolescence,
- (2) Most subspecialty specific efficacy and safety studies have been conducted in neonatology,
- (3) Off-label use is most widely spread in neonatology.

In this context they would like to see the following medicines in such an EML besides those already listed:

- all available surfactant products (?)
- epoetin alpha (rhEPO)
- adenosine

- amiodarone
- captopril
- cefotaxime
- chloral hydrate
- disoprivan (propofol)
- dobutamine
- esmolol
- flecainide
- fentanyl
- flucloxacillin
- ganciclovir
- indomethacin
- meropenem
- metamizol (dipyrone)
- milrinone
- nifedipine
- norepinephrine
- octenisept
- omeprazole
- pancuronium
- phytomenadione (vitamin K)
- propafenone
- prostaglandin E1
- sildenafil
- sodium hydrogencarbonate
- sotalol
- tobramycin
- theophylline
- vitamin B6