

APPM MASTER FORMULARY 2015

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Formulary Subgroup)

APPM Master Formulary

- Aims
- Why is it needed?
- How has it been updated?
- Future direction(s)

Aims of the Formulary

- Provide a single, standardised reference source including all appropriate drugs for paediatric palliative care
- Provide safe and effective dosage recommendations and key information (e.g. administration, warnings, side-effects etc)

Aims contd

- Alert users when specialised/expert advice should be sought (e.g. methadone, ketamine)
- Review and update the evidence base for existing drugs and consider the evidence base for new drugs
- Encourage users to offer comments and feedback to continually develop and improve the formulary in preparation for future editions

Why is the Formulary needed?

- APPM recognised there are various drug formularies within the UK with potentially differing doses of medicines
- Limited information on doses for paediatric palliative medicine
- Users need confidence in drug doses to enable safe and effective prescribing in palliative medicine

Why is the Formulary needed?

- Number of potential issues for prescribers:
 - ❖ Lack of evidence based medicine
 - ❖ Need for understanding of paediatric drug handling
(doses may be based on extrapolation from adult data or other better studied populations)
 - ❖ Large proportion of prescribing involves use of off-label or unlicensed medicines
 - ❖ Lack of suitable formulations for children

Lack of Evidence Based Medicine

- Paucity of evidence based medicine for paediatric palliative care
- Most of the research is of a descriptive nature
- Number of issues preventing good quality RCTs in this field
- Recent years - number of UK and European initiatives to promote research into children's medicines

Paediatric Drug Handling

- For many drugs, the Formulary extrapolates evidence /doses from adult practice or from use in other paediatric situations
- Need to consider PK/PD differences of neonates, infants and children compared to adults
- Drug handling may also be affected by the disease state (Gabapentin, Sanderson et al, 2014)

Licensing

- Suggested that 50% or more of medicines used in children are not licensed for purpose (even greater in palliative care)
- **Off-label** (e.g. not licensed in children, unlicensed route of administration, unlicensed dose, use outside licensed age limits, unlicensed indication)
- **Unlicensed** (any manipulation of the original dosage form; use of 'specials', imported medicines)
- **GMC advice** (prescribers must be satisfied there is sufficient evidence / experience of using an off-label or unlicensed medicine to demonstrate its safety and efficacy)

Lack of Suitable Paediatric Formulations

- Lack of suitable formulations can cause a number of potential problems (inaccurate dosing; increased risk of adverse effects; ineffective treatment; small dose increments not possible)
- Need for advice on manipulation of licensed formulations, extemporaneous formulations, specials and alternative routes of administration
- Extemporaneous formulations for children may exhibit poor or inconsistent bioavailability, low quality and safety

How has the Formulary been updated?

- Collaborative piece of work
- Doctors from the subgroup divided the Formulary and reviewed all of the drugs
- 12 new drugs identified for possible inclusion were subject to a full literature review
- 9 new drugs added
- All other drug monographs substantially updated

Update contd

- Many drug doses amended to improve safety and avoid confusion
- Notes sections add additional practical information
- References reviewed and updated
- Additional 132 references added to support the evidence
- Once all the work was combined and all queries resolved, the draft Formulary was sent out for peer review

Literature Review

- Search strategy identified
- Number of databases used
 - ❖ MEDLINE
 - ❖ EMBASE
 - ❖ CINAHL
 - ❖ MICROMEDEX
 - ❖ COCHRANE
 - ❖ NHS EVIDENCE

Literature Review

- Also:
 - ❖ reference lists of key articles
 - ❖ hand search through relevant journals
 - ❖ author search
- **Other reference sources** (e.g. BNF, BNFC, PCF, Syringe Driver, MfC, Neonatal Formulary, LexiComp and other national and international paediatric formularies, adult guidelines; on-going clinical trials; Google)

Clonidine

- Potential use for a number of palliative symptoms (anxiety/sedation pre-procedure; pain including opioid sparing effects and synergy with LAs; spasticity; behavioural symptoms)
- Use in children off-label (age and indication) and unlicensed if dosage forms manipulated
- Literature review – no studies in paediatric palliative care identified (isolated case reports)
- Extensive use in other paediatric populations (e.g. pre-operative sedation; PICU pain/sedation; epidurals and regional nerve blocks, ADHD)

Clonidine

- **Pre-operative /pre-procedure:** Cochrane Systematic Review 2014
- **Analgesia / sedation and opioid sparing:** Large number of case reports and small studies
- **Nerve blocks** (requires specialist input): 2011 systematic review of 20RCTs including 993 children
- **Movement disorders/spasticity:** Evidence limited to case reports/series and review articles
- **Behaviour:** NICE and SIGN for ADHD. Other situations limited to isolated case reports and clinical experience

Clonidine

- Also considered PK studies
- ❖ Oral (oral bioavailability in children may be less than in adults which is suggested as 75-100%)
- ❖ Rectal (rapid and complete)
- ❖ Intranasal (possible pain and irritation on administration; interindividual variation with possible delayed, erratic and incomplete absorption)
- ❖ Transdermal (adult data 1:1 conversion from established oral dose)
- ❖ Parenteral (most experience IV; anecdotal SC)
- Peer review: approved for inclusion

Sativex

- Oromucosal spray of THC and CBD licensed in adults for moderate to severe spasticity in MS
- Interest for chronic pain and/or spasticity in palliative patients
- Literature review: no paediatric studies identified (Aug 2013). Adults 2 multicentre RCTS in chronic cancer pain – some improvement in pain scores
- Clinical trial currently on-going in children with spasticity associated with CP or CNS injury (2016)

Sativex

- Further adult studies in chronic cancer pain with potential licence extension 2015
- Given lack of any paediatric data at this time – not included
- Subgroup will continue to monitor and await results of clinical trials

Queries

- Opioid equivalence ratios e.g. hydromorphone
 - ❖ Variety of sources (BNFc; WHO pain guidelines 2012; PCF4; manufacturers information; Physicians drug reference)
 - ❖ Oral morphine 5-10mg: Oral hydromorphone 1mg
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- Hydromorphone starting dose in opioid naive patients

Queries contd

- Levomepromazine oral dose for N+V (lower doses may be effective with fewer side-effects)
- Paracetamol (all mg/kg doses rather than age bands)

Future Direction(s)

- Questionnaire / Survey
https://www.surveymonkey.com/s/APPM_prescribing_2015
- ❖ Who are the users? Should content reflect this?
- ❖ Does the Formulary provide too much/too little detail in the notes section?
- ❖ Should the Formulary provide information on availability of drugs outside the UK?
- ❖ Additional drugs for inclusion?

Future Direction(s)

- **Evidence Base**
- Continue to develop the evidence base for included drugs
- Develop a consistent grading scale to give users confidence in the advice and dose(s) provided
- Review and update on a regular basis

- **Neonatal Doses**

Future Direction(s)

- **Formulations:** work with company(ies) specialising in formulation issues concerning palliative care
- The ideal formulation needs:
 - ❖ Small dose increments
 - ❖ Non-toxic excipients (of concern: alcohol, propylene glycol, benzoates)
 - ❖ To be palatable
 - ❖ To be easy for the child/carer to administer
 - ❖ A robust and stable formulation
 - ❖ To be commercially viable

Future Direction(s)

- **Alternative routes of administration**
- Buccal / sublingual / intranasal opioids (and others)
- Intranasal diamorphine
- ❖ Could this be used buccally?
- ❖ Can the solution be diluted to allow smaller doses?
- ❖ Is it suitable for prolonged use?
- Survey of current practice
- Extensive literature review

THANK YOU

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