Management of distressing symptoms in neonates

Background:

Provision of physical comfort is one of the main treatment goals in babies receiving end of life care. Babies at the end of their life should therefore be regularly assessed for such symptoms and alleviating treatments should be initiated without delay. Once treatments have been started, babies need to be re-assessed frequently in order to adjust treatments as necessary. Treatments may include pharmacological as well as non-pharmacological interventions.

In addition, many babies undergoing intensive care (not end of life care) may experience distressing symptoms; these can occur as a result of their underlying illness or due to intensive care provision (invasive ventilation, surgery and other procedures etc.). All babies should therefore actively be monitored for pain as well as other distressing symptoms and promptly treated if these should occur.

With the exception of medications suggested for palliative seizure management, the following guide can therefore be used for babies receiving end of life care as well as those undergoing intensive care who are experiencing distressing symptoms.

Commonly used pharmacological treatments:

The drug doses in the table below are appropriate for neonates and infants older than 1 month of age. Suggested dosing is as per BNFc if available, or alternatively as per the APPM Master formulary (2020).

Conversion from intravenous to oral Morphine dosing is outlined in Box 1.

In palliative medicine drug dosages are traditionally calculated over a 24-hour period. This is the therefore the standard way of prescribing medications for babies that are transferred for end of life care from the hospital to a hospice or family home. Please find guidance of how to prescribe for 24 hourly dosing in Box 2.

Indication	Drug	Dose	Frequency	Route
Pain	**Morphine**	10 – 50 microgram/kg/hour	Continuous	Intravenous *For oral conversions please see Box 1.*
		50-100 microgram/kg/dose *For breakthrough dosing please also see Box 1.*	PRN – maximum 1 hourly	Intravenous bolus
		25-50 microgram/kg/dose *If opioid-naïve; if opioid-established please use breakthrough dosing as per Box 1.*	PRN – maximum 6 hourly	Oral
Respiratory secretions	**Glycopyrronium bromide**	40-100 microgram/kg/dose	6-8 hourly	Oral
	Hyoscine Hydrobromide	250 microgram (Quarter of a 1.5mg patch – whole patch releases 1mg per 72 hours)	Continuous - change patch every 72 hrs	Transdermal
Seizures *(end of life management only – please see additional notes on seizures below)*	**Midazolam**	*Initially* 60 microgram/kg/hour *Increasing in steps of:* 30 microgram/kg/hour every 30 minutes *Maximum* 300 microgram/kg/hour	Continuous	Subcutaneous/Intravenous infusion
		300 microgram/kg/dose	Single dose repeated once if necessary	Buccal
	Phenobarbitone	20 mg/kg/dose	Loading dose	Oral *Or* Subcutaneous/Intravenous infusion over 20 minutes
		Followed by 2.5 -5mg/kg/dose	Once or twice daily	Oral *Or* slow Intravenous injection/infusion
Anxiety, distress, agitation	**Chloral Hydrate**	30mg/kg/dose *Can be increased up to a maximum of 45mg/kg/dose in neonates and 50mg/kg/dose in babies older > 1month*	Once daily (usually single dose at night)	Per Rectum (round dose to give whole suppository) or Oral (when administering orally dilute with milk or water to reduce gastric irritation)
	Midazolam	25 microgram/kg/dose	PRN (max. 1 hourly)	Buccal *Or* Intranasal
		50 microgram/kg/dose	PRN (max. 1 hourly)	Oral
		25 microgram/kg/dose	PRN (max. 1 hourly)	Subcutaneous/Intravenous bolus

		0.5-1mg/kg/day		Continuous	Subcutaneous/Intravenous infusion
Gastro-oesophageal reflux	Carobel feed thickener	Start at ½ scoop per 90 ml *Increase up to a maximum of 3 scoops per 60mls if required*		Every feed	Oral
	Lansoprazole	0.5 – 1 mg/kg/dose		Once daily	Oral
Constipation	Glycerol infant suppository	< 1 month	Tip of 1g suppository ('chip')	PRN	Per Rectum
		> 1 month	1g		
	Lactulose	2.5 ml/dose		Twice daily	Oral
Dyspnoea	Morphine	25 microgram/kg/dose *If opioid-naïve; if opioid-established please use breakthrough dosing as per Box 1*		every 6-8 hours	Oral *Or* Slow Subcutaneous/Intravenous bolus (over at least 5 minutes)
	Midazolam	25 – 50 microgram/kg/dose		PRN – Maximum 4 hourly	Buccal/ intranasal/ Oral/ Subcutaneous or Intravenous bolus
		0.5-1 mg/kg/day		Continuous	Subcutaneous or Intravenous infusion

Box 1. Additional calculation Information

Oral Morphine conversion

Calculate the total daily IV dose in microgram; double the dose to convert to oral, then divide into six doses 4 hourly doses/24 hours.

Breakthrough dose calculations

If pain occurs between regular doses of Morphine (Breakthrough pain) then additional doses (rescue doses) can be administered.

The standard dose for breakthrough pain is $1/6^{th}$ of the total dose administered over the previous 24 hours.

Then

Adjust the next 24 hourly dose by adding any administered breakthrough doses given in the previous 24 hours to the corresponding 24 hourly dose. The new breakthrough dose will be a $1/6^{th}$ of the new 24 hourly dose; therefore both the new 24 hourly dose and new breakthrough dose will be higher (if breakthrough doses were required).

Box 2. 24 Hourly Dosing

Indication	Drug	Dose	Frequency	Route
Pain	Morphine	120 microgram/kg/day	Continuous	Subcutaneous/Intravenous infusion
Seizures	Midazolam	1-3mg/kg/day increasing up to 7 mg/kg/day (maximum 60 mg within 24 hours)	Continuous	Subcutaneous/Intravenous infusion
Anxiety, distress, agitation	Midazolam	0.5-1 mg/kg/day	Continuous	Subcutaneous/Intravenous infusion
Dyspnoea	Morphine	40-60 microgram/kg/day	Continuous	Subcutaneous/Intravenous infusion
	Midazolam	0.5-1 mg/kg/day	Continuous	Subcutaneous/Intravenous infusion

Additional notes

Pain relief

- All babies receiving palliative care must have consideration given to relief of pain and discomfort. This includes the type of medication, the dose, route of administration and the likely duration of need. The use of pain tools may be helpful in recognising discomfort and monitoring response to alleviating measures.

- If a baby is already receiving analgesic medication this should be continued. If opiates are to be initiated, an initial bolus dose should be given before commencing an infusion so that adequate analgesia is achieved promptly. The dose may be increased or reduced depending on ongoing assessment of distress and development of tolerance.

- If the baby has intravenous access in place, this route is preferred in the immediate period during and following discontinuation of life-sustaining treatments. If intravenous access is not available, then the buccal or oral route is usually recommended rather than subcutaneous administration as this route can be unreliable in babies and may cause additional pain.

- If the intravenous route is not available and adequate analgesia cannot be achieved through oral medication, a subcutaneous infusion may be necessary. Intramuscular medication is never appropriate. For rapid symptom management, buccal medication may be considered, usually in addition to longer acting medication via the enteral route or a subcutaneous infusion.

- Non-opioid analgesia such as paracetamol and oral sucrose may be used for less severe pain or in combination with opioids. Paracetamol dosing should be as per local unit guideline if available (available at CAV) or as per BNFc.

- Non-pharmacological interventions to reduce pain and discomfort should be used in conjunction with analgesic medication. These include a calm environment with minimal noise and light stimuli, non-nutritive sucking with a pacifier, music and positioning with arms and legs flexed close to the trunk using a blanket or rolls and complimentary therapies such as massage.

- Assist the parents to hold their baby. Skin to skin may be offered to reduce discomfort for the infant and may have additional calming benefits for parents.

- Support continued suckling at the breast if the mother wishes.

Seizures

- Loading doses of anticonvulsants are not usually necessary unless it is for rapid control of terminal seizures in a patient not already receiving anticonvulsants. During end of life care,

the aim of seizure treatment is relief from cerebral irritation rather than control of seizures per se.

Fluids and feeding

- The overall goal of treatment is provision of comfort rather than nutrition.
- In those babies able to tolerate milk feeds their ongoing provision should be determined by their clinical condition and the feeding cues that the infant demonstrates.
- Feeds can be offered orally (breast or bottle) if the baby is able to feed safely and is showing interest in feeding. Otherwise feeds can be administered naso- or orogastrically.
- If the baby is displaying signs of reflux and/or vomiting, conservative measures such as frequent, smaller volume feeding and upright positioning after feeds can be helpful. If symptoms persist, pharmacological treatment with feed thickeners and proton pump inhibitors as outlined in the table above should be initiated.
- If vomiting or feed intolerance occurs, feeds should be reduced in decrements of 20 - 30ml/kg/day. If poor tolerance of milk feeds continues, Dioralyte fluids may be administered.
- Enteral nutrition/fluids can be withheld if it is felt that providing them will cause pain or discomfort.
- It may be appropriate to allow the infant to suckle at the (empty) breast for comfort only.
- In infants where the duration between the withdrawal of life-sustaining treatments and death is expected to be short, it is reasonable to cease all feeds if it is felt feeding could cause distress, and to discontinue intravenous hydration and nutrition. Medications that are being infused intravenously for the analgesic purposes should continue to be administered until the baby has passed away.

References

APPM (2020) *The Association of Paediatric Palliative Medicine Master Formulary*. 5th Edition Available at: https://www.appm.org.uk/_webedit/uploaded-files/All%20Files/Event%20Resources/2020%20APPM%20Master%20Formulary%202020%20protected.pdf

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