Neonatal and paediatric intensive care

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This article looks at the contribution pharmacists can make to medicines management within neonatal and paediatric intensive care. Also discussed are the pharmaceutical issues arising within intensive care, including the use of drugs for sedation and analgesia.
The NICU and PICU are highly specialised and complex clinical areas that require a multidisciplinary team approach to the provision of patient care. Pharmacists are integral members of the multidisciplinary team, which includes medical staff, nursing staff, dietitians, physiotherapists, occupational therapists and speech therapists. Pharmacists contribute to treatment decisions during consultant-led ward rounds. This enables pharmaceutical problems to be solved as they arise and a patient’s long-term needs can be organised in advance (eg, continuity of drug supply).

**ROLE OF THE PHARMACIST**

The pharmacist has the clinical skills to provide services that ensure the efficacy, safety and cost-effectiveness of drug therapy. It is important to treat children in a holistic manner to maximise pharmaceutical care. The roles carried out by the pharmacist in neonatal and paediatric intensive care are described below.

Prescription monitoring Pharmacists visit the NICU and PICU daily. The responsibilities of pharmacists within intensive care units include reviewing all prescriptions to ascertain that they are written clearly and have the appropriate indication, correct dose and most suitable route of administration. A patient’s needs and preferences should be incorporated into their pharmaceutical care package, and therapeutic outcomes, drug interactions and adverse drug reactions should be monitored. The effect on the paediatric patient of any medication taken by women while they were pregnant or are breastfeeding must be considered.

The criteria for using unlicensed or “off-label” medicines in paediatric patients should be based upon randomised, controlled trials and evidence based medicine. However, the availability of information on unlicensed medicines is limited. The potential benefit of using an unlicensed medicine must outweigh any risks associated with its use.

It should be the responsibility of the pharmacist to maintain continued supplies of unlicensed medicines for the patient. This may involve the extemporaneous preparation of unlicensed products by “specials” manufacturing units. The effect of excipients in drug formulations may be considered.

The reconstitution, administration, dilution and compatibility of intravenous drugs are important considerations, especially in neonates receiving multiple drug therapy. Neonates also have a limited number of suitable access points for IV therapy.

Risk management There is a relatively high risk of errors occurring within the NICU and PICU because of the frequent use of unlicensed and “off-label” medicines, for which there is limited information about appropriate doses, etc. Errors in prescribing and dose calculations and the inappropriate administration of medicines can lead to adverse drug events. Glover and Sussman concluded that poor performance by paediatric residents (ie, senior house officers) in drug dosage calculations should be addressed through training. Dean et al recommended that hospitals should train junior doctors in the principles of drug dosing and the importance of accurate and legible prescription writing.

Medication errors can be reduced by ensuring prescriptions are unambiguous and legible, and by avoiding the use of unnecessary decimal points in prescribed doses. The risk of medication errors can be reduced by the pharmacist monitoring prescriptions, providing medicines information, training nursing and medical staff, and through the provision of a CIVA service. A “no blame” culture for medication error reporting and improved communication between nursing, medical and pharmacy staff will help reduce the risk of errors occurring.

Information technology, such as computerised physician order entry (ie, doctors prescribing drugs online) and computerised physician decision support, has been shown to reduce medication errors. Pharmacists actively contribute to the development and review of formulary information and guidelines at local, regional and national level. Audits are performed to identify the benefits or problems with current therapy and to identify any changes in clinical practice. The information obtained from these audits is used to make recommendations to improve clinical practice and reduce the incidence of medication errors.

Discharge planning Discharge planning is essential to ensure seamless care for patients. It involves evaluating and organising a patient’s medical, physical and social requirements at the time of hospital admission. Such planning leads to an efficient, timely, safe and patient-focused discharge system.

Children discharged from intensive care may be taking medicines that are of high cost or are not readily available from community pharmacies. Issues such as funding and continuity of drug supply must be organised by the pharmacist before discharge. Information about a paediatric patient’s present and future care must be transferred efficiently between secondary and primary care.

Parenteral nutrition Pharmacists are involved in prescribing decisions for parenteral nutrition. They also monitor therapy and prepare parenteral nutrition formulations. Paediatric pharmacists are usually part of a nutrition team that includes doctors, nurses and dietitians. Education Pharmacists have the clinical knowledge to advise and educate health care professionals about pharmaceutical issues, such as the calculation of paediatric drug doses.

Educational sessions established by a pharmacist for nursing and medical staff facilitate an exchange of knowledge and expertise between health care professionals.

Pharmacists contribute greatly to patient care through the provision of advice on the safe and effective use of medicines.

Clinical trials Pharmacists are involved in the design, setting up, and running of clinical trials within hospitals. In addition, pharmacists have been involved in research on the efficacy and safety of clinical trial medicines used within the NICU and PICU.

**INTRAVENOUS THERAPY**

Intravenous therapy is widely used in intensive care for paediatric patients who are in shock, nil-by-mouth, post-surgery, or have impaired oral absorption. In addition, IV therapy is indicated when high concentrations of drug are required rapidly within the systemic circulation (eg, for the treatment of meningitis).

The paediatric pharmacist gives advice on the different types of IV administration devices and their suitability for use with a prescribed medication, or with parenteral nutrition. There are two major forms of IV access, and these are peripheral (eg, cannula) and central (eg, tunnelled central venous catheters, peripherally inserted central catheters and implantable ports). Central venous catheters can have either single or multiple lumens. Peripheral venous access has the advantage of being accessible, but it is not suitable for the administration of drugs that are irritant because of the risk of extravasation.

Complications associated with IV access include pain, thrombophlebitis, extravasation and infection. Pneumothorax can occur if central venous catheters
are positioned incorrectly.

The following are the pharmaceutical aspects that need to be considered by the pharmacist monitoring IV therapy.

Displacement value
Displacement value is the volume occupied by the powder in a vial when a suitable diluent is added during reconstitution. For example, the displacement value of amoxicillin 250mg is 0.2ml. Therefore, if 4.8ml of diluent is added to a 250mg vial, the resulting volume is 5ml (ie, amoxicillin 250mg in 5ml).

The displacement value is important because the dose used in children constitutes only a proportion of the vial content. Displacement values of the same drug can differ between brands.

Compatibility of drugs, fluids, parenteral nutrition and diluent It may be necessary to infuse a number of drugs, fluids and a parenteral nutrition formulation simultaneously through the same catheter because of limited IV access, especially in neonates. It is therefore important for the pharmacist to ascertain the number of lumens present, the drug concentrations used and the time of contact between drugs, fluids and parenteral nutrition in the catheter.

The diluent used for drug reconstitution and flushing of catheters must be compatible with the drug. For example, glucose should be used to reconstitute and flush the catheter before and after administration of liposomal amphotericin. Adequate mixing of drugs with diluents (eg, potassium chloride in 500ml of glucose 5 per cent) is important to avoid the risk of a bolus dose being given.

Stability Factors that could affect the stability of IV drugs are the diluent used and environmental conditions, such as light and temperature. Interactions between drugs and delivery systems (eg, syringe pumps) may occur through adsorption (eg, insulin) or absorption (eg, glyceryl trinitrate).

Dilution and sodium content
Pharmacists can advise on the dilution of drugs for children who are fluid restricted. In addition, the sodium content of drugs, fluids and flushes, needs to be taken into account to avoid the development of hypernatraemia and fluid retention.

Contamination
Contamination of infusions and injections can occur from particulate and microbial sources. Infusions and injections should be monitored closely for particulate matter. The use of in-line filters can reduce the risk of contamination.

CIVA service
CIVA service involves the preparation of individualised drug doses in syringes or infusion bags in the pharmacy aseptic unit. The products prepared are “ready for administration” on the ward. CIVA services have been shown to reduce the wastage of drugs and diluents through use of part doses from a drug vial and reusing materials for several patients. The service also improves the timeliness of drug administration and saves nursing time.

Sedation
Sedation is required in the PICU to ensure that the patient is comfortable during invasive procedures, such as intubation, and because of the severity of their illness. In the NICU, certain factors have to be considered for the use of sedative drugs, and these are gestational age and renal and hepatic function.

Sedation and analgesia are usually used together because sedation does not provide analgesia. Although a child is asleep, it does not mean that he or she is not in pain.

Commonly used sedatives in paediatric intensive care are discussed below:

Midazolam
Midazolam is a short acting, water soluble benzodiazepine that reduces seizure activity. It is used as first line sedation in the PICU. Midazolam has a large volume of distribution and an IV bolus needs to be given before initiating an infusion. In the paediatric patient, therapy is initiated with an IV bolus of 100–200µg/kg. The time to onset of effect is two to three minutes, with a duration of action of 30 to 60 minutes. The bolus dose is followed by continuous infusion at a dose ranging from 30–200µg/kg/h. The dose is titrated to achieve the required level of sedation.

Treatment beyond one or two weeks, especially at large doses, has been associated with an acute benzodiazepine withdrawal syndrome. Infusions should be gradually reduced over several days. Diazepam is the treatment of choice for withdrawal symptoms.

IV administration of midazolam may cause respiratory depression and should be used with caution in the NICU because it can accumulate in neonates. This is because of inadequate clearance of midazolam by a newborn’s immature renal and hepatic systems.

Propofol
Propofol is used for the sedation of ventilated patients in the PICU. On IV administration, propofol has an onset of action of 30 seconds and a duration of action of three to 10 minutes.

Propofol is highly lipophilic, which accounts for its large volume of distribution and rapid onset of central nervous system effects. Propofol is metabolised in the liver and excreted in urine. Lipid accumulation can lead to multi-system organ failure in critically ill patients. Propofol is not recommended in children younger than three years of age.

Chloral hydrate and triclofos
Chloral hydrate and triclofos belong to the same class, and have properties similar to those of barbiturates. They are used for night sedation and for additional sedation in ventilated patients if other IV therapy is not achieving a sufficient response.

Chloral hydrate is rapidly absorbed following oral administration, and acts within 15 to 60 minutes. However, triclofos is usually the first choice sedative because it is more palatable and causes less gastric irritation than chloral hydrate. Both drugs can cause hypotension in susceptible infants. The presence of liver disease can prolong the duration of action of chloral hydrate and triclofos.

Alimemazine
Alimemazine (trimipramine) Alimemazine is used in the PICU setting at a dose of 2 to 3mg/kg. It is used to supplement sedation.

Analgesia
Analgesia is required to calm the agitated child and to promote healing. Pain is stressful to the neonate. Multiple sources of stress can have a deleterious effect on brain development, especially in the preterm neonate. The assessment of pain control can be difficult because of a patient’s age and communication skills, and the level of sedation that they are under. Pain scores have been developed,
but the accuracy of these cannot always be relied upon.

The following analgesics are used widely within paediatric intensive care.

Morphine Morphine is the most widely studied opioid in infants and children. It acts on m opioid receptors in the brain and spinal cord to produce analgesia. It also acts synergistically with hypnotics.

An IV loading dose is given to achieve therapeutic levels, followed by an infusion that is titrated according to the clinical response. There is a wide inter-patient variability, making it difficult to predict the effect of morphine in a neonate. Doses higher than 20µg/kg/h can lead to accumulation, and babies may become narcosed, leading to difficulties in ventilation.27

Prolonged use of morphine can lead to dependence and patients need to be weaned off the drug gradually.

Fentanyl Fentanyl is a synthetically manufactured opioid. It is one hundred times more potent than morphine, with a quicker onset of action and a shorter half-life because it is rapidly distributed into fat. Fentanyl can cause chest wall rigidity, which can interfere with ventilation. Rapid tolerance to fentanyl can occur within one or two days and withdrawal symptoms may be experienced.

Ketamine Ketamine is a useful agent when there is a risk of hypotension at induction of anaesthesia, or when analgesia or anaesthesia are required for short, painful procedures. The onset of action after IV injection is rapid, and it has a short duration of action of five to 10 minutes.28 Ketamine is contraindicated in head injuries and meningitis because it elevates intracranial and intraocular pressure.24

Paracetamol Paracetamol is well tolerated in the paediatric patient. The rectal and oral routes of administration are used, with the former being more commonly used in the NICU. However, because paracetamol is absorbed irregularly from the rectal route, larger loading doses are required compared with those given orally.27

There is a risk of paracetamol toxicity in paediatric patients with hepatic disease.

CHANGES TO PROTOCOLS

There have been recent changes in practice and protocols within the NICU and PICU. The following drugs are now being used in intensive care.

Clonidine There has been a lot of interest in the use of clonidine as a sedative and an analgesic. It stimulates opiate receptors in the central nervous system. Clonidine is used as an adjunct to sedation (eg, with morphine) and control of opiate/benzodiazepine withdrawal.24,29,29

Clonidine can be administered orally or via IV injection. It has been shown to be effective by both routes of administration.29,29 It is well absorbed orally, with peak plasma levels being achieved in three to five hours. Clonidine has a plasma half-life of six to 20 hours in normal renal function. An overdose of clonidine may be reversed with naloxone.

Ibuprofen Indometacin is the conventional treatment for patent ductus arteriosus (PDA) in preterm neonates.25 However, its use is associated with various adverse effects on mesenteric, cerebral and renal haemodynamics. Ibuprofen has been shown to be as effective as indometacin for the closure of PDA without reducing mesenteric, cerebral31,32 and renal blood flow.32

Ibuprofen is administered by IV injection, although a small study has been carried out showing it may be effective orally.33 A licensed IV product is not available in the UK. However, an injection for parenteral administration is available from Germany, as the lysine salt. Comparative studies of indometacin versus ibuprofen, with regard to long-term outcomes, are needed before ibuprofen replaces indometacin as the current standard of practice.34

Dexamethasone Dexamethasone is used in preterm neonates for the treatment and prevention of chronic lung disease (CLD). However, recent studies suggest that, in the long-term, it may produce neuromotor dysfunction, with an increased risk of cerebral palsy.24

Dexamethasone is currently used in doses ranging from 0.5 to 0.6mg/kg/day in divided doses. Lower doses of dexamethasone (0.2mg/kg/day) improve pulmonary function,25 but have not been shown to reduce the risk of neuromotor side effects. Current recommendations by the American Academy of Pediatrics and the Canadian Pediatric Society discourage routine use of dexamethasone in preterm infants. Its use in the prevention or treatment of CLD outside randomised, controlled trials should be considered carefully.26 Further clinical trials are needed to determine the risk of neurological side effects.27

Sildenafil Persistent pulmonary hypertension (PPHN) is an important cause of morbidity and mortality in the neonatal population.28 Current management of PPHN includes therapies that are targeted at lowering pulmonary vascular resistance. Drugs commonly used in treatment are inhaled nitric oxide, tolazoline, dipri-damole and prostacyclin. Recently, studies have shown that sildenafil, a selective vasodilator, decreases pulmonary vascular resistance in PPHN.29

Sildenafil has also been shown to be effective in the treatment of primary pulmonary hypertension in paediatrics.30 One of the theoretical advantages of sildenafil over current therapies is its greater selectivity for the pulmonary vascular bed.31 Sildenafil inhibits phosphodiesterase type-5 inhibitor, and this results in increased levels of cyclic-guanosine 5-monophosphate (cGMP), potentiating pulmonary smooth muscle relaxation.

Vancomycin Recently, the value of vancomycin therapeutic drug monitoring in the NICU has been the subject of debate, resulting in new recommendations.24 Vancomycin bactericidal action has been shown to be time-dependent, and hence a constant rate of infusion over 24 hours might provide optimum bactericidal efficacy.41,42

Vancomycin is excreted primarily in the urine. However, in neonates, urinary excretion is dependent on corrected gestational age (CGA). Many studies have confirmed the significant relationship between vancomycin clearance and CGA in newborns.

A regimen to improve vancomycin steady state concentration has been developed. This includes a loading dose followed by a 24 hour infusion based on CGA and body weight.43 The use of continuous vancomycin is not currently widespread within NICUs and further studies are needed before its efficacy can be confirmed.

CONCLUSION

Neonatal and paediatric intensive care is a specialised area that benefits from the clinical input of a paediatric pharmacist, especially since many of the medicines used are unlicensed or are being used outside their licence indications.

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REFERENCES


