Prescribing for newborns and infants: Part 2 – practical issues

In the second of three articles on prescribing in neonates the principles and uncertainties behind the construction of a dosage regime, the practical issues in formulating and administering medicines, and the use of therapeutic drug monitoring are described.

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Key points

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1. Standard dosing regimes are based on the average patient.
2. Dosing regimes should be updated as new evidence emerges regarding efficacy and side effects.
3. There needs to be a clear rationale to undertake therapeutic drug monitoring before it can be useful.

As described in the previous article[1], after doses have been normalised for weight or surface area, it is well recognised that not all infants respond similarly to the same amount of medication because of individual differences in pharmacokinetics (absorption, distribution, metabolism and elimination) or pharmacodynamics (what happens at the receptor level). In principle, the most appropriate way of adjusting dosage to a particular patient would be by assessing the clinical effect of the drug. This is possible when the response is easily measurable (e.g. blood pressure and dopamine, surfactant and oxygen requirement). However, the majority of medications do not have these readily assessable end points. The usual recommended dose regimens are therefore designed for the 'average' patient and based on drug concentrations in blood or other tissues/fluids and related to reported outcomes and pharmacokinetic data. For some drugs it is possible to bypass the pharmacokinetic interindividual variability by measuring the serum drug level directly and matching it to a known therapeutic range previously established by good quality randomised control trials in a similar patient population.

Creating 'average' dosing regimens

The standard pharmacokinetic approach in adult trials involves administering either single or multiple doses of a drug to a small (6-12) group of trial subjects and obtaining relatively frequent blood samples. Samples are collected over specified time intervals and subsequently assayed for concentrations of drug and relevant metabolites, where appropriate. Pharmacokinetic parameters are therefore established, such as AUC, Cmax, clearance, volume, and half-life. Data can be expressed as mean values with a spread of inter-individual variation. These parameters can be used to calculate a dose per kg enabling an 'average' patient to achieve drug serum concentration in the target range.

The preferred and often only possible approach in neonatal studies is the use of population pharmacokinetics. This relies on infrequent sampling of blood (2-4 per subject) from a larger population (50+). It poses few ethical issues as blood samples are taken opportunistically when sampling for other reasons. Since a relatively large number of patients are studied and samples can be collected repeatedly, at various times of day in a given subject, estimates of both population and individual means, as well as estimates of intra- and inter-subject variability, can be obtained. With larger trials the population of infants recruited will achieve a spread of drug concentration; these can be correlated to pharmacodynamic endpoints to provide some understanding of concentration-response relationships for both efficacy and toxicity.

Earlier studies utilised data collected in the course of routine drug monitoring, while more recent studies have examined data collected during new drug development or clinical research. More sophisticated techniques such as Bayesian analysis can utilise established adult pharmacokinetic data as a template to produce neonatal pharmacokinetic curves with an even smaller number of subjects[2].

Medicines used in neonates

Without sufficient pharmacokinetic data many drugs used routinely in neonatal care remained unlicensed for the neonatal age group and for specific indications. Reliable safety or efficacy data are therefore not available. Where there is no alternative, either unlicensed drugs have to be used, or drugs which are licensed in different age

- The drug has a narrow therapeutic index
- Blood concentration is related to clinical effect
- Dose given is poorly related to serum concentration
- The pharmacokinetics of the drug are already known
- Laboratory measure of serum concentration is specific and accurate
- Significant consequences are associated with under treatment or overdosing

TABLE 1 Characteristics of drugs considered good candidates for therapeutic drug monitoring.

groups, for different indications, or as different formulations of the product (off-label use) need to be utilised. Surveys have shown that up to 90% of all patients in a neonatal unit received at least one unlicensed or off-label medicine, 45% of all prescription episodes were off label and 10% were unlicensed[3].

Off-label medicine use

This describes the use of medicines outside the conditions of their original license. It may concern differing doses, age range, routes of administration or indications. Notable common off-label neonatal medicines include Oramorph (neither licensed for infants less than one year old nor for treatment of neonatal abstinence syndrome) and caffeine for apnoea[4].

Unlicensed medicines

When no commercially available, suitable formulation is available, unlicensed medicines have to be used. They include extemporaneous preparations where pharmacies make up suitable formulations by for example, crushing tablets, opening capsules or suspending drugs in agents to produce liquid formulations. This produces an unlicensed medicine which may have unknown bioavailability, shelf life or quality assurance. Hence the same drug obtained from different pharmacies may differ in its properties and call into question whether results from published controlled trials are truly applicable when such a product is used[5]. Examples include caffeine, spironolactone and thyroxine. Other types of unlicensed medicines include imports from other countries or medicines specially produced on a 'named patient basis' by pharmaceutical companies. These have the additional disadvantage of irregular supply.

Therapeutic drug monitoring

Individualisation of drug dosages to produce serum drug levels in a target range would remove the uncertainties between different infant pharmacokinetics to avoid over or under treatment. For specific drugs certain conditions must be met before therapeutic drug monitoring is deemed useful (**TABLE 1**).

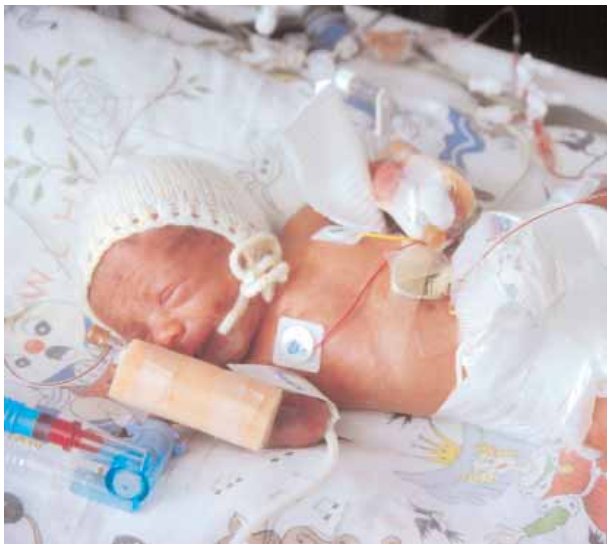

FIGURE 1. Therapeutic drug monitoring can help to optimise therapy for individual infants. *Photo: Eddie Lawrence.*

A robust 'therapeutic range'

Traditionally, data from large trials are analysed to produce a specific therapeutic range. When neonatal trials are unavailable, ranges are extrapolated from paediatric or adult data. The lower limit is the concentration that produces half the maximal possible therapeutic effect and the upper limit is the concentration at which no more than 5-10% of patients will develop toxicity[6]. Due to inter individual variations some patients will respond to concentrations below the range, some will experience side effects in the therapeutic range and others will require concentrations higher than the upper limit.

Medicines such as antibiotics have a measurable basis to calculate the therapeutic range. The killing abilities of antibiotics are either time dependent (e.g. penicillin), requiring sufficiently high concentration constantly over a threshold; or concentration dependent, requiring intermittent high peak concentrations (e.g. gentamicin). Vancomycin exerts its bactericidal actions by inhibiting bacterial cell wall synthesis, a process that is relatively independent of concentration. As a time dependent antibiotic, vancomycin has dosages calculated to achieve at least three to four times the minimal inhibitory concentration (MIC) in the average patient[7]. The minimal inhibitory concentration is the lowest concentration of an antibiotic that will inhibit the visible growth of bacteria after overnight incubation *in vitro*.

Therapeutic drug monitoring is recommended to ensure the serum drug level is within target range and also monitor for excessive accumulation, which can lead to side effects such as excessive histamine release, the 'red man syndrome'[8].

Therapeutic ranges should be adjusted when new evidence is available for the neonatal population. Initial guidelines for patient monitoring were extrapolated from studies performed in adult patients. Accumulated research suggests that some of the recommendations for adults are inappropriate for the neonatal population. For example, the traditionally accepted loading dose of phenobarbital to treat neonatal seizure is 20mg/kg. We now know that neonates with seizures may require higher serum concentrations for therapeutic effect, and a modified target range of unbound phenobarbital of 25 micrograms/mL seems to be more effective without excessive adverse effect. This equates to a loading dose of 35-45mg/kg for an average term infant[9,10]. Conversely the use of theophylline for treatment of neonatal apnoeas produces adverse effects at a lower serum level (14mg/L) in neonates than in adults (20mg/L).

Not all drugs have an agreed therapeutic range. Despite multiple controlled trials there remains no consistent serum indomethacin range which correlates with closure of the ductus arteriosus[11].

Appropriate samples

To be useful it is important that a full drug monitoring service is in place, with consideration given to reproducible results

within and between laboratories, timely turnabout time and the appropriate skills to interpret results within the clinical setting. Microtechniques with sample requirements of <75 microlitres of serum is desirable to avoid iatrogenic anaemia with repeated sampling. With the neonatal blood volume being 80mL/kg, a 500g infant has only approximately a 40mL blood volume and therefore cannot afford to lose very much due to repeated sampling. Immunoassays need to be specific, avoiding cross reactivity with endogenous substrates and metabolites, for example, digoxin and endogenous digoxin-like substances, giving erroneous and potentially harmful results[12]. Other bodily fluids such as saliva, that carry unbound drugs, have been shown to be reliable candidates for drug monitoring as an alternative to blood; as yet this remains a research tool.

Timing of samples

The timing of samples is entirely dependent on the indication for monitoring and on drug characteristics. Ideally drug levels are taken at steady state when assessing whether a drug is in the therapeutic range. Without a loading dose, steady state is only reached after four half lives have elapsed, when doses have been administered regularly. In practice, pre and post dose measures are more pragmatic. The pre dose or trough level is to ensure there is no excessive drug accumulation due to impaired clearance. Most peak levels are taken at one hour after the dose, but due to its extensive volume of distribution, digoxin levels are taken six hours after the dose as it has a prolonged distributive phase.

Practical issues

Theoretically the intravenous (IV) route guarantees that the dose prescribed will reach the patient's circulation. Studies have shown that bioavailability by this and other routes can be significantly altered by formulation and administration factors.

Formulation

The addition of excipients is necessary to produce drug preparations appropriate for different routes of administration, provide palatability and ensure their stability. Some excipients are pharmacologically active when present in sufficient concentration. Historically severe adverse drug reactions have occurred because of the inability of neonates to excrete or metabolise these excipients sufficiently, resulting in accumulation of fatal levels. Subtle changes in preparation can have inadvertent large effects on the bioavailability of the drug. For example in the 1970s in Australia after calcium was removed from phenytoin preparations, there was an unexpected rise of toxicity in adult epileptic patients. This was later attributed to increased bioavailability[13]. **TABLE 2** illustrates some common excipients and their function.

Function	Examples
Antioxidant	Ascorbic acid, vitamin E
Antimicrobial preservative	Ethyl alcohol, hydrobenzoates
Solvents	Ethanol, benzyl alcohol, propylene glycol
Chelating agent	EDTA
Emulsifers	Lecithin
pH adjusters	Hydrochloric acid, sodium hydroxide

TABLE 2 Common excipients and their function.

Solvents

Medications which are not highly water soluble present a problem for pharmaceutical manufacturers. The product must be made soluble enough for oral or parenteral use, without altering its stability. Propylene glycol, a commonly used solvent has been associated with a number of adverse effects, including nephrotoxicity, cardiac arrhythmias, seizures, respiratory depression, severe hyperosmolality, lactic acidosis, and severe thrombophlebitis, especially when administered by rapid IV injection[14]. Thus medications such as phenobarbital, phenytoin, and diazepam need to be administered slowly, when given IV.

Ethanol is commonly used as a solvent in oral liquid formulations. Phenobarbitone contains 38% ethanol. Two concerns exist with its use – acute intoxication with accidental overdose, and toxicity associated with chronic use.

Preservatives

Antimicrobials and antioxidants are added to drugs to prolong shelf life and maintain sterility. The link between the preservative benzyl alcohol and neonatal cardiovascular collapse, 'the gasping baby syndrome,' was a widely publicised adverse reaction related to the use of these 'inert' ingredients. In 1982 a series of neonates in the US died or developed a severe illness associated with gasping respirations, metabolic acidosis, and haematologic abnormalities[15]. These cases were linked to the repeated use of IV water flush solutions containing 0.9% benzyl alcohol which the babies accumulated. In the adult, benzyl alcohol is converted to benzoic acid, and then conjugated with glycine to form hippuric acid which is excreted. Infants with gasping syndrome were found to have significantly increased concentrations of benzoic acid, which because of their immature metabolism and excretion pathways was not effectively conjugated and removed. The large total dose received, coupled with the decreased capacity of the neonate to eliminate the benzyl alcohol, culminated in the toxic concentration.

Administration

The need to miniaturise every line and port in neonatal intensive care means that meticulous care is needed to ensure that the baby receives all the prescribed medication. For oral administration small spillages or regurgitation result in a significant proportion of the medication not reaching the gut. For IV infusions the limited IV infusion rate (3-5mL/hr for babies <1000g) means that it can take up to 160 minutes from starting the line for the drug to reach the baby's circulation[16], depending on the site of the line ports. The delay in the administration of a drug may compromise therapy. In addition, without knowing when exactly a drug infusion reaches the baby's circulation, it is difficult to determine the correct timing for therapeutic drug monitoring.

A baby on NICU has an average of ten IV injections or infusions per day[17] either in series or in combination. Care has to be taken as significant drug dosages can be lost with the repeated change in giving sets and lines. New equipment has to be rigorously tested; previous line filter chambers have been found to bind antibiotics[18]. With increasing poly-pharmacy and simultaneous drug administration the risk of drug-drug interaction increases, either during drug delivery in the lines, *in vivo*

within the infant, or in the blood sample collected for therapeutic drug monitoring. Interaction has been demonstrated between gentamicin and ampicillin *in vitro* in umbilical cord serum[19].

Overdosing can easily occur when very small volumes of drugs are drawn up from adult vials to be diluted down. For example, a 1mL vial of morphine with 10mg in 1mL, contains 100 times the dose for a neonate requiring 100 micrograms. It has been demonstrated with a variety of IV preparations including digoxin, adrenaline and midazolam that the volume contained in the dead space of a typical syringe can contain up to 2-3 times the dose volume required for a neonate[20].

Conclusion

Drug dosages in formularies are designed for the average neonate with average absorption, distribution and clearance. Due to immaturity and the continuing development of the baby's body processes, especially in the ill neonate receiving multiple medicines, care must be taken to watch for adverse events occurring as a result of under or over dosing. With judicious use of therapeutic drug monitoring coupled with emerging research in neonatal pharmacology the ultimate aim is to individualise drug therapy for each infant and condition.

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