Prescribing for newborns and infants: Part 1 – pharmacology

In the first of three articles on prescribing in neonates the basic principles of pharmacology in the newborn are explained. Principles of drug absorption, distribution, metabolism and excretion are described with reference to commonly used drugs in the newborn.

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Key points

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1. Drug prescribers and administrators need to understand the basis of drug therapy to ensure efficiency and avoid adverse drug events.
2. The key stages in pharmacokinetics are absorption, distribution, metabolism and elimination.
3. Significant developmental changes occur in newborns at each of these stages and there can be wide variations between individuals.

Inadequate information is available on how newborn babies and infants handle drugs, due to a large extent to the many ethical, financial and practical issues which discourage drug trials in neonates. The reluctance of drug companies to license neonatal drugs has been highlighted recently in the media. Such reticence is not surprising as the commonly used drugs in neonates have been around for a long time (**TABLE 1**) and there are few incentives to investigate better alternatives[1]. The neonatal population suffers from being the patient group with the most adverse drug reactions[2]. The goal of the neonatal team has shifted from producing survivors to producing NICU graduates with minimal disability. It is important to know about the drugs being given, when they should be prescribed and in what quantity, in order to optimise health and reduce adverse drug events.

Choice of drug

Pharmacology is the study of drugs and their actions, pharmacokinetics describes what the body does to drugs and pharmacodynamics describes the effects of drugs on the body. All body systems work by a complex interaction of molecular signalling pathways, cell receptors, enzyme reactions and the transformation of genes to molecules. The aim of drug therapy is to interact with specific receptors and predictably alter function to obtain the desired effect. A drug that activates or potentiates a receptor is an agonist, while a drug that reduces or blocks function is an antagonist. There is a dose response effect at the receptor level, with a larger amount of drug causing an increased response, that manifests itself clinically, e.g. greater rise in blood pressure with increasing dose of dopamine. However, often the clinical end points are not quantitative, as above but qualitative, e.g. alive or dead.

■ Gentamicin	■ Vitamin K
■ Benzylpenicillin	■ Frusemide
■ Folic acid	■ Caffeine
■ Multivitamins	■ Flucloxacillin
■ Albumin	■ Morphine

TABLE 1 Ten most commonly prescribed drugs in one neonatal intensive care unit. *From Conroy et al. 1999*[1]

As the drug is cleared from the site of action its effect wears off. Since drugs or their metabolites can never be entirely receptor specific, side events occur when they interact with other systems and cause undesirable effects.

Marked maturation changes occur throughout gestation and in the months after birth and these are reflected in both the pharmacokinetics and pharmacodynamics of administered drugs. As with other areas of development, such as growth and speech, individuals develop at different rates. Equal amounts of a drug given to babies of different gestational or chronological ages may result in different concentrations at the site of action. One infant can clear the drug more rapidly than another. Furthermore, developmental maturation at the receptor and enzymic level may result in different dose-responses at the site of action. As an example, salbutamol is ineffective in infancy as a bronchodilator because β_2 receptors are less expressed in the lungs before 18 months of age[3].

Pharmacokinetics

Pharmacokinetics considers the movement of drugs within the body and the way in which the body affects the drugs with time. Once a drug is administered it undergoes four basic processes: absorption into the systemic circulation, distribution around the body, metabolism into (mainly) inert molecules and excretion from the body.

The balance of these processes determines the amount of drug present at the site of action (**FIGURE 1**).

Absorption into the systemic circulation

In the neonatal setting most drugs are given intravenously to provide as direct access to the systemic circulation as possible, although this is not always technically feasible or desirable. When giving intravenous drugs with cardio-active side effects, e.g. vancomycin or phenytoin, it is recommended to give them slowly, rather than by 'push,' as the latter may result in a high transient blood level and cause cardiac arrhythmias[4]. Other drugs that need to be given slowly include acyclovir, high transient doses of which may lead to precipitation in the renal tubules[5].

Oral

Bioavailability refers to the proportion of the administered drug that reaches the systemic circulation and is available to exert an effect. The bioavailability of orally administrated drugs is unpredictable in the newborn and is not recommended for essential drugs for a number of reasons[6].

In the first few days of life there is often feed intolerance, vomiting or possetting. A particular practical problem of the necessary use of small volumes of liquid medication is that any spillage or spitting represents a significant drug loss of that required to be given.

Several gastrointestinal changes occur with maturation. Gastric juice pH is neutral at birth but becomes acidic from two weeks of age[7]. Generally, molecules in the intestinal lumen can only cross cell membranes to reach the circulation if they are not ionised. Absorption of acidic drugs, such as phenobarbitone, is increased in an acidic environment and basic drugs such as penicillin are better absorbed in an alkaline environment. These early gastric changes can alter the bioavailability of certain oral drugs.

Gastric emptying, intestinal motility, concurrent feeding, changes in intestinal flora and bile salt availability for lipophilic drugs can all potentially vary the rate of absorption and bioavailability of different drugs[8], as can splanchnic blood flow, which increases rapidly during the first three weeks of life[9].

Little information is known on the effects of systemic illness or breast versus formula feeding on enteral drug absorption.

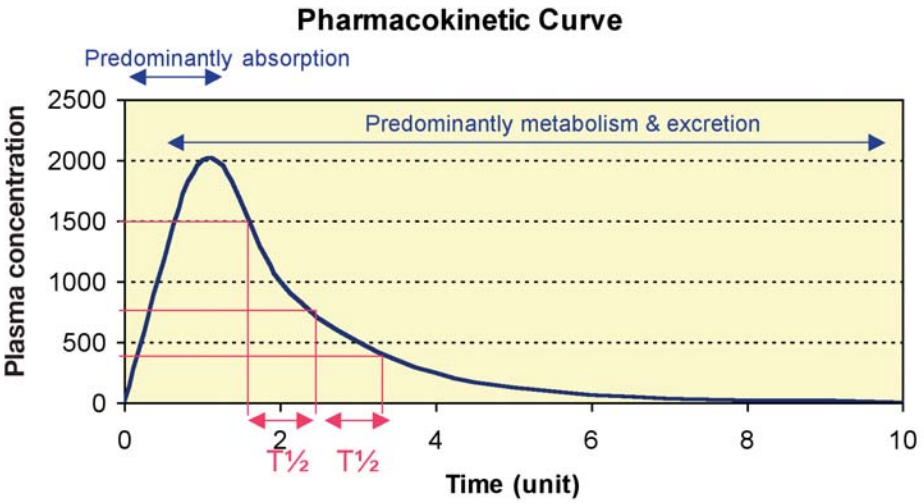

FIGURE 1 A concentration time curve for a drug administrated to a theoretical patient. The rate of rise depends on the route of administration. Metabolism and excretion begins as soon as the drug enters the body. The half life (T½) of a drug is the time taken for plasma concentration to fall to half.

Transport across intestinal epithelium is by four major mechanisms: passive, facilitated, active or pinocytosis – where the cell membrane envelops the molecules and physically pulls it into the cell. Specific cell membrane molecules, such as the P-glycoprotein group, transport various molecules and drugs across the intestinal mucosa as well as provide access to other restricted sites, such as the blood brain barrier, renal tubule cells and hepatocytes. These transporter molecules have been shown to increase in number from birth until around four months of age[10]. Some drugs, e.g. gentamicin, cannot be sufficiently absorbed in neonates due to a lack of specific transporters.

Drugs absorbed from the gastrointestinal tract are carried via the hepatic portal vein to the liver, where they are metabolised to varying extents by the hepatocytes before entering the systemic circulation, this is called 'first pass' metabolism. The bioavailability of oral morphine after first pass metabolism is around 35%[11]. As usual there are inter-individual variations in metabolism, such that some opiate withdrawing babies may not respond to relatively high doses of oral morphine because of extensive first pass metabolism.

Oral preparations of some common drugs have been found to be hyperosmotic. This has been associated with necrotising enterocolitis and therefore particular consideration is required in prescribing oral medication to premature infants[12].

Rectal

In standard neonatal practice few drugs apart from paracetamol and paraldehyde are given rectally. Rectal absorption is variable and prolonged with many infants in one rectal paracetamol study not reaching therapeutic blood concentrations after being given the standard recommended dose per kg. Mechanical factors are mainly responsible for this. The surface area of the rectum is relatively small compared to the intestine and suppositories are not designed for small premature infants, so absorption from a highly placed suppository may drain into the superior rectal vein which drains into the liver and undergoes first pass metabolism[13].

Intramuscular

Apart from vaccinations, where good immunological response has been demonstrated in ex-preterm infants, there have been few studies of this route[14]. Absorption is variable and dependent on local blood flow. In very low birthweight infants, where muscle mass is limited, practical concerns and local trauma from injections limit its usefulness.

Percutaneous absorption

As yet no commercially available neonatal drug is designed for this potentially useful route, however significant amounts of iodine and alcohol containing antiseptic solutions can be absorbed, causing local damage and significantly adverse systemic effects.

Drug distribution

The movement of drugs from the systemic circulation into various body compartments, tissues and cells is termed

distribution. There needs to be a sufficient concentration of the drug at the site of action for it to be effective. Drugs are distributed into 'compartments' depending on their molecular makeup and these compartments may be anatomical – caused by physical restraints (e.g. blood-brain, adipose tissue, extra/intra cellular) – or physiological (e.g. perfusion of organs, extent of protein binding). These compartments can act as storage sites where drugs can accumulate, e.g. diazepam in fat tissue. The apparent volume of distribution describes the relationship between the amount of drug infused into the body and its plasma concentration which can be measured. Therefore drugs with a larger volume of distribution require higher doses to achieve similar effective concentrations at the site of action than drugs with lower volumes of distribution. What does this mean in practice?

Changes in body compartment size with age and gestation

Age-dependent changes in body composition (**TABLE 2**) set the size of the compartments in which a drug may be distributed[15]. Aminoglycosides are distributed in the extracellular fluid, so a premature infant which has a disproportionately large extracellular fluid compartment compared to term and older babies, may require a larger dose per kg to achieve comparable concentrations. After birth there is often a postnatal diuresis affecting both intra- and extracellular fluid compartments equally. The fat compartment increases throughout fetal life and infancy.

Plasma protein binding

Once in the vascular space, most drugs bind to plasma protein and/or red cells. Neutral and acidic drugs bind mainly to albumin, while basic drugs bind to lipoproteins and α_1-acid glycoproteins. Drug binding to plasma protein is reversible. It is the free unbound proportion which is the active drug. Therefore changes in plasma protein quantity and protein binding due to alterations in blood pH, temperature or the presence of competing binding substances, can increase or decrease the proportion of active free drug. Serum albumin and α_1-acid glycoproteins concentrations rise with gestation and age and fall with disease and malnutrition[16]. After birth, circulating albumin is predominantly fetal albumin and this has a lower affinity for drugs.

	Prem 25/40	Term
Total body water	85%	75%
Extra cellular fluid	60%	45%
Fat	1%	15%

TABLE 2 Body composition at birth and gestation (% of body weight).

A number of endogenous molecules such as free fatty acids or bilirubin also bind to plasma protein and compete with the drug for binding sites. It is possible that drugs which are highly bound to protein may displace bilirubin from plasma proteins, allowing free bilirubin to cross the blood-brain barrier and increase the risk of kernicterus. Frusemide, indomethacin and diazepam are all >90% protein bound. However, it is unclear whether polypharmacy with these drugs or high bilirubin levels increase the free drug level to any significant clinical effect.

Blood-brain barrier

The capillaries surrounding the brain have specialised tight junctions that limit what can pass into the cerebral tissues. Only small molecules (<500 Dalton), lipophilic molecules that can diffuse across cell membranes or those carried by specialised transporters can pass. This allows the brain to be a sanctuary site, preventing many infectious substances and toxins from crossing, but many therapeutic drugs are also blocked – some antibiotics cannot cross the blood-brain barrier. In general, the higher bactericidal doses rather than the lower bacteriostatic doses of suitable antibiotics are required to treat meningitis, as there are no natural white cells in the brain, nor can antibodies cross the blood-brain barrier.

Drug metabolism

Drug metabolism, or biotransformation, refers to the process of modifying or altering the chemical composition of the drug, usually with a concomitant loss of pharmacological activity. Metabolites are produced which are more polar and less lipid-soluble than the original drug and this ultimately promotes their excretion from the body by the kidney. Most drug metabolism occurs in the liver, where hepatic enzymes catalyse various biochemical reactions. Metabolism of drugs may also occur in the kidneys, intestinal mucosa, lungs or plasma.

Some drugs have metabolites that are active. Theophylline is metabolised to caffeine which acts as a respiratory stimulus[17]. Morphine is metabolised into morphine-3-glucuronide and morphine-6-glucuronide[18], the latter having greater analgesic properties than morphine itself. Like many physiological processes, liver enzyme levels are dependent on age, for example lower levels of morphine-6-glucuronide are produced by neonates compared to older children.

Metabolism is classified into phase I or II reactions, in various combinations depending on the drug. Phase I reactions are oxidation, reduction and hydrolysis reactions, utilising cytochromes P450. At least 50 different cytochromes metabolising various combinations of drugs have been characterised and catalogued with an identifier beginning with CYP. As a general principle, expression of these CYPs is low or absent at birth, each increasing at various times and different rates to reach adult levels between one week to six months of life[19]. For example, mean phenytoin half-life changes dramatically with age – 75 hours in preterm infants, 20 hours from term to one week of age and eight hours in the second week of life. This parallels the rise of hepatic enzyme CYP2C9 levels after birth. This is the system which oxidises phenytoin and is not present in the fetal liver.

Phase II are conjugation reactions, which combine the drug with endogenous molecules. The resulting water-soluble conjugates are then readily excreted by the kidneys.

When some drugs such as phenytoin or phenobarbitone are given repeatedly, metabolism of the drugs becomes more effective due to enzyme induction. The half-life of phenobarbitone is halved from four to two days after one week of administration, and a higher regularly repeated dose is required to maintain therapeutic levels[4]. Due to differences in genetic make-up, individual babies exhibit different concentrations of hepatic enzymes. This genetic polymorphism may account for the wide range of drug clearance rates between individuals.

Drug excretion from the body

Clearance of drugs from the body is mainly via the kidneys, with some occurring via the bile. Renal excretion is dependent on glomerular filtration, tubular reabsorption and tubular secretion.

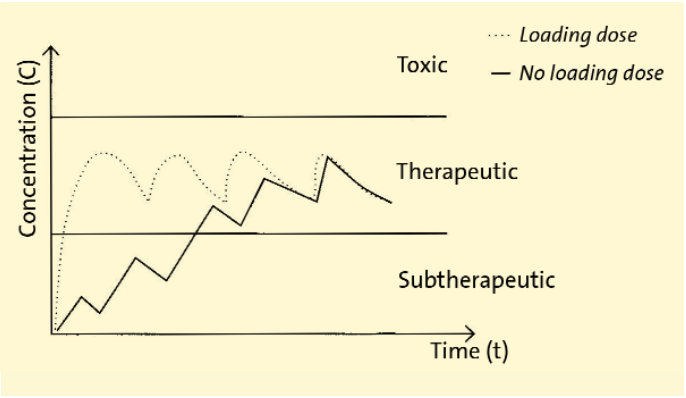

FIGURE 2 Giving a loading dose allows the drug to reach its therapeutic level quickly.

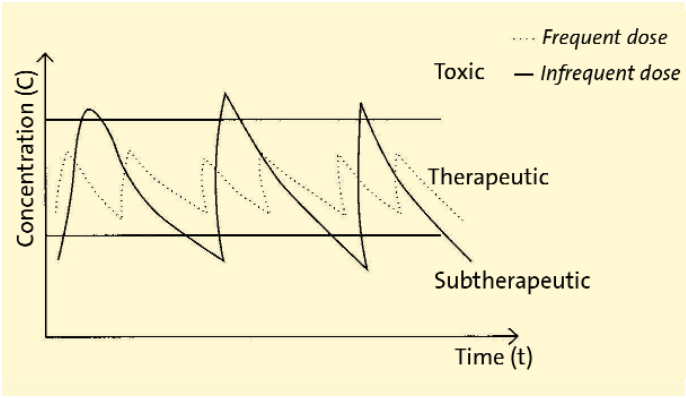

FIGURE 3 At steady state, where drug absorption equals drug elimination, giving lower but more frequent doses keeps a drug within the therapeutic range.

At birth, excretion of nearly all drugs is hindered by a low glomerular filtration rate (GFR), due to low renal blood flow and high intrarenal vascular resistance. In both term and preterm infants this low GFR rapidly increases with age. A term neonate's GFR of 15-20 mL/min/m^2 rises to 40 mL/min/m^2 at two weeks and doubles again to 80 mL/min/m^2 at eight weeks of age. At birth preterm infants may have a GFR as low as 2-4 mL/min/m^2 which also rises rapidly with age[20]. Therefore it is important to manipulate the drug-dosing schedules in the neonatal period to ensure that drugs do not accumulate to toxic levels. Reduced clearance as a result of renal failure or during concurrent administration of medications which can alter renal function, such as ibuprofen or indomethacin, should be considered. Similarly, tubular secretions rise with age after birth. Penicillin and amoxicillin are excreted by this route.

Drugs excreted by the liver in the bile may be reabsorbed further down in the intestinal tract. This enterohepatic circulation is not usually a significant component in the healthy neonate but in certain disease states, such as gut stasis, drugs may accumulate rapidly.

The half life (T½) is the time taken for the amount of drug to halve in the body generally, or in a compartment, e.g. blood, and is an indirect indicator of drug metabolism and excretion (**FIGURE 1**). The majority of drugs follow first-order kinetics principles, e.g. the more drug there is in the body, the faster the rate of removal. The T½ for a drug is the same, irrespective of the dose given and represents an indirect but useful way to compare different drugs, different age groups and the effects of different diseases on drug metabolism and elimination.

Dosing schedules

There is a therapeutic drug concentration range in a body fluid for which a drug is effective, but not toxic (**FIGURE 2**). The aim of an appropriate dosing schedule is to maintain the drug concentration at a relatively steady level with minimal fluctuation between doses. A 'steady-state' is reached after about 5-6 half lives have elapsed, assuming the drug dose given is similar at each administration. At this point of steady-state, the amount absorbed equals the amount eliminated. Within steady-state, a dose interval approximating the half-life time would mean that concentrations – in blood, for example – would not fall lower than half the peak concentration. This degree of fluctuation is considered 'acceptable' for drugs for which there is a close relationship between concentration and clinical effect.

When commencing drug treatment there will be a time lag between starting treatment and seeing a therapeutic response, which is dependent on achieving steady-state concentrations with the regular dose schedule employed. For drugs such as anticonvulsants, antibiotics or analgesics where a rapid response is required, a loading dose can be given to achieve therapeutic 'steady-state equivalent' concentrations, without having to wait for the five half-lives time to elapse. The loading dose is calculated such that the volume of distribution is filled to a therapeutic level without reaching toxic levels. Similarly, when a drug is discontinued the serum level only falls to zero after a period of five half-lives, so there may be a considerable hang-over period before the drug effect wears off.

Some drugs, such as dobutamine and dopamine, have such a short half life (2-4 seconds) that a continuous IV infusion is required to maintain therapeutic serum levels[21].

Gentamicin

For drugs with a narrow 'therapeutic index' (difference between the concentration in blood at which a beneficial effect occurs and that at which adverse effects begin to occur), more frequent administration of lower doses, but with the same total daily dose, will result in less fluctuation between doses and less likelihood of producing toxic and/or subtherapeutic levels (**FIGURE 3**).

Gentamicin is a common aminoglycoside antibiotic which blocks binding of tRNA to ribosomes in bacteria, disrupting protein synthesis. Gram –ve bacteria display adaptive resistance whereby they stop taking up the drug after an hour, so a prolonged peak level is not required. Thus gentamicin is more effective when given at a higher dose but less frequently, thereby reducing the total dose, because distribution to its sites of action and probably its bactericidal effect is better achieved by a rapid high concentration in blood[22].

The toxic effect of aminoglycosides on hearing and kidneys is directly related to the total cumulative dose, rather than isolated concentrations. Accordingly a once-daily regimen has been recommended for term infants. Blood levels are monitored after three doses, to check for any drug accumulation resulting in potentially toxic concentrations, which identifies those infants with lower rates of drug excretion. Gentamicin is entirely excreted from the kidneys and its half life mirrors GFR, being 12 hours in 24 week gestation premature infants, compared to seven hours in the term neonate.

Summary

The principles of giving drugs to newborn babies are similar to those for individuals of all ages. There is an added layer of complexity with neonates because of the marked developmental changes occurring at this time, which have an effect on all drug-handling processes. Administration of excessive drug levels causes adverse side effects and inadequate dosage leads to suboptimal treatment. Even if all components of drug handling are considered and accounted for in drug dosing regimens, there can still be wide variations between babies of similar size, maturity and pathology. Many of these influential factors relate to unpredictable genetic variations or disease processes and their effects will only be discovered with good quality trials.

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