THE PHARMACOKINETICS, PHARMACOLOGY AND ACTIVITY OF ANTIBIOTICS IN THE NEWBORN: THE CLASSICAL DRUGS

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The description by Chain in 1940 of the therapeutic properties of penicillin initiated the present antibiotic era. During the following decades many other antibiotics were discovered mainly as a result of soil surveys. This paper will be confined to those antibiotics which have found some use in the treatment of neonatal infection and particularly those which remain in use today.

ACTIVITY

The evolution of antibiotic usage in the newborn may be related to which drugs were initially available and their spectrum of activity, and subsequently to the development of bacterial resistance and the changing pattern of infection in the neonate.

In 1950 antibiotic therapy in the neonate hinged on the use of sulphonamides, penicillin and streptomycin. These agents provided a wide spectrum of activity against most neonatal pathogens, many staphylococci still being sensitive to penicillin. Interestigly, the potential toxicity to the newborn of both streptomycin and sulphonamides were appreciated to some extent, but aureomycin and chloramphenicol were viewed as new antibiotics with a low degree of toxicity (Nelson, 1950). Topical antibiotics in use at this time included tyrothricin and gramicidin.

By 1959 several advances in antimicrobial chemotherapy had occurred. Chloramphenicol and tetracycline were regarded as the drugs of choice in both Gram-negative and some Gram-positive infections. Polymyxin was available for use in pseudomonal infections and erythromycin for cases of penicillin hypersensitivity. Novobiocin, extremely active against *Staphylococcus aureus*, was a useful agent which has now been usurped by the isoxazoyl penicillins. At the end of the decade kanamycin was introduced and used extensively throughout the next ten years especially in the United States of America. This resulted in the emergence of resistance in a large proportion of strains of *E. coli* (Howard and McCracken, 1975). A combination of ampicillin and cloxacillin was also employed in many units but increasing resistance of *Escherichia coli* to ampicillin and the decline in the importance of *Staph. aureus* as a neonatal pathogen necessitated a change. Since this time, gentamicin plus penicillin or ampicillin has been the mainstay of therapy in most nurseries.

PHARMACOLOGY

Pharmacokinetics

The study of the pharmacokinetics of antibiotics in the neonate has been sadly neglected and reliable information regarding the older antibiotics which are now sel-

dom used is not available. Much of the work published before 1970 is of dubious value, for the number of infants studied was small and indications of postnatal age, prematurity, renal function and disease state were rarely recorded. The failure to undertake the necessary studies of antibiotic pharmacokinetics may be attributable to the many difficulties encountered during investigations of this population and an erroneous assumption that pharmacokinetics in the neonate would be similar to those observed in adults.

There are a number of problems in studying the pharmacokinetics of antibiotics during the first month of life. Ethical considerations demand that investigations are only undertaken on sick neonates requiring treatment and controlled studies on therapeutic agents are not possible. Many infants receiving antibiotics are critically ill and cannot be studied, others treated for only suspected infection may discontinue antibiotics after 48 hours and be lost to further investigation. Due to the rapid changes occurring in the first days of life, study of the first one or two injections may not provide an accurate prediction of pharmacokinetics later in the course of treatment. The number of blood samples which can be collected from premature babies is limited and accurate renal clearance studies impossible. Volumes of serum are usually restricted to less than 200 μl and all assays must therefore be adapted to a microscale.

Many factors may influence the pharmacokinetics of antibiotics in the neonate. During the first months of life there are dramatic changes in physiology and these changes are most striking in the premature neonate. The enzyme systems of the liver, kidney and gastrointestinal tract are all deficient at birth and develop at different rates.

Drug absorption in the neonatal period is affected by the low muscle mass for injection, and differences in the biochemistry and cell physiology of the developing gastrointestinal tract. Pronounced differences in drug absorption in the neonate should therefore be anticipated.

Drug distribution may be affected by quantitative and qualitative changes in serum proteins which affect the degree of protein binding of antibiotics and thus the kinetics of these drugs in serum (Wallace, 1977). Differences in membrane permeability particularly that of the blood/brain barrier may also affect antibiotic distribution. Thirty-seven per cent of the bodyweight in the newborn appears as extracellular water and this is reduced to 28 per cent at one year of age (Flynn *et al.*, 1967). As a result, antibiotics have a larger volume in which they may be distributed and may fail to attain therapeutic concentrations unless adult per kilogram dosage rates are altered. The concentrations and activity of hepatic enzymes responsible for the metabolism of some antibiotics, for example chloramphenicol, are low in the neonate and young infant (Young and Lietman, 1978). Termination of drug action and subsequent excretion of polar metabolites via the kidney may therefore be delayed with serious consequences.

Glomerular filtration rate in the neonate is reduced to 30 to 60 per cent of adult levels and tubular function is also decreased (Driscoll and Hsia, 1958). Prematurity may also affect renal function but following birth maturation of renal function is similar in term and preterm infants (Fawer *et al.*, 1979).

TABLE 1. — *Mean (±S.E.) serum concentrations and total body clearance of chloramphenicol after all routes of administration.*

		Dosage (mg/kg/day)	Trough concentration (mg/l)	Peak concentration (mg/l)	Clearance (ml/min/kg)
Neonates	76	43±2.5	16±1.5	24±1.9	1.5±0.12
		12 - 170 *	3 - 76	3 - 114	0.4 - 4.5
		(95)	(77)	(82)	(58)
Infants	14	69±4.7	9±1.5	24±1.9	1.5±0.12
		17 - 210	3 - 84	3 - 55	0.9 - 17.6
		(84)	(64)	(61)	(28)

The figures in brackets are the number of observations.

* Range

One of the most prominent features of pharmacokinetics in the neonate is the wide interpatient variation. Is it possible to determine which physiological characteristics account for this observed variation? Postnatal age is of particular importance. During the first two weeks of life there is a dramatic increase in renal function (Guignard *et al.*, 1975). This is reflected by a rapid fall in plasma creatinine concentration during this time (Rudd *et al.*, 1983). The serum elimination half-life of antibiotics will therefore decrease with increasing postnatal age and decreasing plasma creatinine concentration. For example, serum concentrations of chloramphenicol are significantly higher and clearance slower in neonates when compared with infants (table 1). Similarly, the clearance of gentamicin increases with increasing postnatal age and decreasing serum creatinine concentrations (Mulhall *et al.*, 1983a). Similar changes have been demonstrated for penicillin and ampicillin (McCracken *et al.*, 1973; McCracken and Nelson, 1983). Studying babies greater than 28 days old, we have shown that the age related increase in chloramphenicol clearance may also continue after the neonatal period (figure 1).

Gestational age may also affect the pharmacokinetics of antibiotics in the newbor. Peak and trough serum concentrations of both chloramphenicol and gentamicin may be significantly higher and clearance slower in preterm when compared with term babies (tables 2 and 3).

Interactions between antibiotics and other drugs may also occur. Phenobarbitone is a known inducer of chloramphenicol metabolising enzymes in the adult and administration of phenobarbitone in neonates has been associated with reduced levels of the antibiotic (Windorfer and Pringsheim, 1977). We have been unable to confirm these findings in our studies (Mulhall *et al.*, 1983b).

Toxicity

Some of the first pharmacokinetic studies to ben undertaken in neonates were prompted by a therapeutic disaster – the Gray Baby Syndrome (Weiss *et al.*, 1960).

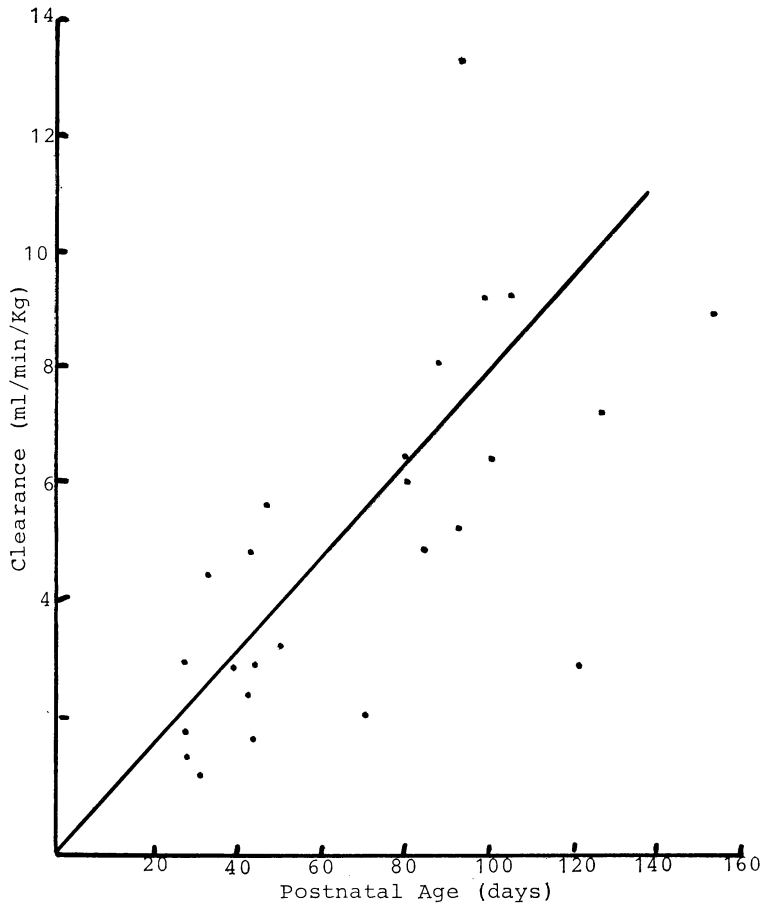

Fig. 1. — The effect of postnatal age on the clearance of chloramphenicol in infants. Correlation coefficient r = .7326.

Following the recognition of this syndrome it was realised that drug disposition and excretion in the neonate might differ from that in adults or laboratory animals. Many of the other classical antibiotics, despite having a wide spectrum of activity, are potentially toxic to the neonate and would not, therefore, be used today.

The haemolytic anaemia associated with the administration of sulphanilimide to babies with glucose-6-phosphate deficiency was recognised by 1959. In the same year, Odell (1959) published his observations on the displacement of bilirubin from albumin binding sites with a subsequent risk of kernicterus in the premature neonate. Sutherland and Keller (1961) reported a threefold increase in hyperbilirubinaemia amongst newborn infants given novobiocin. This was a result not of bilirubin displacement, but of potent inhibition of glucuronyl transferase, the enzyme catalysing the conjugation of bilirubin. The potential toxicity of tetracyclines

TABLE 2. — *Mean (± S.E.) concentrations and clearance of chloramphenicol in preterm and term neonates.*

Gestational age (weeks)	Trough concentration (mg/)	Peak concentration (mg/l)	Clearance (ml/min/kg)
<37	19±3 (26)	28±3 (33)	1.16±0.15 (22)
	p >0.05	p <0.02	p <0.005
⩾37	13±1 (34)	20±2 (32)	1.86±0.18 (25)

The figures in brackets are the number of observations.

were not fully appreciated until the description both of tooth discolouration and skeletal growth deformities in the early 1960's (Walman and Hilton, 1962; Cohlan *et al.*, 1963). The vestibular toxicity of streptomycin was recognised as early as 1960 but at that time it was a valuable antibiotic for the treatment of infections caused by Gram-negative organisms.

The paucity of pharmacokinetic studies often resulted in the use of excessive dosages as was the situation for chloramphenicol which was used at a dosage of 100 mg/kg/day both for proven infection and prophylaxis. Following rudimentary pharmacokinetic studies, a revised dosage of 25 mg/kg/day was proposed for neonates. Even using this revised dosage, it is essential to monitor the serum levels of every baby receiving this drug. This point is well illustrated in table 4. Of twenty-five babies receiving the recommended dose, only eleven had levels within the normal range. Infants in particular may not achieve therapeutic serum concentrations even when given the recommended dose of 100 mg/kg/day. Ten of sixty-four neonates in a recent study (Mulhall *et al.*, 1983 c) exhibited signs of chloramphenicol toxicity. Serious toxicity was associated with either overprescription or over-

TABLE 3. — *Effect of gestational age on the pharmacokinetics of gentamicin in babies less than 7 days old.*

	Mean (±SEM)			
	Peak concentration (mg/l)	Trough concentration (mg/l)	AUC (mg/min/ml)	Clearance (ml/min/kg)
Preterm (⩽37 weeks gestation)	7.8±0.34 (41)	2.9±0.21 (42)	3.7±0.21 (33)	0.8±0.05 (33)
Term (>37 weeks gestation)	5.7±0.66 (8)	1.5±0.36 (8)	2.7±0.46 (8)	1.16±0.11 (8)

Figures in brackets are number of babies.

dosage. Peak serum concentrations ranging between 28-180 mg/l and trough concentrations between 19-47 mg/l were recorded in babies showing signs of toxicity.

In comparison to chloramphenicol, when studies of the pharmacokinetics of gentamicin were completed, it was shown that neonates required a higher dose per kg than adults because of their greater volume of distribution. The ototoxicity and nephrotoxicity of gentamicin which are well documented in the adult, have not been extensively studied in the neonate. We have recorded potentially toxic trough serum concentrations i.e. >2 mg/l in 57/91 premature neonates receiving gentamicin (5.5 mg/kg/day) (Mulhall *et al.*, 1983a). Babies exhibiting putatively toxic serum concentrations were younger and of a significantly lower gestational age than the rest of the population. These pharmacokinetic studies have demonstrated that, to prevent accumulation, it may be necessary to increase the dosage interval to eighteen hours in premature babies in the first week of life.

In summary, the lack of modern technical methods and an assumption that neonates were "miniature adults" resulted in a complete lack of comprehensive pharmacokinetic studies in the neonate before 1970. It is imperative that new antimicrobial agents are more thoroughly appraised than in the past. Additionally, thorough investigations of older antibiotics still in use e.g. chloramphenicol and gentamicin and others enjoying renewed usage for the treatment of resistant organisms e.g. vancomycin, would be rewarding.

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