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# Clinical pharmacokinetics of penicillins in the neonate: a review of the literature

G. M. Pacifici · J. Labatia · H. Mulla · I. Choonara

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## Abstract

**Background** Sepsis is common in neonates and a major cause of morbidity and mortality. Sixty percent of preterm neonates receive at least one antibiotic during the first week of life, with penicillins being the most frequently administered antibiotics. The clearance (Cl), serum half-life ( $t_{1/2}$ ) and volume of distribution (Vd) of penicillins are different in the neonate than in the adult. As such, the pharmacokinetics of penicillins need be studied in neonates in order to optimise therapy in this age class with these drugs.

**Objectives** The aim of this study was to review the published data on the pharmacokinetics of penicillins in the neonate in order to provide a critical analysis of the literature and, consequently, a useful tool in the hands of the physician.

**Methods** The bibliographic search was performed electronically using the PubMed and EMBASE databases as search engines. An initial search was performed with the keywords

“pharmacokinetics”, “penicillins” and “neonates”. Secondly, other searches were performed using the keywords “pharmacokinetics” and “neonates”, followed by the name of a single antibiotic. The search included articles up to 2007.

**Results** There have been few pharmacokinetic studies on the use of penicillins in neonates. The results from those few studies that have been carried out suggest that the Cl is reduced and  $t_{1/2}$  prolonged in the neonate as compared with the more mature infant. There is little variation in Vd during the first week of life. In the premature neonate, Cl is reduced compared to the full-term infant. As postnatal age proceeds, the Cl of penicillins increases.

**Conclusions** More pharmacokinetic studies are required to provide a sound scientific basis for planning a dosage regimen with penicillins in the neonate.

**Keywords** Amoxicillin · Ampicillin · Azlocillin · Clavulanic acid · Flucloxacillin · Methicillin · Mezlocillin · Neonate · Penicillins · Pharmacokinetics · Piperacillin and ticarcillin

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## Introduction

Neonatal sepsis is common in neonates and can be acquired at delivery passing through the birth canal or later from hospital-acquired sources [1]. Infection is a major cause of morbidity and mortality, especially for those who are preterm and low birth weight. Mortality occurs in 10–20% of those infants with neonatal sepsis, with sequelae occurring in 25–30% of the infants who survive [2]. An evaluation of the use of antibiotics revealed that 60% of preterm neonates received at least one antibiotic during the first week of life [3], with over half of the antibiotics being

penicillins [3]. The extensive use of penicillins in the newborn infants requires that the pharmacokinetics (PK) of these drugs should be studied in this age group.

Penicillins are water-soluble compounds and are mainly eliminated by the kidney. Renal glomerular filtration and tubular secretion are reduced in the newborn infant [4]. The reduced renal elimination affects the disposition of penicillins, and their clearance (Cl) is reduced in the newborn as compared to children. The Cl is even lower in preterm neonates. The volume of distribution (Vd) of penicillins is greater in the neonate than in the adult because of the larger water body content in the newborn infant. In the latter, 75% of the total body weight is constituted by water [4].

The aim of this study was to review the PK of penicillins in neonates. The PK parameters of penicillins are summarised in Tables 1, 2, 3, 4, 5, 6, 7. In this study, the penicillins have been divided into the following groups:

1. Benzylpenicillin (penicillin G) and phenoxymethylpenicillin (penicillin V)
2. Broad spectrum penicillins—ampicillin, amoxicillin and co-amoxiclav (amoxicillin and clavulanic acid)
3. Penicillinase resistant penicillin (flucloxacillin)
4. Antipseudomonal penicillins—azlocillin, mezlocillin, ticarcillin and piperacillin

### Bibliographic search

The bibliographic search was performed electronically using the PubMed and EMBASE databases as search engines; December 2007 was the cutoff point. Initially, a search was performed with the following keywords “pharmacokinetics”, “penicillins” and “neonates” with the limit of “human”. Secondly, other searches were performed using the following keywords “pharmacokinetics” and “neonates”, followed by the name of any one of the following antibiotics: penicillin, ampicillin, amoxicillin, azlocillin, carbenicillin, clavulanic acid, flucloxacillin,

mezlocillin, piperacillin, pivmecillinam and ticarcillin. The bibliography of each article was read carefully, and the selected articles were critically read.

### Benzylpenicillin (penicillin G)

There have been three separate studies on benzylpenicillin (penicillin G) [5–7] (Table 1). The first detailed study of the PK of penicillin in neonates [5] was performed in the early 1970s in 47 newborn infants (no details are given of the gestation except that the group included both preterm and term neonates). The half-life ( $t_{1/2}$ ) decreased from 3.2 h in the first week of life to 1.4 h in week 3. A study in 18 very low birth weight (VLBW) neonates confirmed that the  $t_{1/2}$  in VLBW neonates is longer (4.2 h), and these authors concluded that  $15 \text{ mg kg}^{-1} 12 \text{ h}^{-1}$  results in serum concentrations above the minimum inhibitory concentration for 90% of group B streptococci strains ( $\text{MIC}_{90}$ ) [6]. Another group of researchers suggested that  $30 \text{ mg kg}^{-1} 12 \text{ h}^{-1}$  was adequate [7].

### Broad spectrum penicillins

#### Ampicillin

Original studies of ampicillin PK in neonates did not provide extensive details of either gestational age (GA) or weight [8–12], but instead focused on  $t_{1/2}$  and peak plasma concentrations (Table 2). These studies confirmed that preterm neonates have a longer  $t_{1/2}$  (4–5.5 h) [11, 12] and that the  $t_{1/2}$  decreases rapidly with postnatal age during the first few weeks of life [12].

#### Amoxicillin

The studies of ampicillin PK have been used to extrapolate recommended doses for amoxicillin, which is a derivative

**Table 1** Pharmacokinetic parameters of benzylpenicillin

GA (weeks)	PNA (days)	Weight (kg)	n	Dose ( $\text{mg kg}^{-1}$ )	Cl ( $\text{ml min}^{-1}$ )	Vd ( $\text{l kg}^{-1}$ )	$t_{1/2}$ (h)	Plasma concentration ( $\mu\text{g ml}^{-1}$ )		Reference
								Peak	Trough	
?	0–6	?	24	10–30 IM	-	-	3.2	22–36	-	5
?	>14	?	6	10 IM	-	-	1.4	-	-	5
<28	0–3	<1.2	8	30 bid	$1.2 \text{ kg}^{-1}$	0.41	3.8	146	7	6
<28	0–3	<1.2	9	15 bid	$1.5 \text{ kg}^{-1}$	0.65	4.6	59	3	6
<32	3	0.6–2.0	20	30 bid	1.72	0.5*	3.9	-	-	7

GA, Gestational age; PNA, post-natal age; Cl, clearance; Vd volume of distribution (given in litres);  $t_{1/2}$ , half-life; IM, intramuscular; bid, twice daily

Values are given as the mean or range

**Table 2** Pharmacokinetic parameters of ampicillin

GA (weeks)	PNA (days)	Weight (kg)	n	Dose (mg kg <sup>-1</sup> )	t <sub>1/2</sub> (h)	Peak concentration (μg ml <sup>-1</sup> )	Reference
>37	2-4	>2.5	3	50-100 IV infusion	2.2	-	9
>37	1-7	?	}27	50-100 IM bid	3.9	36-257	11
<37	1-7	?		50-100 IM bid	5.5	78-293	11
?	7-35	?	4	50 IM tid	1.6	58	11
<37	2-7	<2	9	10 IM	4.0	13-19	12
<37	8-14	<2	6	10 IM	2.8	13-19	12
<37	15-30	<2	11	10 IM	1.7	13-19	12
<37	61-68	<2	9	10 IM	1.6	13-19	12

tid, three times daily; IV, intravenous

Values are given as the mean or range.

of ampicillin with a greater bioavailability following oral administration. There have been a total of six amoxicillin PK studies in neonates [13–18] (Table 3). Preterm infants (<32 weeks GA) have a longer t<sub>1/2</sub> (6.7 h) [13] than term neonates (3.7 h) [13, 18].

A study of 40 preterm neonates (<32 weeks GA) looked at the effects of gentamicin on amoxicillin Cl and found that there was a significant decrease of 25% in amoxicillin Cl with co-administered gentamicin [14]. They also found a twofold increase in the Vd of amoxicillin and that the t<sub>1/2</sub> in preterm babies was longer when given with gentamicin (6.9 h) than when given without concurrent gentamicin (5.2 h).

Two studies looked at the PK and dosing of amoxicillin in neonates [13, 15]. In one study, the authors recommended a dose of 15 mg kg<sup>-1</sup> 8 h<sup>-1</sup> for GA <34 weeks and 20 mg kg<sup>-1</sup> 8 h<sup>-1</sup> for GA >34 weeks [15]. The authors of the second study suggested that preterm infants with GA <32 weeks in the first week of life should receive a maximum amoxicillin dose of 25 mg kg<sup>-1</sup> 12 h<sup>-1</sup> [13]. In both studies, the Cl and Vd of amoxicillin were found to increase with GA and body weight.

The most recent study looked at the effects of postnatal age and found that the Cl was greater in neonates >9 days old (3.0 ml min<sup>-1</sup> kg<sup>-1</sup>) [17] than had been shown in previous

studies in neonates of a similar gestation (1.6 ml min<sup>-1</sup> kg<sup>-1</sup>) [15]. Similarly, the t<sub>1/2</sub> was considerably shorter (3 h vs. 5.2 h). These authors recommended an amoxicillin dose of 40 mg kg<sup>-1</sup> 8 h<sup>-1</sup> for infants >9 days post-natal age (PNA).

Cardiopulmonary bypass surgery decreased the mean plasma concentration of amoxicillin by 36%, from 73 to 47 μg ml<sup>-1</sup> [16]. The GA of these patients was not stated, but they appear to have been term infants. It is therefore difficult to compare these patients with a similar group in terms of cardiopulmonary bypass.

### Penicillinase-resistant penicillins

#### Flucloxacillin

There have only been three studies of the PK of flucloxacillin in neonates [16, 19, 20] (Table 4). A Dutch group that looked at both preterm and term neonates suggested that the current dosage regime (25–50 mg kg<sup>-1</sup> every 8 or 12 h) did not result in effective plasma concentrations for the treatment of *Staphylococcus aureus* in one third of the neonates treated [19]. They therefore suggested an initial dose of 25 mg kg<sup>-1</sup> 4 h<sup>-1</sup> for all

**Table 3** Pharmacokinetic parameters of amoxicillin

GA (weeks)	PNA (days)	Weight (kg)	n	Dose (mg kg <sup>-1</sup> )	Cl (ml min <sup>-1</sup> )	Vd (l kg <sup>-1</sup> )	t <sub>1/2</sub> (h)	Peak concentration (μg ml <sup>-1</sup> )	Trough concentration (μg ml <sup>-1</sup> )	Reference
<32	3	<1.5	17	25 BD	1.0	0.67	6.7	54	16	13
≤32	1-3	<1.5	40	50 BD	1.3 kg <sup>-1</sup>	0.68	-	74	-	14
25-42	0-3	2.3	150	30	1.6 kg <sup>-1</sup>	0.65	5.2	101	21	15
26-41	10-52	2.3	32	50-100	3.0 kg <sup>-1</sup>	0.66	3.0	-	-	17
>37	1-3?	?	16	50	-	-	-	38	13	18
<37	1-3?	?	7	50	-	-	-	59	19	18
n/a	3-60 <sup>a</sup>	3.6	11	30 TDS	1.4 <sup>a</sup>	0.4 <sup>a*</sup>	3.1 <sup>a</sup>	n/a	n/a	16

n/a, Not available

Values are given as the mean or range

<sup>a</sup> Patients on cardiopulmonary bypass

**Table 4** Pharmacokinetic parameters of flucloxacillin

GA (weeks)	PNA (days)	Weight (kg)	n	Dose (mg kg <sup>-1</sup> )	Cl (ml min <sup>-1</sup> kg <sup>-1</sup> )	Vd (l kg <sup>-1</sup> )	t <sub>1/2</sub> (h)	Peak concentration (µg ml <sup>-1</sup> )	Reference
26-42	0-44	0.4-4.1	55	25-50 bid/tid	3.0	0.54	2.6	38-114	19
33-41	?	?	9	50	0.7	0.28	4.6	-	20
?	3-60	3.6	11	30	2.0 <sup>a</sup>	0.45 <sup>a</sup>	2.6 <sup>a</sup>	15-70 <sup>a</sup>	16

Values are given as the mean or range

<sup>a</sup>Patients on cardiopulmonary bypass

neonates. This is in contrast to the 12-h recommendation for neonates in the first week of life in formularies such as the British National Formulary for Children (BNFC) [21]. A small study of nine neonates also suggested that the t<sub>1/2</sub> was related to GA [20]. Cardiopulmonary bypass decreased the plasma concentrations of flucloxacillin by over 40%, from 75 to 43 µg ml<sup>-1</sup> [16].

### Antipseudomonal penicillins

Within the UK, the two main antipseudomonal penicillins are piperacillin and ticarcillin. Ticarcillin is only available in combination with clavulanic acid. In other countries, acylureidopenicillins such as azlocillin and mezlocillin are used.

#### Azlocillin

There have been two PK studies of azlocillin in neonates [22, 23], both of which were performed in Germany in the 1980s (Table 5). The first study involved 53 neonates (average GA 34 weeks) [22]. The authors of this study recommended 50 mg kg<sup>-1</sup> 12 h<sup>-1</sup> for preterm neonates in the first 7 days of life and 100 mg kg<sup>-1</sup> 12 h<sup>-1</sup> for full term neonates in the first 7 days of life. A subsequent study suggested no difference in t<sub>1/2</sub> in preterm and term infants [23]. The GA of the preterm infants, however, was not given (their weights ranged from 1.77 to 2.5 kg).

**Table 5** Pharmacokinetic parameters of azlocillin

GA (weeks)	PNA (days)	Weight (kg)	n	Dose (mg kg <sup>-1</sup> )	Cl (ml min <sup>-1</sup> )	Vd (l kg <sup>-1</sup> )	t <sub>1/2</sub> (h)	Peak concentration (µg ml <sup>-1</sup> )	Trough concentration (µg ml <sup>-1</sup> )	Reference
<37	?	1.8	7	50 BD IM/IV	n/a	0.34	4.4	122	20	22
37-42	?	?	27	50 BD IM/IV	n/a	0.30	2.6	128	27	22
37-42	?	?	22	100 BD IM/IV	n/a	0.30	2.6	260	17	22
<37	2-26	2.1	12	50 IV	3.7	0.33	2.5	-	-	23
37-42	2-26	3.1	13	50 IV	4.9	0.32	2.6	-	-	23

Values are given as the mean or range

#### Mezlocillin

There were two PK studies in neonates in the USA in the 1980s (Table 6). One involved treatment with mezlocillin and an aminoglycoside [24]. The majority of the neonates (34) were in the first week of life and of these, 30 were <34 weeks GA. The mezlocillin serum concentration was influenced by the weight, route of administration and concurrent administration of an aminoglycoside. Clearance increased with increasing GA and weight. There was also a direct relationship between Vd and body weight. However, there was no significant correlation between t<sub>1/2</sub> and weight. The clearance was less when mezlocillin was given concomitantly with an aminoglycoside. The authors presented individual data for all the PK parameters in relation to weight but, unfortunately, not in relation to GA. They suggested a dosage of 75 mg kg<sup>-1</sup> every 8–12 h.

The other study involved 47 neonates, the majority of whom were premature and <7 days old [25]. This group recommended that mezlocillin be administered at 12-h intervals (75 mg kg<sup>-1</sup>) to preterm infants in the first week of life, at 8-h intervals to preterm infants >7 days and term infants <7 days. They also recommended the administration of 6-h doses to term infants >7 days of age [25].

#### Ticarcillin

There have been three PK studies of ticarcillin in neonates where it has been given in combination with clavulanic acid

**Table 6** Pharmacokinetic parameters of mezlocillin following 75 mg kg<sup>-1</sup> (IV or IM)

GA (wk)	PNA (days)	Weight (kg)	<i>n</i>	Cl (mg kg <sup>-1</sup> )	Vd (l kg <sup>-1</sup> )	<i>t</i> <sub>1/2</sub> (h)	Peak concentration (μg ml <sup>-1</sup> )	Trough concentration (μg ml <sup>-1</sup> )	Reference
26-40	1-72	0.6-3.0	53	1.3 <sup>a</sup>	0.38	3.7	231	43	24
<38	0-7	n/a	26	9.3 <sup>b</sup>	0.34	4.5	252	72	25
38-42	0-7	n/a	13	12.3 <sup>b</sup>	0.37	3.0	272	34	25
38-42	>7	n/a	8	21.0 <sup>b</sup>	0.42	1.8	139	9	25

Values are given as the mean or range

<sup>a</sup> ml min<sup>-1</sup> kg<sup>-1</sup>

<sup>b</sup> ml min<sup>-1</sup> per 1.73 m<sup>2</sup>

[26–28] (Table 7). The first study looked at the use of prophylactic ticarcillin and clavulanic acid (ratio 15:1) in neonates from 25 to 39 weeks GA. As well as studying the PK of ticarcillin, these researchers also looked at the PK of clavulanic acid [26]. A subsequent study looked at a 25:1 combination of ticarcillin and clavulanic acid and showed that term neonates had a shorter *t*<sub>1/2</sub> (2.7 h) than preterm infants (4.2 h) [27]. The third study looked at a different ratio (30:1 ticarcillin-clavulanic acid) [28] and found a similar *t*<sub>1/2</sub> to that of previous studies but also calculated Cl. These authors also suggested that it would be more appropriate to use a dosage of 50 mg kg<sup>-1</sup> 6 h<sup>-1</sup> than the 75 mg kg<sup>-1</sup> 12 h<sup>-1</sup> used in their study.

#### Piperacillin

There has only been one study of the PK of piperacillin in neonates [29]. This was a study of 28 neonates (GA 29–40 weeks), and the authors confirmed that as the GA increased, the *t*<sub>1/2</sub> decreased and Cl increased. They suggested that 75 mg kg<sup>-1</sup> of piperacillin be administered a 12-h intervals in the first week of life and at 8-h intervals from day 7 onwards in preterm neonates; for full term neonates they recommended a dose of 75 mg kg<sup>-1</sup> 8 h<sup>-1</sup> in the first week of life and at 6-h intervals from day 7.

#### Pharmacokinetic–pharmacodynamic relationship

Antibiotic pharmacokinetic–pharmacodynamic (PD) relationships integrate a knowledge of the microbiology with parameters of drug exposure, such as peak concentrations (C<sub>max</sub>) or area under the curve (AUC) [30]. By relating exposure parameters to a measure of antibiotic potency (e.g. minimum inhibitory concentration for the pathogen in question), the dose can be optimised and the desired microbiological or clinical effect (e.g. eradication of infection) can be achieved. Such rational approaches to selecting doses also enable the desired response to be achieved in the largest proportion of patients—i.e. high probability of therapeutic success and low probability of toxicity [31]. Furthermore, by defining the antibiotic PK–PD relationship, sub-optimal antibiotics and doses can be avoided, thereby minimising the emergence of resistance and improving outcome for patients [32].

Specific PK/PD parameters [e.g. peak/MIC, AUC/MIC ratio and time above MIC (T > MIC)] have all been shown to be major determinants of *in vivo* activity [30]. For a given antibiotic class, the specific PK/PD parameter correlating with efficacy is largely dependent on whether bacterial killing is concentration- or time-dependent. Penicillins (and other beta-lactams) are time-dependent

**Table 7** Pharmacokinetic parameters of ticarcillin

GA (weeks)	PNA (days)	Weight (kg)	<i>n</i>	Dose (mg kg <sup>-1</sup> )	Cl (ml min <sup>-1</sup> kg <sup>-1</sup> )	Vd (l kg <sup>-1</sup> )	<i>t</i> <sub>1/2</sub> (h)	Peak concentration (μg ml <sup>-1</sup> )	Trough concentration (μg ml <sup>-1</sup> )	Reference
31	?	1.7	24	75 bid	-	-	4.5	183	43	26
34-36	?	2.4	7	83 tid	-	0.34	4.2	279	64	27
>37	?	3.3	7	100 tid	-	0.27	2.7	405	56	27
30	9	1.2	11	75 bid	0.78	0.26	4.2	976	42	28

Values are given as the mean or range

agents, meaning that it is important that the dosing regimen maximises the  $T > MIC$  of the target organism. A  $T > MIC$  of 30–40% is acceptable in adults, but a higher level of 40–50% is required in neonates [33]. Concentrations higher than the MIC do not greatly increase bacterial kill [30].

The optimum penicillin dose for treating an infection is one that balances the risk (adverse effect)–benefit (efficacy) profile. It is clear that in order to be able to optimise penicillin dosing in neonates, a knowledge of the PK correlated with a measure of microbiological potency is of importance in developing a dosing regimen that maintains serum penicillin levels greater than the MIC for at least 40–50% of the dosing interval.

## Discussion

Penicillins are a key component of drug therapy in neonatal intensive care units in both developed and developing countries [34, 35] and have been used extensively for several decades. They play a crucial role in the management of Group B streptococcal disease, which remains a significant problem [36]. The efficacy of penicillin in the prevention of neonatal Group B streptococcal disease has been demonstrated in several randomised clinical trials [37, 38]. Retrospective studies have shown the benefit of ampicillin and aminoglycoside combination therapy for the management of neonatal septicaemia and meningitis [39].

It is however surprising that there have been few PK studies performed. Those studies that have been carried out show that both GA and PNA have an impact on clearance and hence plasma  $t_{1/2}$  [5, 11, 12, 15, 17, 20, 27, 29]. Most of these PK studies have been classical PK studies where several blood samples were taken from each infant. There have only been five population PK studies, and these have involved benzylpenicillin [7], amoxicillin [14, 15, 17] and flucloxacillin [19]. The findings from the population PK studies are consistent with those involving traditional sampling.

Antibiotics in the neonatal period have been associated with drug toxicity—notably kernicterus in association with the use of sulphonamides and cardiovascular collapse in association with the use of chloramphenicol [40]. Neurotoxicity in association with the use of ampicillin has been reported [41]. The combination of ampicillin and cefotaxime has been associated with a greater mortality than the combination of ampicillin and gentamicin in neonates with sepsis [42]. The minimal toxicity associated with penicillins in comparison with other antibiotics, such as aminoglycosides and second- and third-generation cephalosporins is probably one of the reasons why there have been very few PK studies.

An additional reason is the fact that intravenous formulations of the penicillins are cheap and there are no longer patents on these medicines. Therefore, no major pharmaceutical company is keen to promote clinical trials where the PK is studied in both very preterm and term infants. There is, however, considerable inter-individual variability in the PK of penicillins in the neonatal period. The clearance of amoxicillin in one study showed a five fold inter-individual variation [15].

The dosage regime for penicillins is shown in Table 8. This is based on the BNFC and the Neonatal Formulary (NF) [43]. The dose is constant for neonates of all gestations, and the frequency of administration is twice daily in the first 7 days of life and thereafter three times daily. There is a considerable dose variation for both benzylpenicillin and flucloxacillin and, to a lesser extent, for ampicillin and amoxicillin. The recommended dose is based on the type of infection. It is clear that the doses recommended in the BNFC and the NF are not entirely evidence based and do not take into account GA.

We feel further research is required to ensure that the doses recommended for the treatment of sepsis in neonates are evidence-based. Such research may result in an improvement in the efficacy of penicillins in the neonatal period, as treatment failure has been reported in 20% of

**Table 8** Recommended doses of penicillins in the British National Formulary for Children (BNFC) and the Neonatal Formulary (NF)

Drug	Dose (mg/kg)		Frequency in relation to age	
	BNFC	NF	< 7 days	7–28 days
Benzylpenicillin	25–75	30–60	bid	tid <sup>b</sup>
Ampicillin	30–50	50–100	bid	tid <sup>a</sup>
Amoxicillin	30–50	50–100	bid	tid <sup>b</sup>
Flucloxacillin	25–100	50–100	bid	tid <sup>a</sup>
Ticarcillin	80	-	bid	tid
Piperacillin	90	-	bid	tid

<sup>a</sup> tid for 7–21 days and qid (four times daily) for 21–28 days

<sup>b</sup> NF only: tid for 7–21 days and qid for 21–28 days

neonatal infections, despite the organisms being sensitive to the antibiotics [39].

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