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Principles of Drug Biodisposition in the Neonate
A Critical Evaluation of the Pharmacokinetic-Pharmacodynamic Interface (Part II)[1]

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1 Part I of this article appeared in the previous issue of the Journal.

5.3 Indomethacin

Since the original description of its efficacy, indomethacin has been used widely for the pharmacological closure of patent ductus arteriosus (Friedman et al. 1976; Heymann et al. 1976). This activity is believed to be related to the potency of indomethacin as an inhibitor of the cyclo-oxygenase pathway.

5.3.1 Absorption

The absorption of orally administered indomethacin is poor and incomplete (Bhat et al. 1979; Evans et al. 1979, 1981). Evans et al. (1979) reported the oral bioavailability to range from 10 to 20% in 18 neonates given both oral and intravenous indomethacin. This poor bioavailability may be an artifact due to the chemical instability of indomethacin in many solutions (Roberts 1984). Alpert et al. (1979) demonstrated excellent absorption when indomethacin was dissolved in a phosphate buffer. In addition to a reduced extent of absorption, the rate of absorption for oral indomethacin is also believed to be slow, with peak serum concentrations attained 4 hours after a dose (Bhat et al. 1979).

5.3.2 Protein Binding

Protein binding studies have demonstrated that indomethacin is 98% protein bound in neonates (Bhat et al. 1979; Evans et al. 1979).

However, at therapeutic doses and serum concentrations indomethacin has not been shown to displace bilirubin from albumin binding sites (Honore et al. 1983; Shankaran et al. 1982). In fact, Shankaran et al. (1982) did not find a significant displacement reaction until indomethacin plasma concentrations reached 10 to 40 mg/L. Serum indomethacin concentrations below 2 mg/L are generally achieved following a standard 0.2 mg/kg dose.

5.3.3 Distribution

Yaffe et al. (1980) reported a mean Vd_{area} for indomethacin of 0.262 ± 0.017L (mean ± SEM) in 28 preterm infants, whereas Thalji et al. (1980) reported a mean apparent Vd of 0.35 ± 0.21 L/kg (mean ± SD) in 16 preterm infants. Others (Evans et al. 1981; Vert et al. 1980) have also reported the Vd to approximate 0.35 L/kg.

The wide variation in Vd could not be explained by differing states of hydration. Differences in serum protein concentrations are another possible explanation, but they were not measured in this study. A further alternative explanation is that indomethacin undergoes enterohepatic recirculation. Thalji et al. (1980) provide evidence for enterohepatic recirculation of indomethacin in some premature infants. Kwan et al. (1976), in a study involving adult volunteers, reported that 50% of an intravenous, oral, or rectal indomethacin dose undergoes enterohepatic recirculation. In addition

to these explanations, the wide variations in Vd may be a mathematical artifact, resulting from the utilisation of different methods for reporting Vd (i.e. Vd_{area} *vs* Vd). Indomethacin has a mean half-life of distribution of 1.58 hours (Thalji et al. 1980).

5.3.4 Metabolism and Elimination

There are no data available on the metabolic or elimination pathways for indomethacin in neonates. In adults, indomethacin undergoes *O*-demethylation and *N*-deacylation to inactive metabolites (Helleberg 1981). Approximately 60% of a dose in adults is excreted in the urine as free metabolites or conjugated to glucuronide, and 40% of a dose is eliminated via biliary excretion as metabolic products of hepatic biotransformation (Helleberg 1981). Only a small percentage of a dose is excreted unchanged in the urine.

The immaturity of these metabolic pathways in neonates is responsible for the slower clearances for indomethacin found in newborns compared with adults. Additionally, one would expect marked prolongation of $t_{½\beta}$ in newborns with significant hepatocellular damage.

5.3.5 Half-Life and Clearance

There are limited neonatal data on clearance of indomethacin. Values ranging from 5 to 25 ml/kg/h have been reported (Bianchetti et al. 1980; Brash et al. 1981; Evans et al. 1981; Thalji et al. 1980; Vert et al. 1980). Elimination half-life also shows considerable variation, with most studies showing values between 15 and 30 hours (Alpert et al. 1979; Bhat et al. 1979; Brash et al. 1981; Evans et al. 1981; Friedman et al. 1978; Mehta & Calvert 1983; Peterson et al. 1981; Seyberth et al. 1982; Thalji et al. 1980; Vert et al. 1980; Yaffe et al. 1980). Again, the large variations in clearance and $t_{½\beta}$ are multifactorial, with variability in metabolism, elimination, and enterohepatic recirculation all contributing. A clear relationship between $t_{½\beta}$, clearance, and gestational age has not yet been defined.

5.3.6 Clinical Efficacy

The effectiveness of indomethacin in promoting ductal closure was clearly demonstrated in a national collaborative study (Gersony et al. 1983). Of 149 symptomatic infants who received indomethacin, 79% had ductal closure within 48 hours, compared with 28% of 270 infants receiving traditional medical therapy only. 26% of all treated infants had reopening of the ductus arteriosus; however, only 8% with initial closure required surgical intervention. In the placebo group (medical therapy only), 65% eventually required surgical ligation of the ductus arteriosus *versus* 21% in the indomethacin group (13% who initially failed indomethacin therapy plus 8% in whom the ductus arteriosus reopened). Closure rates did not correlate with birthweight, gestational age, gender, or race. However, they were significantly higher for infants who were initially treated with indomethacin when they were older than 5 days. There was no difference in serum concentrations between responders and non-responders.

The rates for initial closure, reopening, and final closure are comparable to those reported previously (Brash et al. 1981; Halliday et al. 1979; Merritt et al. 1981; Vert et al. 1980; Yanagi et al. 1981). Although Gersony et al. (1983) found no correlation between serum indomethacin concentrations and ductal closure, others have reported a relationship (Brash et al. 1981; Thalji et al. 1980; Vert et al. 1980). Vert et al. (1980) found a correlation between ductal closure and area under the indomethacin serum concentration-time curve (AUC), but not between closure and peak plasma concentration. Thalji et al. (1980) reported significant differences for both peak concentration and AUC between responders and non-responders.

Mahony et al. (1985) evaluated the prophylactic effectiveness of indomethacin in infants with birthweights between 700 and 1300g. There was a significant reduction in the number of patients who subsequently developed a large shunt and required surgical ligation. However, the placebo group only had a 21% incidence of developing a large shunt. Therefore, routine prophylactic use of indomethacin cannot be supported at this time.

5.3.7 Drug-Drug Interactions

The interaction of indomethacin with digoxin has been described above (see section 5.1.6). Since indomethacin reduces glomerular filtration rate, any

drug which relies on glomerular filtration for elimination may accumulate when administered concomitantly with indomethacin. Zarfin et al. (1985) reported such an interaction between indomethacin and the aminoglycosides gentamicin and amikacin. These investigators demonstrated a significant rise in both peak and trough aminoglycoside serum concentrations after initiation of indomethacin therapy. Thus, caution should be exercised when administering drugs dependent upon renal elimination concomitantly with indomethacin administration.

5.3.8 Adverse Reactions

Complications of indomethacin use in neonates have included renal dysfunction (Betkerur et al. 1981; Cifuentes et al. 1979; Halliday et al. 1979; Seyberth et al. 1983), gastrointestinal disorders such as bowel perforation and possibly necrotising enterocolitis (Alpan et al. 1985; Campbell et al. 1981; Harinck et al. 1977; Nagaraj et al. 1981; Yanagi et al. 1981), and bleeding as a result of platelet dysfunction (Friedman et al. 1978). At present, there does not appear to be a correlation between adverse effects of indomethacin and plasma indomethacin concentration (Bianchetti et al. 1980; Gersony et al. 1983). Whether indomethacin causes an increased incidence of retinopathy of prematurity remains controversial. Lindemann et al. (1982) found an increased incidence, whereas Procianoy et al. (1980) found no association with indomethacin use.

Halliday et al. (1979) noted a reduction in urinary output of more than 50% in 36 infants below 1500g bodyweight treated with indomethacin. Approximately 50% of these infants experienced elevations in serum creatinine to more than 15 mg/L. Cifuentes et al. (1979) reported reductions of 56, 27, and 66% in urine output, GFR, and free water clearance, respectively. The fractional excretion of sodium was also reduced; however, due to impaired free water clearance, serum sodium concentration and osmolality fell. All values except GFR and sodium excretion returned to normal by 1 to 2 weeks after discontinuation of indomethacin.

Betkerur et al. (1981) noted similar results, although they did not observe a reduction in GFR. Seyberth et al. (1983), in a study of renal function in 11 preterm infants, found reduced urine output, creatinine clearance and serum sodium, and an increased bodyweight and serum potassium. The changes were transient and were associated with suppression of renal and systemic prostaglandin synthesis.

Most of the reported adverse gastrointestinal effects have been associated with enteral administration of indomethacin. The true incidence of these effects is difficult to ascertain since the underlying disease is associated with several of them, including necrotising enterocolitis.

With respect to increased bleeding tendency, Maher et al. (1985), using serial head ultrasounds, evaluated 36 preterm infants for extension of intraventricular haemorrhage. 17 infants were treated with indomethacin for a patent ductus arteriosus after intraventricular haemorrhage was diagnosed. The incidence of extension of the haemorrhage did not differ between those infants receiving indomethacin and those who did not. In fact, Ment et al. (1985) reported a statistically significant reduction in the incidence of intraventricular haemorrhage in low birthweight infants (600 to 1250g) who received indomethacin prophylactically in a randomised, controlled study evaluating the prevention of intraventricular haemorrhage with indomethacin.

5.3.9 Dosing Recommendations

The current indomethacin dosing recommendations outlined in table XV are dependent upon the postnatal age of the infant. If ductal closure does not occur with the first dose, then 2 addi-

Table XV. Indomethacin dosing for pharmacological closure of a patent ductus arteriosus

Age of infant	Initial dose (mg/kg)	Doses 2, 3 (mg/kg)
0-48h	0.2	0.1
2-7 days	0.2	0.2
≥ 8 days	0.25	0.25

Table XVI. Contraindications to the use of indomethacin for patent ductus arteriosus

Blood urea nitrogen ≥ 30 mg/dl
Serum creatinine ≥ 1.8 mg/dl
Total urine output ≤ 0.6 ml/kg/h over the preceding 8 hours
Platelet count < 60,000/mm^3
Stool haematest ≥ 3+ (or 'moderate to large')
Evidence of a bleeding diathesis
Clinical or radiographic evidence of necrotising enterocolitis
Evidence of intraventricular haemorrhage within the preceding 7 days[a]

a Recent data suggest that the use of indomethacin does not result in extension of a pre-existing intraventricular haemorrhage (see text).

tional doses may be administered every 12 hours unless closure occurs following the second dose. If the ductus arteriosus closes, but subsequently reopens more than 48 hours after initiation of therapy, then a second course of indomethacin may be warranted. If a significant patent ductus arteriosus persists at 48 hours or if the patient fails to respond to a second course of therapy, then surgical ligation of the ductus arteriosus is indicated. Contraindications for the use of indomethacin are listed in table XVI.

5.4 Phenytoin

5.4.1 Absorption

Conflicting data exist concerning the oral absorption of phenytoin in neonates. Painter et al. (1978) reported an inability to detect phenytoin in the plasma of 9 newborns given phenytoin orally. Doses as high as 12 mg/kg/day were administered in a variety of formulations including suspension, crushed tablets, powder, and the intravenous preparation given orally. When phenytoin 5 mg/kg/day was given intravenously to the same neonates, a mean steady-state concentration of 26 mg/L was achieved. Loughnan et al. (1977) reported a mean steady-state phenytoin serum concentration of 11 mg/L in 8 neonates (mean age 8 days) receiving a mean oral dose of 8 mg/kg/day of a phenytoin suspension. Recently, Leff et al. (1986) reported almost complete absorption of oral phenytoin in 7 neonates. Their findings in support of this conclusion included recovery of less than 3% of an orally administered dose in the faeces as either phenytoin or metabolites, and similar extents and patterns of drug metabolite excretion in infants given the drug orally or intravenously. This excretion pattern of phenytoin is also comparable to that observed in adults (Berg et al. 1983).

In summary, the extent of absorption of oral phenytoin is dependent on the formulation used, and almost complete absorption should be expected with phenytoin suspension. Further, the higher phenytoin dose necessary to maintain therapeutic serum concentrations in newborns compared with adults does not appear to be due to impaired absorption of the drug.

5.4.2 Protein Binding

As discussed in section 2.1 (table V) reports of phenytoin protein binding in newborns range from 74 to 90%, compared with 90% in adults (Ehrnebo et al. 1971; Kurz et al. 1977a; Rane et al. 1971). Because the fraction of free drug is increased in many newborns, the free phenytoin serum concentration may be within the accepted therapeutic range, whereas the total phenytoin serum concentration which is routinely monitored and reported by clinical laboratories may be in a range considered to be subtherapeutic.

5.4.3 Distribution

Phenytoin distribution is rapid and extensive. The mean apparent Vd of phenytoin ranges in neonates from 0.73 to 1.2 L/kg (Bourgeois & Dodson 1983; Loughnan et al. 1977; Painter et al. 1978, 1981), compared with 0.6 L/kg reported in adults (Morselli et al. 1980); the increased Vd in neonates is attributed to both a reduction in protein binding and an increase in total body water. The Vd shows no dependence on gestational age (Loughnan et al. 1977). Phenytoin rapidly distributes into the brain, with concentrations reaching 1.3 times the plasma concentration in neonates (Painter et al. 1981).

Table XVII. Apparent half-life ($t_{1/2}$) of phenytoin in children following various initial concentrations. The values for the group ⩽ 8 days old are a mean and standard deviation. All other values are linear estimates and standard deviations of the linear estimate determined from regression analysis of Ci *versus* $t_{1/2}$ for that age group (from Bourgeois & Dodson 1983)

			$t_{1/2}$ (h)			
Age group	n	r	5 mg/L	10 mg/L	15 mg/L	18 mg/L
⩽ 8 days	10	NS				57.3 (48.2)
9-21 days	13	0.880	10.4 (4.16)	21.3 (3.4)	32.1 (3.98)	38.6 (3.92)
21-36 days	7	0.930	7.18 (1.68)	12 (1.12)	16.8 (1.1)	19.7 (1.31)
1.5-7 months	8	0.863	9.63 (4.47)	18.2 (3.43)	26.8 (3.46)	31.8 (4.02)
1-4 years	7	0.904	17.8 (4.69)	20 (4.33)	22.3 (4)	23.7 (3.81)
4-7 years	7	0.96	10.6 (4.4)	15.7 (3.93)	20.7 (3.51)	23.8 (3.3)

5.4.4 Metabolism and Elimination

Phenytoin undergoes capacity-limited metabolism in newborns by the hepatic cytochrome P_{450} mono-oxygenase pathway (Bourgeois & Dodson 1983; Horning et al. 1975). The major metabolite found in the urine of both adults and newborns is p-hydroxy phenytoin (Berg et al. 1983; Leff et al. 1986; Rane 1974). More than 90 to 95% of this inactive metabolite is excreted in the urine conjugated to glucuronide.

5.4.5 Clearance and Half-Life

Several studies have demonstrated saturation kinetics (i.e. zero-order kinetics) for phenytoin metabolism when serum concentrations are maintained within the accepted therapeutic range (Bourgeois & Dodson 1983; Chiba et al. 1980; Richens 1979). In addition, phenytoin clearance appears to be much more rapid in infants between 2 weeks and 1 year of age than in infants younger than 2 weeks or older than 1 year (Bourgeois & Dodson 1983). This partially explains the necessity for higher phenytoin doses in this age group to maintain equivalent serum concentrations.

The serum half-life of phenytoin also varies markedly in newborns and infants. Painter et al. (1978) described a mean $t_{1/2\beta}$ of 104 ± 17 hours in 9 newborns more than 1 week of age, with a steady-state serum concentration of 26 mg/L. Loughnan et al. (1977) pooled data from several studies and reported mean $t_{1/2\beta}$ values of 80, 15, and 6 hours in infants 0-2, 3-14, and 15-150 days old, respectively. However, as shown by Bourgeois and Dodson (1983), there exists considerable variation within these age groups. They reported the following ranges for $t_{1/2\beta}$ in infants: 6 to 140 hours for infants less than 8 days old; 5 to 80 hours for infants 9 to 21 days old; and 2 to 20 hours for infants 21 to 36 days old. They then analysed these reported elimination half-lives with respect to serum concentrations, and their data are shown in table XVII.

5.4.6 Dosing Recommendations

The marked changes that occur in phenytoin clearance with increasing postnatal age combined with the extreme interindividual variations in $t_{1/2\beta}$ and clearance make dosing recommendations difficult. Leff et al. (1986) found a mean serum concentration (± SD) of 4.8 ± 4.6 mg/L in 7 infants (mean age 22 days) given a mean dose of 8.1 ± 4.4 mg/kg/day. Whelan et al. (1983) reported the use of an intravenous maintenance dose of 25 mg/kg/day administered every 6 hours to a newborn with seizures in order to achieve a serum phenytoin concentration above 10 mg/L. On the other hand, Painter et al. (1978) described drug accumulation with a mean serum phenytoin concentration of 26 mg/L in neonates less than 1 week of age receiving 5 mg/kg/day.

From the data reviewed above, it is suggested that an intravenous loading dose of 15 mg/kg phenytoin be administered over 20 to 30 minutes in neonates. Given the range of Vd cited previously, this loading dose should yield post-distri-

bution peak serum concentrations between 12 and 20 mg/L. Maintenance therapy should be instituted 24 hours after the loading dose in infants less than 1 week of age, or 12 hours after the loading dose in older infants. In infants less than 1 to 2 weeks of age, maintenance therapy should be started with 4 to 8 mg/kg/day given every 12 to 24 hours. Older neonates may require much higher doses and shorter dosing intervals, i.e. up to 8 to 12 mg/kg every 8 to 12 hours. Changes in dose or dosing interval should be guided by serum concentration monitoring.

5.5 Phenobarbitone

5.5.1 Absorption

Phenobarbitone is absorbed in the small intestine following oral administration. Although bioavailability studies have not been performed in newborns, absorption from the gastrointestinal tract is considered to be complete (Walson et al. 1980a). The presence of food delays the rate but not the extent of absorption.

5.5.2 Distribution

Distribution of phenobarbitone in the neonate is rapid and extensive, most likely due to the drug's lipophilic properties. The reported range of Vd is 0.6 to 1.2 L/kg, with most studies demonstrating a value between 0.90 and 1.0 L/kg (Donn et al. 1985; Grasela & Donn 1985; Heimann & Gladtke 1977; Jalling 1975; Lockman et al. 1979; Painter et al. 1978; Pitlick et al. 1978). No correlation between gestational age and phenobarbitone Vd has been described (Grasela & Donn 1985; Painter et al. 1978; Pitlick et al. 1978); however, Heimann and Gladtke (1977) reported an inverse relationship between Vd and postnatal age. The Vd at steady-state in infants up to 4 months of age did not differ significantly from newborns, but the Vd for infants 4 to 12 months and older than 12 months of age averaged 0.57 L/kg and 0.67 L/kg, respectively. This is comparable with a Vd of 0.6 to 0.75 L/kg reported in adults (Lous 1954; Waddell & Butler 1957).

The distribution $t_{1/2\alpha}$ of phenobarbitone in neonates is approximately 1.34 hours following an intravenous dose (Heimann & Gladtke 1977). Brain tissue concentrations demonstrate a significant linear relationship with plasma concentrations. Painter et al. (1981) found the brain : plasma phenobarbitone concentration ratio in newborns to be 0.71 ± 0.21, which agrees well with values reported in adults. The ratio appears to increase with increasing gestational age, but there is considerable variation. Painter et al. (1981) also found similar concentrations in the white and grey matter of the brain.

5.5.3 Protein Binding

Taburet et al. (1982) reported a range of protein binding from 10 to 30% in neonates between 1 and 8 days of age, compared with approximately 45 to 50% for adults (Lous 1954; Waddell & Butler 1957). As a result, the newborn brain is exposed to a higher free fraction of phenobarbitone than an adult brain. Taburet et al. (1982) observed a mean (± SEM) CSF : total plasma phenobarbitone concentration ratio of 0.67 ± 0.2, compared with a mean CSF : free plasma concentration of 0.82 ± 0.02, thus demonstrating that most of the free fraction of phenobarbitone crosses the blood-brain barrier in neonates.

5.5.4 Metabolism and Elimination

Phenobarbitone is hydroxylated by the microsomal P_{450} system to an inactive metabolite, p-hydroxy phenobarbitone. Boreus et al. (1978) compared urinary excretion patterns of phenobarbitone in newborns and adults and found striking similarities. Both groups excreted 16 to 17% of a dose as unchanged drug and 9 to 10% as the p-hydroxy metabolite. However, there was a significant difference in urinary excretion of the metabolite conjugated to glucuronide, with adults excreting 15% of a dose in this form compared with 5% in neonates, suggesting a reduced capacity to conjugate p-hydroxyphenobarbitone in the neonate but not to hydroxylate phenobarbitone. The urinary excretion of unchanged phenobarbitone is pH dependent and can be enhanced in the alkaline urine excreted by the newborn.

5.5.5 Clearance and Half-Life

Grasela and Donn (1985) reported mean phenobarbitone clearance and $t_{½\beta}$ values of 4.7 ml/kg/h and 141 hours, respectively, in 59 preterm infants. These parameters were not affected by gestational age. Half-life is, however, inversely related to postnatal age (Heimann & Gladtke 1977; Painter et al. 1978, 1981; Pitlick et al. 1978). Pitlick et al. (1978) found a mean $t_{½\beta}$ of 115 hours in 1-week-old neonates and 67 hours in the same infants at 4 weeks of age. This is similar to the findings of Heimann and Gladtke (1977) who reported mean $t_{½\beta}$ of 188 hours in neonates, compared with 63 and 68 hours in 2- to 3-month-old and over 12-month-old infants. Heimann and Gladtke (1977) also described a mean clearance rate of 5.7 ml/kg/h in neonates. The range in reported $t_{½\beta}$ is considerable, with Jalling (1975) reporting a range from 59 to 182 hours. In asphyxiated newborns, mean $t_{½\beta}$ may be prolonged: Donn et al. (1985) found a mean $t_{½\beta}$ of 148 ± 55 hours in 10 such neonates. Neither renal nor hepatic function were reported in these patients.

5.5.6 Dosing Recommendations

Serum concentrations of phenobarbitone effective for the treatment of seizures range from 15 to 40 mg/L. Jalling (1975) found serum concentrations of 12 to 30 mg/L to be effective in controlling seizures, whereas Lockman et al. (1979) did not find any abatement of neonatal seizures until serum phenobarbitone concentrations exceeded 16.9 mg/L. Since toxicity is rarely seen with serum concentrations less than 30 μg/L, the stated range of 15 to 30 mg/L appears reasonable. However, if a patient remains difficult to control, increasing the serum concentration above 30 mg/L should be considered before changing the medication or adding additional anticonvulsants. This recommendation is supported by data describing beneficial clinical effects of higher phenobarbitone concentrations in neonates without significant toxicity (Gal et al. 1982). In these patients, serum phenobarbitone concentrations should be monitored closely since profound lethargy has been described with serum concentrations exceeding 40 mg/L.

Donn et al. (1985) demonstrated the safety of a 20 mg/kg loading dose in newborns. Based on a mean Vd of approximately 1 L/kg, this would yield a post-distribution peak serum concentration of approximately 20 mg/L. Since accumulation of phenobarbitone may occur in the first week of life with maintenance doses of 5 mg/kg/day, but is unusual with doses of 2.5 to 4.0 mg/kg/day (Painter et al. 1978), an initial maintenance dose of 3 to 5 mg/kg/day oral, intravenous or intramuscular phenobarbitone, with the first dose administered 12 to 24 hours after the loading dose, is recommended. The efficacy of once daily dosing has been clearly established (Davis et al. 1981; Walson et al. 1980b).

5.6 Aminoglycosides

5.6.1 Absorption

Aminoglycosides are highly polar molecules which are poorly absorbed after oral administration. Absorption is rapid following intramuscular administration; however, repeated intramuscular injections may lead to tissue scarring and erratic absorption (Roberts 1984).

5.6.2 Distribution

The aminoglycosides distribute mainly into the extracellular fluid space. As discussed earlier (section 2.3.2), the extracellular fluid space decreases from 65% of bodyweight early in gestation to 35 to 44% of bodyweight by 40 weeks gestation. Two studies evaluating the disposition of gentamicin in very low birthweight infants less than 32 weeks gestation found a mean Vd of 0.5 L/kg (Kildoo et al. 1984; Landers et al. 1984), which is approximately what would be predicted from knowledge of the fluid spaces in neonates. Aminoglycosides are not highly protein bound, nor do they achieve effective concentrations in cerebrospinal fluid (Chang et al. 1975; McCracken et al. 1980; 1984).

5.6.3 Elimination

The aminoglycosides are eliminated from the body by glomerular filtration. As mentioned in section 4.1.2, glomerular filtration remains relatively constant at low rates until 34 weeks gestation, co-

inciding with the completion of glomerulus formation. The increase in GFR after birth is dependent on postconceptual rather than postnatal age. Hindmarsh et al. (1983) found a correlation between renal clearance of gentamicin and gestational age; however, Landers et al. (1984) did not find this relationship, but instead found a linear relationship between postconceptual age and renal clearance of gentamicin.

Kildoo et al. (1984) studied gentamicin pharmacokinetics in very low birthweight infants who required 2 to 3 courses of gentamicin for suspected sepsis. The mean postnatal age at the time of the second and third studies were 19 ± 9 and 68 ± 26 days, respectively. Gentamicin clearance was found to correlate well with creatinine clearance and with postconceptual age at all 3 study periods. The mean clearance values for the 3 age groups were 0.38 ± 0.14, 0.44 ± 0.18, and 1.21 ± 0.39 ml/kg/min, respectively. The clearance in the infants with a mean postnatal age of 68 days was significantly greater than in the other age groups, whereas a statistically significant difference was not observed between the infants studied at birth and 19 days of age.

The $t_{1/2\beta}$ of the aminoglycosides, as would be expected, varies inversely with renal clearance, gestational age, and postconceptual age (Arbeter et al. 1983; Granati et al. 1985; Kasik et al. 1985; Landers et al. 1984; Nahata et al. 1983; Szefler et al. 1980). Kasik et al. (1985) reported gentamicin half-lives of 8.86, 6.62 and 5.12 hours in infants of postconceptual ages of 30 weeks or less, 30 to 37 weeks, and 37 weeks or more, respectively. These are similar to the results of Szefler et al. (1980)

5.6.4 Adverse Effects

The 2 primary complications associated with aminoglycoside therapy are ototoxicity and renal proximal tubular injury. Ototoxicity may be sensorineural or vestibular, depending upon the specific aminoglycoside used. Neomycin (Beukelaer et al. 1971), streptomycin (Robinson & Cambon 1964) and kanamycin (Frost et al. 1960; Yow et al. 1962) appear to be more likely to cause sensorineural damage, whereas gentamicin and tobramycin have been implicated in vestibular dysfunction (Elfing et al. 1973). The true incidence of aminoglycoside-induced ototoxicity is not known in neonates because of the many confounding variables, including birth asphyxia, hyperbilirubinaemia, and the concurrent use of other ototoxic agents such as frusemide. Furthermore, and despite speculation in the literature, it is not clear whether the ototoxic potential of an aminoglycoside relates to its peak or trough concentration, or total area under the plasma concentration-time curve.

Transient proteinuria and cylinduria may occur with prolonged use of aminoglycosides, most likely as a result of proximal tubular damage. However, as stated previously, overt signs of aminoglycoside-induced renal impairment have been rarely described in the neonate (Siegel & McCracken 1982; Wellwood et al. 1976).

5.6.5 Dosing Recommendations

Studies in adults suggest that aminoglycoside nephrotoxicity is associated with a trough serum concentration above 2 mg/L for extended periods (Schentag et al. 1978). Gentamicin nephrotoxicity is uncommon in neonates (Wellwood et al. 1976; Siegel & McCracken 1982) and correlation with trough concentrations above 2 mg/L is not clear. Nevertheless, it would appear prudent in the absence of additional data to accept 2 mg/L or less as a target trough serum concentration. Peak serum concentrations between 4 and 10 mg/L are considered to be sufficient to treat most Gram-negative enteric bacterial infections.

Landers et al. (1984) assessed the relationship between gentamicin serum concentrations and dosing interval in premature infants. Nine infants with a mean postconceptual age of 30.5 ± 0.6 weeks received 2.4 mg/kg every 12 hours, while 11 infants with a mean postconceptual age of 29.2 ± 0.7 weeks received 2.4 mg/kg every 18 hours. Peak serum concentrations did not differ between the 2 groups (8.04 *versus* 9.10 mg/L, respectively); however, trough concentrations differed significantly for the infants with birthweights above 1000g (2.92 *versus* 2.08 mg/L, respectively). The mean trough concentration for neonates below 1000g in both groups exceeded 3.3 mg/L.

These data suggest that a dosing interval of 18 hours is too short for neonates with a birthweight below 1000g (less than 28 to 30 weeks gestation). Although trough concentrations reported by Landers et al. (1984) were frequently above 2 mg/L, renal function matured normally. Of interest, trough gentamicin concentrations did not correlate with urinary β_2-microglobulin excretion, a parameter reported to be a sensitive indicator of gentamicin-induced proximal renal tubular damage in adults (Schentag & Plaut 1980; Wellwood et al. 1976). β_2-Microglobulin, a low molecular weight protein, is filtered and then reabsorbed in the proximal convoluted tubules. Since the reabsorptive capacity of the premature infant has not been shown to be deficient, these results most likely reflect the relative insensitivity of the newborn kidney to the toxic effect of aminoglycosides.

Husson et al. (1984) demonstrated that trough gentamicin concentrations decreased with increasing gestational age when neonates were treated with 2.5 mg/kg every 12 hours. Mean trough gentamicin concentrations were 2.21, 1.82, and 1.24 mg/L for neonates 32-34, 34-36, and over 36 weeks gestational age, respectively. The percentage of infants with trough gentamicin serum concentrations above 2 mg/L in each of the 3 gestational age groups was 22.4, 9.4, and 0.6%. There were no differences in peak serum concentrations among the different age groups.

Finally, Kildoo et al. (1984) treated neonates under 32 weeks gestation with 2 mg/kg/day gentamicin and reported mean peak and trough serum concentrations of 5.9 ± 1.1 and 1.6 ± 0.6 mg/L, respectively.

Our dosing recommendations based on these studies of premature infants are outline in table XVIII. Dose adjustments should be considered in neonates with compromised renal function, and serum drug concentrations monitored closely. Sirinavin et al. (1980) found a significant relationship between gentamicin $t_{½\beta}$ and serum creatinine in infants, including several neonates. Serum creatinine (if stable) multiplied by 3.6 appears to provide a reasonable estimate of $t_{½\beta}$. A full dose may be administered every 2 to 3 half-lives, accompanied by serum concentration monitoring.

Table XVIII. Gentamicin/tobramycin dosing in neonates

Postconceptual age (weeks)	Dose (mg/kg)
<30	2.5/24h
30-34	2.5/18h
≥35	2.5/12h

5.7 Frusemide (furosemide)

Frusemide, a sulphonamide derivative, is a 'high ceiling' loop diuretic which inhibits sodium and chloride transport in the ascending loop of Henle.

5.7.1 Absorption

The bioavailability of oral frusemide has not been studied in neonates. In adults, the bioavailability of both the tablet and liquid formulations is 40 to 60% in a non-oedematous state (Kelly et al. 1974). Postprandial administration results in a slower rate of absorption without affecting the extent of absorption (Kelly et al. 1974), as does a decompensated congested state (Brater et al. 1984). This delayed absorption may result in a reduced peak urinary excretion rate of frusemide (Brater et al. 1984). Since the efficacy of a loop diuretic depends on its rate of urinary excretion (Brater 1985), a blunted response may be observed when the rate of absorption is impaired.

5.7.2 Protein Binding

Frusemide is 97% plasma protein bound in neonates (Aranda et al. 1980) and competes with bilirubin for albumin binding sites (Cashore et al. 1983; Peterson et al. 1980; Wennberg et al. 1977). On a molar basis, Wennberg et al. (1977) found frusemide to be as potent or more potent than sulphafurazole (sulfisoxazole) in displacing bilirubin from albumin. However, the frusemide concentrations used in this study far exceeded serum concentrations observed with clinically recommended doses. Cashore et al. (1983) and Aranda et al. (1978)

could not demonstrate a significant bilirubin displacement reaction following parenteral frusemide doses of 1 to 1.5 mg/kg.

5.7.3 Distribution

Large variations in frusemide Vd have been reported in neonates. Aranda et al. (1978) reported a mean Vd of 0.83 L/kg in 8 neonates with postconceptual ages ranging from 31 to 40 weeks. In contrast, Peterson et al. (1980) calculated a mean Vd of 0.24 L/kg in 14 premature infants of 26 to 36 weeks gestation and 1 to 20 days postnatal age. Vert et al. (1982) reported a Vd of 0.2 L/kg and 0.52 L/kg for preterm (mean postconceptual age of 32 weeks) and term infants (mean postconceptual age of 39 weeks), respectively.

5.7.4 Metabolism and Elimination

Although most of an administered frusemide dose is excreted unchanged in the urine, a fraction is metabolised to an acid metabolite (2-amino-4-chloro-5-sulphamoylanthranilic acid) or conjugated to glucuronide. Aranda et al. (1982) reported 84.4% urinary recovery of a single intravenous dose within 24 hours. At 6 hours, the percentages of total urinary excretion found as unchanged frusemide, conjugated to glucuronide, and as the acid metabolite were 55.4, 23.3, and 21.2%, respectively.

Frusemide is both filtered and actively secreted via the para-amino hippurate pathway in the proximal tubule (Radde 1985). Evidence for tubular secretion can only be inferred from adult data describing reduced plasma clearance and urinary excretion following concurrent probenecid administration (Odlind & Beermann 1980).

5.7.5 Clearance and Half-Life

The $t_{1/2\beta}$ of frusemide in term and preterm infants is prolonged compared with older children and adults. Peterson et al. (1980) described a mean $t_{1/2\beta}$ and plasma clearance of 19.9 hours (range 8.6 to 46 hours) and 10.6 ml/kg/h (range 2.4 to 29.4 ml/kg/h) in 14 preterm infants 1 to 20 days of age. Aranda et al. (1978) reported a mean $t_{1/2\beta}$ and plasma clearance of 7.7 hours (range 4.5 to 12 hours) and 82 ml/kg/h (range 34 to 166 ml/kg/h), respectively, in 8 term and preterm infants. Neither gestational age nor postnatal age correlated with these parameters. Vert et al. (1982), however, found a significantly prolonged $t_{1/2\beta}$ of 26.8 hours (range 8.4 to 44 hours) in 8 premature infants compared with 13.4 hours (range 4.7 to 292 hours) in term infants. Mean plasma clearance values were 7 ml/kg/h and 11 ml/kg/h, respectively.

In summary, frusemide has a markedly prolonged $t_{1/2\beta}$ in neonates, due primarily to immature renal function, and if repeated doses are necessary over a short period, drug accumulation is likely to occur. This accumulation may lead to heightened systemic side effects attributed to frusemide.

5.7.6 Toxicity

The primary adverse effects associated with frusemide therapy are fluid and electrolyte abnormalities and hearing loss. Hearing loss is usually transient, but may be potentiated by the concomitant use of other ototoxic drugs (Weiner & Mudge 1985). In adults, reversible ototoxicity appears to be related to both the frusemide dose and rate of intravenous infusion (Wigard & Heidland 1971). Other side effects may include bone marrow suppression, hepatic dysfunction, interstitial nephritis, pancreatitis, and skin rashes (Bailie et al. 1981; Weiner & Mudge 1985).

Nephrocalcinosis (Gilsanz et al. 1985; Glasier et al. 1983; Hufnagle et al. 1982; Noe et al. 1984) and secondary hyperparathyroidism and bone disease (Venkataramen et al. 1983), resulting from frusemide's hypercalciuric effect, have all been well documented in premature infants receiving long term frusemide therapy. Hufnagle et al. (1982) described renal calcifications in 10 premature infants receiving long term frusemide therapy at a dose of at least 2 mg/kg/day for a minimum of 12 days. These infants excreted 15 to 30 mg/kg/day of calcium compared with 0.6 to 3.7 mg/kg/day in infants not receiving diuretics.

Chlorothiazide has been shown to be effective in the managment of nephrolithiasis resulting from hypercalciuria (Glasier et al. 1983; Hufnagle et al. 1982; Noe et al. 1984). Five of Hufnagle's patients were started on chlorothiazide in addition to fru-

semide. After a minimum of 72 hours of chlorothiazide therapy, urinary calcium excretion declined to 4 to 6 mg/kg/day. Four of the 5 infants had complete resolution of their stones, while the fifth had radiographic documentation of decrease in stone size. Glasier et al. (1983) and Noe et al. (1984) both observed similar clinical courses in their patients once chlorothiazide was started or frusemide discontinued.

The efficacy of chlorothiazide in the prevention or management of nephrolithiasis appears to be a direct result of the drug's ability to reduce renal calcium excretion by promoting the distal reabsorption of calcium (Costanzo & Windhager 1978). Based on our experience in infants, we would recommend an initial intravenous dose of 5 to 10 mg/kg once daily or every 12 hours. However, some infants may require intravenous doses up to 20 mg/kg before a favourable effect on calcium excretion is observed. Our recommended dose for oral chlorothiazide therapy is 20 to 40 mg/kg once daily or every 12 hours.

Urinary calcium excretion or the urinary calcium to creatinine ratio, or both, should be monitored to guide thiazide administration. Normal calcium excretion in non-diuretic-treated patients would be below 4 to 6 mg/kg/day (Ghazali et al. 1973; Hufnagele et al. 1982), and a normal urinary calcium to creatinine ratio would be less than 0.20 (Arant et al. 1983; Goldsmith et al. 1981). Although we usually attempt to discontinue frusemide therapy in infants with nephrocalcinosis, we do not hesitate to continue with it if adequate fluid balance cannot be maintained with chlorothiazide alone.

Frusemide, through its stimulation of renal prostaglandin E_2 (PGE_2), may promote patency of the ductus arteriosus, as PGE_2 is a potent ductal vasodilator. Green et al. (1983) found a significant increase in the incidence of patent ductus arteriosus in 33 premature infants receiving frusemide for the respiratory distress syndrome compared with 33 premature infants receiving chlorothiazide, a diuretic which does not stimulate PGE_2 synthesis. Urinary excretion of PGE_2 tripled between the first and fifth day of life in the frusemide-treated group. However, there was no difference in the number of infants requiring ductal ligation between the 2 groups. In contrast, Yeh et al. (1984) were unable to identify an increased incidence of patent ductus arteriosus in preterm infants with respiratory distress syndrome who were treated with frusemide compared with the control group.

In summary, frusemide therapy may promote ductal patency, but this has not been shown to be clinically significant to date.

5.7.7 Dosing Recommendations

Frusemide therapy may be initiated with 2 mg/kg doses orally or 1 mg/kg doses intravenously. Maximal single doses should not exceed 6 mg/kg intravenously or 12 mg/kg orally. Full term infants may receive doses as frequently as every 6 to 8 hours, but premature infants should not be dosed more frequently than every 12 hours due to the drug's prolonged $t_{½\beta}$. The onset of diuretic action generally occurs within 30 minutes of intravenous administration, with peak effects observed between 1 and 2 hours following an intravenous dose. The onset of action and peak effect are delayed after oral administration.

5.8 Pancuronium

Pancuronium, a non-depolarising neuromuscular blocking agent, is often used in neonatal intensive care units to improve oxygenation and ventilation (Crone & Favorito 1980) in newborn infants with respiratory distress syndrome and severe hypoxaemia or hypercapnoea despite mechanical ventilation. Pancuronium may also reduce the duration of oxygen dependency in these infants (Pollitzer et al. 1981) as well as the incidence of pneumothorax, especially in preterm infants actively expiring against ventilator inflation (Cooke & Rennie 1984; Greenough et al. 1984).

The available data describing the effect of muscle paralysis on the incidence of intraventricular haemorrhage are conflicting. This is most likely due to the numerous variables that may impact on the incidence and severity of intraventricular haemorrhage. Bancalari et al. (1980) reported a signifi-

cant increase in the incidence of this condition (28 of 50) in preterm infants with respiratory distress syndrome who were treated with pancuronium *versus* those who did not receive pancuronium (19 of 53). However, no data were presented with respect to comparability of the 2 groups, or with respect to other variables known to be involved in the pathogenesis of intraventricular haemorrhage. In contrast, other investigators have shown neither a beneficial nor a detrimental effect of pancuronium on the incidence of intraventricular haemorrhage (Greenough et al. 1984; Reynolds et al. 1985).

Recently Perlman et al. (1983) reported a close correlation between a fluctuating pattern of cerebral blood flow velocity and intraventricular haemorrhage in infants with respiratory distress syndrome. Of 23 infants with a fluctuating pattern, 21 subsequently developed an intraventricular haemorrhage; in contrast, only 7 newborns with a stable pattern of cerebral blood flow velocity developed the condition. Of these 7 patients, 4 had a definable aetiology for their intraventricular haemorrhage. Two other issues from this study are noteworthy. The pattern of cerebral blood flow velocity reflected the pattern of arterial blood pressure (either both fluctuated or were stable), and the fluctuating patterns as well as the cases of intraventricular haemorrhage were observed predominantly in infants with moderate to severe respiratory distress syndrome.

In a follow-up study, Perlman et al. (1985) evaluated the efficacy of pancuronium in not only eliminating the fluctuating pattern of cerebral blood flow velocity, but also in reducing the incidence and/or severity of intraventricular haemorrhage. All patients who received pancuronium experienced immediate stabilisation of the cerebral blood flow pattern. Further, all 10 control patients developed intraventricular haemorrhage, with 7 demonstrating a Grade III intraventricular haemorrhage. Five of 14 infants in the treated group developed intraventricular haemorrhage (all Grade II); however, 4 of these 5 infants developed the condition after pancuronium was discontinued.

From a review of the literature, including the above-cited studies, it appears that neuromuscular blockade is beneficial in premature infants with moderate to severe respiratory distress syndrome who are at high risk for the development of intraventricular haemorrhage. The data generated by Perlman et al. (1983, 1985) are supported by other investigators who have demonstrated beneficial effects of pancuronium on intracranial pressure and cerebral perfusion pressure (Fanconi & Duc 1987; Finer & Tomney 1981).

Opponents of this view believe pancuronium may adversely affect systemic haemodynamics. Cabal et al. (1985) reported significant elevations in heart rate and blood pressure in 7 critically ill neonates following the administration of pancuronium. They correlated these haemodynamic changes with acute elevations in plasma concentrations of noradrenaline (norepinephrine) and adrenaline (epinephrine). Other investigators, however, have been unable to demonstrate a significant rise in arterial blood pressure following pancuronium administration (Finer & Tomney 1981; Runkle & Bancalari 1984).

5.8.1 Pharmacokinetics

We were unable to identify any data describing the biodisposition of pancuronium in neonates. Dose-response data, however, are available. Bennett et al. (1975) evaluated the dose of pancuronium necessary to achieve full control of ventilation and adequate relaxation in 25 infants less than 28 days of age undergoing surgical procedures. Infants 0 to 7 days of age required a mean dose of 40 μg/kg (range 33 to 50 μg/kg) *versus* a mean dose of 67 μg/kg (range 35 to 106 μg/kg) in neonates 8 to 14 days of age. Mean doses required for infants 15 to 21 and 22 to 28 days of age were 78 μg/kg (range 62 to 106 μg/kg) and 90 μg/kg (range 59 to 101 μg/kg), respectively. In these last 2 groups, however, the dose required by most infants approximated 60 μg/kg and 100 μg/kg, respectively. The time from administration to onset of paralysis was 30 to 60 seconds, and the duration of the paralysis varied between 50 and 90 minutes.

Goudsouzian et al. (1981) evaluated recovery from neuromuscular blockade in 33 critically ill infants (gestational age 27 to 42 weeks) who received

pancuronium. Recovery was determined by the evoked contraction of the adductor policis following indirect stimulation of the ulnar nerve. Spontaneous recovery occurred in all infants over 32 weeks postconceptual age (with the exception of 1 infant) if their last dose of pancuronium was administered more than 20 hours previously. The one exception was an infant with renal failure who demonstrated evidence of neuromuscular blockade for up to 48 hours after the last pancuronium dose. That this infant did not spontaneously recover is not surprising, since the predominant route of elimination for pancuronium is by renal excretion (Gilman et al. 1985).

In addition, no infant below 32 weeks postconceptual age recovered spontaneously. In fact, this group required more pharmacological antagonist therapy (i.e. atropine and neostigmine) than infants over 32 weeks postconceptual age. Again, this is not surprising considering the ontogeny of renal maturation discussed in section 4.1.

Pancuronium is unlikely to displace bilirubin from albumin binding sites. Robertson and Karp (1982) evaluated this potential displacement reaction *in vitro*. Using serum pancuronium concentrations 10 times greater than those found in adults and assuming an adult value of 70% for protein binding (Thompson 1976), Robertson and Karp found a non-significant pancuronium-bilirubin displacement reaction.

Vecuronium bromide is another non-depolarising neuromuscular blocking agent which differs from pancuronium, at least in adults, by its shorter duration of action (Fahey et al. 1981a) and lack of cardiovascular effects (Morris et al. 1983). This latter difference would make vecuronium an ideal paralysing agent in premature infants with respiratory distress syndrome. Additionally, vecuronium in adults, in contrast to pancuronium, appears to be cleared by the liver (Fahey et al. 1981b). At present, the pharmacokinetics of vecuronium have been described in infants and children (Fisher & Miller 1983; Fisher et al. 1985), but to the best of our knowledge, no pharmacokinetic or pharmacodynamic data are available in neonates.

5.8.2 Adverse Effects

In contrast to the elevations in heart rate and blood pressure observed by Cabal et al. (1985), McIntosh (1985) observed a hypotensive response with 12 of 14 doses of pancuronium in a premature infant with severe respiratory distress syndrome. He proposed that the intravascular volume in this infant was marginal and that muscle paralysis caused a fall in venous return and cardiac output. Although hypotension is an unusual response to pancuronium administration, one needs to be aware of this potentially serious side effect.

Sinha and Levene (1984) reported joint contractions in 3 newborns who received pancuronium. This interesting association has not been described by other investigators (Greenough 1984) and requires further evaluation.

5.8.3 Drug-Drug Interactions

Several drugs may potentiate the neuromuscular blocking action of the non-depolarising neuromuscular blocking agents (Nugent et al. 1979). The most important class of drugs would appear to be the aminoglycosides, due to their common use in neonates. Vital-Brazil and Prado-Franceschi (1969) observed an inhibition of prejunctional release of and a depressed postjunctional response to acetylcholine in rat diaphragms following the administration of neomycin or gentamicin. This interaction is believed to occur as a result of aminoglycoside competition with calcium ions at a common receptor site on the nerve ending or prejunctional membrane (Nugent et al. 1979). The interaction between several antibiotics and the non-depolarising neuromuscular blocking agents has been extensively reviewed by Pittinger and Adamson (1972).

5.8.4 Dosing Recommendations

Our dosing recommendations, based on the dose-response data of Bennett et al. (1975) and our understanding of the ontogeny of renal maturation (see section 4.1.2), are shown in table XIX. Since glomerular filtration remains relatively constant at a markedly reduced rate before approximately 35 weeks postconceptual age, we would recommend

Table XIX. Dosing recommendations for pancuronium in neonates

Age (wks)	Dose (μg/kg)[a]
< 35 postconceptual	40
⩾ 35 postconceptual:	
0-1 postnatal	40
1-3 postnatal	60
> 3 postnatal	100

a Suggested initial dose; see text for subsequent dosing recommendations.

an initial starting dose of 40 μg/kg pancuronium for all infants less than 35 weeks postconceptual age. Infants of 35 weeks or more gestational age may then be dosed according to their postnatal age. Additional doses are usually administered as needed to maintain muscle paralysis.

5.9 Morphine

Morphine, an opioid analgesic, is being used with increasing frequency in neonates for analgesia, anaesthesia, and/or sedation (Yaster 1987). Although in the past many believed the neonate was incapable of 'feeling or remembering' pain, it is quite apparent that the newborn does in fact feel and respond to pain (Yaster 1987), supporting the increased use of these agents in neonatal practice.

The pharmacological effects of morphine are the result of opioid receptor stimulation (Beaumont & Hughes 1979). Age-related differences have been described for the development of opiate receptors (Leslie et al. 1982; Pasternak et al. 1980) and may at least partially explain the belief that neonates are more sensitive to the respiratory depressant effects of morphine (Way et al. 1965; Yaster 1987). However, and as discussed below, the influence of markedly increased serum morphine concentrations commonly observed with routine morphine dosing in neonates (Koren et al. 1985b; Lynn & Slattery 1987) on the incidence and degree of respiratory depression cannot be overlooked.

5.9.1 Pharmacokinetics

The pharmacokinetic properties of morphine in neonates have only recently been described (Lynn & Slattery 1987; Koren et al. 1985b). Lynn and Slattery (1987) evaluated 10 infants between 1 day and 10 weeks of age who received a continuous intravenous infusion of morphine for 14 hours to 15 days. Infusion rates varied between 20 and 100 μg/kg/h. All infants were 36 weeks gestation or older and were haemodynamically stable. Three infants required phototherapy for hyperbilirubinaemia, although none required exchange transfusion.

The pharmacokinetic data generated in this study are outlined in table XX. The mean morphine body clearance in infants 1 to 4 days of age was substantially lower (74%) than in older infants (table XX). These data on morphine body clearance and $t_{1/2\beta}$ are comparable to those of Koren et al. (1985b). By comparison, mean body clearance values in children 3 months to 5 years of age and in adults, were 20 ml/kg/min (Vandenberghe et al. 1983) and 11.5 ml/kg/min (Stanski et al. 1982), respectively.

In adults, morphine is eliminated primarily via conjugation with glucuronide, with a much smaller amount eliminated as a sulphate conjugate (Yeh 1975). As described earlier (section 3.1.4), the capacity of the glucuronidation pathway is limited in neonates. This decreased conjugative capacity most likely explains the markedly decreased morphine total body clearance observed in infants during the neonatal period. In contrast, the ability to conjugate sulphate develops rapidly and is very efficient in neonates, infants and children (see section 3.1.4).

Table XX. Morphine pharmacokinetic parameter estimates during the first 2 months of life (modified from Lynn & Slattery 1987)

Postnatal age (days) [range (mean)]	Body CL (L/h/kg)	Vd (L/kg)	$t_{1/2\beta}$ (h)
1-4 (2.14)	0.377[a]	3.38	6.81[a]
17-65 (42)	1.428	5.15	3.91

a $p < 0.05$ compared with older infants; values presented as the mean.

Lynn and Slattery (1987) reported a substantial capability to form the sulphate conjugate of morphine in infants at 1 month of age, whereas these same infants demonstrated only a limited capability to form the glucuronide conjugate. The more efficient sulphation pathway observed in infants than in adults may explain why morphine body clearance in infants older than 1 month approaches or exceeds values reported in adults.

5.9.2 Adverse Effects

The major clinical adverse effect of opioids is their capacity to depress respiration. Although the newborn has been purported to be more sensitive to the respiratory depressant effects of morphine (Way et al. 1965), this issue, in our opinion, requires re-examination in light of the recently published data on differences in the pharmacokinetic properties of morphine in neonates compared with adults. The clinical observation of a greater sensitivity to the respiratory depressant effects of opioids may be the result of drug accumulation rather than an increased receptor sensitivity to morphine. A similar association has also been suggested for elderly patients (Owen et al. 1983).

Other potential adverse reactions associated with morphine administration include hypotension, decreased bowel motility, and associated histamine release reactions. Obviously, further work is necessary to assess the types and incidence of adverse effects of morphine in neonates when dosing regimens are designed incorporating the recently described pharmacokinetic data.

5.9.3 Dosing Recommendations

Lynn et al. (1984) did not observe elevated $PaCO_2$ values in children weaning postoperatively from assisted ventilation or during spontaneous ventilation when serum morphine concentrations were below 30 μg/L. These investigators also documented adequate analgesia in older children who could cooperate with a verbal pain score when their serum morphine concentration was above 12 μg/L. Thus, these data and others (Dahlstrom et al. 1982; Meiser et al. 1980) would suggest that initial morphine dosing regimens should be designed to obtain serum morphine concentrations between 12 and 30 μg/L. From the available pharmacokinetic data, such concentrations would theoretically be achieved in neonates with an infusion rate between 5 and 10 μg/kg/h. The data of Koren et al. (1985b) suggest that initial infusion rates should not exceed 15 μg/kg/h. For intermittent use, we would recommend a morphine dose of 30 to 60 μg/kg administered every 6 to 8 hours. The efficacy of, or need for, adjustment of these initial morphine dosing recommendations should be measured by careful assessment of physiological correlates to pain; most notably, unexpected elevations in heart rate, blood pressure, or lowered arterial oxygen saturations.

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