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# Disposition of morphine in plasma and cerebrospinal fluid varies during neonatal development in pigs

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## Abstract

The pharmacological effects of morphine are mediated via the central nervous system (CNS) but its clearance from the CNS in neonates has not been investigated. We have proposed that neonatal development of the blood–brain barrier affected CNS clearance mechanisms and CNS exposure to morphine. Male piglets (n = 5) aged one, three and six weeks were given morphine sulfate (0.5 mg $kg^{-1}$, i.v.). Serial blood and cerebrospinal fluid (CSF) samples were withdrawn over 360 min after morphine administration. Morphine concentration was measured by radioimmunoassay. A three-compartment model was fitted to individual data. Estimated parameters were reported as median and range. The peak morphine concentrations in plasma were not significantly different in the one-, three- or six-week-old piglets. Plasma clearance at one week (4.5, 3.8–8.6 mL $min^{-1}$ $kg^{-1}$) was significantly lower than at three weeks (30.0, 19.1–39.0 mL $min^{-1}$ $kg^{-1}$) and six weeks (37.0, 29.7–82.8 mL $min^{-1}$ $kg^{-1}$). The peak morphine concentration in CSF at one week (59.84, 31–67 ng $mL^{-1}$) was higher than at three weeks (18.8, 17.7–25 ng $mL^{-1}$) and six weeks (24.51, 16.5–84 ng $mL^{-1}$), while CSF clearance was lower at one week (1.0, 0.18–9 mL $min^{-1}$ $kg^{-1}$) compared with three weeks (6.2, 2.3–9.3 mL $min^{-1}$ $kg^{-1}$) and six weeks (3.95, 1.3–85.7 mL $min^{-1}$ $kg^{-1}$). Apparent plasma:CSF transfer ratio at one week was greater than at three and six weeks. The reduced plasma and CSF morphine clearance in early infancy resulted in elevated systemic and central morphine exposure in neonatal pigs.

## Introduction

Morphine is used widely in neonatal postoperative care and in pediatric cancer pain management. However, the adverse effects associated with morphine are much higher in neonates and infants as compared with adults. Neonates are more susceptible to morphine-induced respiratory depression, bradycardia, hypotension, urinary retention and seizures (Way et al 1964), while a decrease in analgesic effect has been observed as compared with adults (Lynn et al 1984; Koren et al 1985b; Bhat et al 1990; Chay et al 1992; Olkkola et al 1995). This increased susceptibility to morphine's adverse effects has been attributed to immature organ development such as the liver (Mikkelsen et al 1994). While many enzymes are able to metabolize drugs during the fetal period their activity is low (Hines & McCarver 2002; McCarver & Hines 2002). This decreased function can lead to an accumulation of morphine and its active metabolite morphine-6-glucuronide, prolonging its half-life. The accumulation of morphine 3-glucuronide, a more potentially toxic metabolite, which is present at higher concentrations than morphine 6-glucuronide, is also cause for concern (Barrett et al 1996). Accordingly, Lynn et al (1998) found that the median morphine plasma clearance in the first week of life was approximately one third that of infants older than one-month-old. Thus, adverse effects due to morphine are associated with elevated plasma morphine concentrations in neonates and infants (Koren et al 1985a, b; Chay et al 1992; Lynn et al 1993).

Kupferberg & Way (1963) reported increased central nervous system (CNS) concentration of morphine in infants. This increased exposure was reported to be associated with reduced morphine plasma clearance. However, other mechanisms, such as P-glycoprotein (P-gp) expression in the CNS, associated with postnatal development of the blood–brain barrier (BBB), may also influence distribution of morphine into the CNS and contribute to an increased likelihood of morphine accumulation in the CNS

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in these young neonates. As the BBB is structurally and functionally immature in newborns (Way et al 1964; Assael 1982; Lynn & Slattery 1987; Pokela et al 1993) it would indicate that morphine would have greater access to the CNS due, at least in part, to increased BBB permeability. Therefore, BBB development may play an important role in morphine pharmacokinetics in the CNS. We postulate that there are substantial age-related variations in CNS exposure to morphine during neonatal development.

The purpose of this study was to evaluate morphine pharmacokinetics in plasma and cerebrospinal fluid (CSF) at various stages of development in pigs. Pigs are a suitable animal model for comparison of cardiovascular physiology with man and were used in this study because of their anatomical and physiological similarity to the human system. In this regard, the first 2.5 weeks of a piglet's life corresponds to the first six months of a newborn infant's life (Boudreaux et al 1984). Previous studies have shown that distribution of drugs into the CNS of neonatal pigs correlates with drug disposition in human neonates (Abdel-Rahman et al 2000). Morphine concentrations in the CSF were used as a marker of distribution of morphine into the CNS. Also, serial sampling was made possible due to the large volume of CSF in pigs.

## Materials and Methods

### Animals

Experimental protocols were approved by the Animal Care Committee at the University of Illinois at Chicago. Three groups, each including five male piglets (Oakhill Genetics, Ewing, IL), aged one ($2.2 \pm 0.2$ kg), three ($5.9 \pm 0.2$ kg) and six weeks old ($11.2 \pm 0.4$ kg), were studied. Animals were housed and maintained at the Biological Research Laboratories as per the guidelines of the American Association for Accreditation of Laboratory Animal Care (AALAC).

### Surgical protocol

All experiments were performed under anaesthesia. Piglets were premedicated with intramuscular ketamine ($15\,mg\,kg^{-1}$) and atropine ($0.05\,mg\,kg^{-1}$). The animals were anaesthetized with 4–5% isoflurane, intubated with an endotracheal tube and maintained on 2% isoflurane in air using a ventilator (Harvard Apparatus Inc., South Natick, MA). The left and right femoral veins were cannulated for drug administration and sample collection, respectively. Following vascular cannulation, animals were placed in a left lateral position and a lumbar puncture was performed at the L5–L6 position. The needle was positioned to allow free flow of CSF and secured in place. Animals were killed by an overdose of pentobarbital on completion of the study.

### Morphine administration and sampling

All piglets received a single intravenous bolus dose of $0.5\,mg\,kg^{-1}$ morphine sulfate (equivalent to $0.426\,mg\,kg^{-1}$ base). Serial blood (0.3 mL) and CSF samples (0.2 mL) were obtained immediately before drug administration and at 2, 15, 30, 45, 60, 120, 240 and 360 min after dose administration. Due to limited CSF availability the samples were collected for a period of up to three half-lives instead of five half-lives. Blood samples were centrifuged and the harvested plasma, together with CSF samples, was stored at $-70\,^{\circ}C$ until analysis.

### Morphine assay

Plasma and CSF morphine concentrations were determined by a sensitive and specific $^{125}$I-labelled morphine radioimmunoassay (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA, USA). The principle of the assay is based on [$^{125}$I]morphine competing with morphine in the sample for antibody sites. Briefly, sample or standards were incubated with [$^{125}$I]morphine for 1 h in antibody-coated tubes. Samples were diluted to fall within the range of standards used. The assay was validated for plasma and CSF using the standards provided in the radioimmunoassay kit. Following incubation, tube contents were decanted and the tubes were counted in a gamma counter (Cobra model 5005, Packard Instruments Co., Downers Grove, IL, USA). Standard curves were plotted as counts vs log standard concentration. The assay was linear in the range 0.6–250 $ng\,mL^{-1}$ with interassay variability of less than 5%. Antiserum was highly specific for unconjugated morphine, with low cross-reactivity to glucuronidated morphine analogues and codeine ($<2\%$) (Matejczyk & Kosinski 1985). The presence of plasma proteins, bilirubin and haemolysis did not interfere with the assay. The limit of detection for morphine was $0.8\,ng\,mL^{-1}$.

### Pharmacokinetic analysis

Plasma and CSF data were analysed using noncompartmental and compartmental analysis methods (WinNonlin Professional version 2.1, Pharsight Corporation, Mountain View, CA, USA). The peak morphine concentration ($C_{max}$) in plasma and CSF and the time to $C_{max}$ ($T_{max}$) were determined directly from the data. Area under the concentration vs time curve up to the last concentration drawn at 360 min ($AUC_{0-360}$) was determined using the linear trapezoidal rule.

Based on graphical evaluation and noncompartmental analysis which suggested age-related differences in plasma and CSF morphine pharmacokinetics, and because of the small number of animals per group, initial exploratory modelling was performed using pooled data for each of the three groups of pigs. Following model development, final pharmacokinetic parameter estimation was performed for each animal. For the model development, the pharmacokinetic model for morphine in plasma and CSF was developed sequentially. Initially, the form of the model describing plasma morphine concentrations was determined. One and two compartment models were tested and the two compartment model was chosen based on goodness of fit. Morphine concentrations in

CSF were then included in the data set and the model was modified accordingly to include a CSF compartment. The three compartment model was fitted to the combined morphine plasma and CSF concentration data for each group of pigs. It was used to calculate plasma clearance (CL), CSF clearance ($CL_{OUT,CSF}$), and the plasma:CSF transfer ratio (TR). The model, depicted schematically in Figure 1, was a three compartment open model with first-order elimination from the central (plasma) compartment and first-order distribution between plasma and the CSF:

$$V_1(dC_1/dt) = Q \cdot C_2 - (Q + CL) \cdot C_1 \quad (1)$$

$$V_2(dC_2/dt) = Q \cdot (C_1 - C_2) \quad (2)$$

$$V_{CSF}(dC_{CSF}/dt) = f_{CSF} \cdot (CL_{IN,CSF} \cdot C_1 - CL_{OUT,CSF} \cdot C_{CSF}) \quad (3)$$

where C represents morphine concentration, V is the apparent compartment volume, Q is the intercompartment plasma morphine exchange flow rate, $f_{CSF}$ is the fraction of the dose that enters the CSF, CL is the clearance of morphine from the central compartment, and $CL_{IN}$ and $CL_{OUT}$ represent transfer of morphine from plasma into the CSF and from CSF into plasma, respectively. The subscripts 1, 2 and CSF represent the central compartment, peripheral compartment and CSF, respectively. The fraction of the dose that enters the CSF, $f_{CSF}$, is not uniquely estimable; $V_{CSF}/f_{CSF}$ was estimated. The plasma:CSF transfer ratio was calculated as the ratio of $CL_{IN,CSF}$ to $CL_{OUT,CSF}$. It was assumed that maximum saturation was reached by 6 h and equilibrium was reached between compartment 1 and 3.

### Statistical analysis

Pharmacokinetic parameter estimates were summarized as median and range. Intersubject variation in pharmacokinetic parameter estimates within age groups was calculated as the coefficient of variation. Non-parametric *t*-test and one-way analysis of variance, as appropriate, were used to compare parameters among age groups. $P < 0.05$ was considered significant.

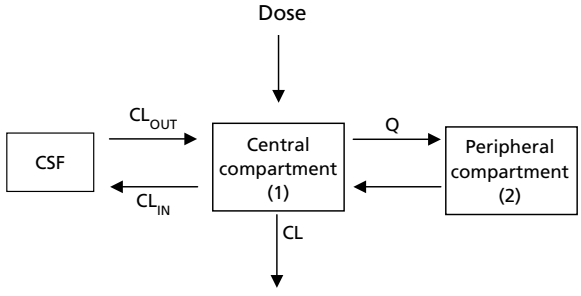


**Figure 1** Schematic of the pharmacokinetic model.

## Results

Mean morphine plasma and CSF concentration vs time profiles are shown in Figure 2. Plasma morphine $C_{max}$ values at 1 week (267.4, 232–298 ng mL$^{-1}$), 3 weeks (212.5, 123.7–250 ng mL$^{-1}$) and 6 weeks (199.8, 137.8–250 ng mL$^{-1}$) were not significantly different. Intersubject variation in plasma morphine $C_{max}$, which was calculated as percent coefficient of variation (%CV), was greater in the 3-week (25.0%) and 6-week (22.2%) age groups as compared with the 1-week age group (10.7%). Although there was

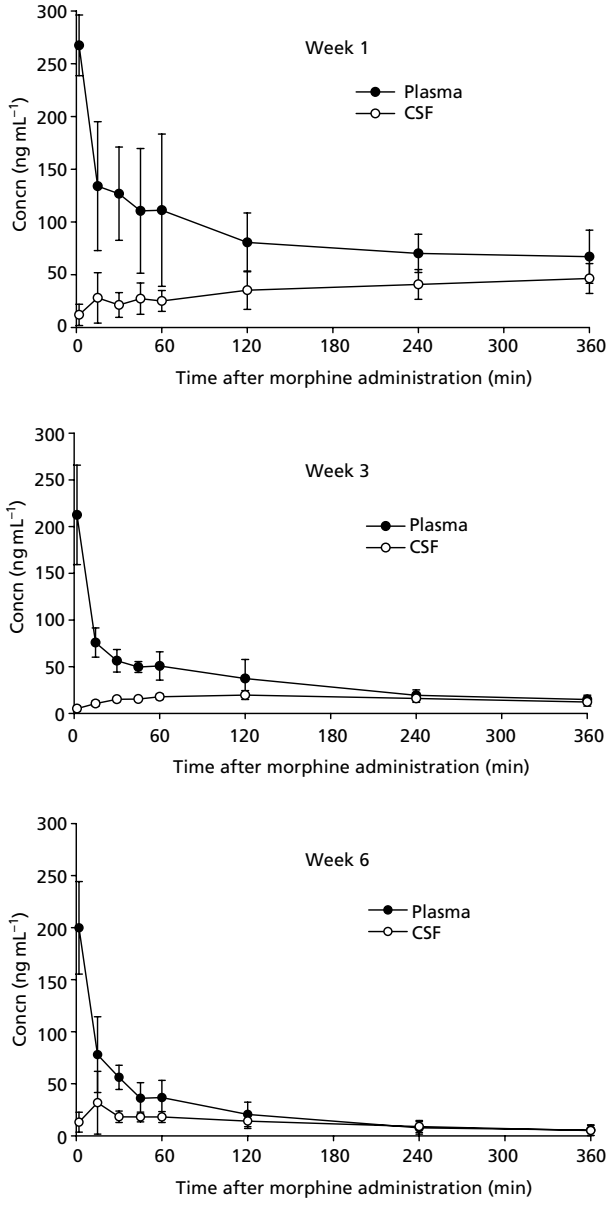


**Figure 2** Morphine concentration vs time curves for one-, three- and six-week-old neonatal pigs (n = 5). Error bars represent standard deviation for each measured concentration.

no significant difference among age groups in plasma morphine $C_{max}$, systemic exposure was significantly greater in 1-week pigs (29.21, 23.61–49.33 min $\mu g\,mL^{-1}$), as shown by $AUC_{0-360}$ estimates 2.3- and 3.0-fold greater relative to that at 3 weeks (12.56, 8.94–18.25 min $\mu g\,mL^{-1}$) and 6 weeks (9.81, 4.73–12.49 min $\mu g\,mL^{-1}$), respectively.

CSF morphine $C_{max}$ in 1-week piglets (59.84, 31–67 $ng\,mL^{-1}$) was significantly higher than at 3 weeks (18.8, 17.7–25 $ng\,mL^{-1}$) and 6 weeks (24.51, 16.5–84). Large intersubject variations were observed in CSF morphine concentrations in the 6-week age group (80.5%) compared with the 1-week (33.7%) and 3-week (15.1%) age groups. The 1-week age group also experienced greater and more sustained morphine exposure in the CSF, as indicated by significantly greater $AUC_{0-360}$ estimates (14.06, 6.8–18.32 min $\mu g\,mL^{-1}$) compared with 3 weeks (6.05, 3.96–6.72 min $\mu g\,mL^{-1}$) and 6 weeks (4.88, 1.83–5.9 min $\mu g\,mL^{-1}$).

Pharmacokinetic parameter estimates from the model-based analyses are summarized in Table 1. In this analysis, median plasma morphine clearance was reduced 6.7-fold and 8.2-fold in 1-week piglets relative to 3- and 6-week piglets, respectively. An increase in estimated intersubject variability for morphine plasma clearance was observed at 6 weeks (46.8%) compared with 3 weeks (28.4%) and 1 week (37.8%).

Similarly, the apparent clearance of morphine from the CSF was relatively reduced but was not statistically significant ($P > 0.05$) in 1-week piglets compared with 3-week and 6-week piglets. In addition, there was a trend toward a greater CSF to plasma transfer ratio in 1-week and 3-week piglets relative to the 6-week age group.

## Discussion

The observed age-related increase in apparent plasma morphine clearance corresponded to the progressive functional maturation of organ systems of drug elimination during neonatal development (Assael 1982). Studies have shown that renal and hepatic elimination mechanisms are not well developed in neonates and develop at varying rates during the postnatal period. Uridine 5′-diphosphate glucuronosyltransferase isoform 2B7 (UGT2B7), the primary enzyme system involved in the biotransformation of morphine to glucuronidated metabolites in man (Stone et al 2003), is depressed in neonates, reaching adult capacity after 6–18 months of age (de Wildt et al 1999). Accordingly, morphine-6-glucoronide could not be detected, or could only be found in low concentrations in the plasma of approximately 25% of infants in previous studies (Bhat et al 1992; McRorie et al 1992). In addition, age-related changes in the clearance of morphine may be associated with developmental changes in the neonatal kidney, which has reduced excretory and limited drug metabolizing capacity at birth (Assael 1982). Large intersubject variability in morphine plasma concentrations during postnatal development in this study was consistent with previous reports for morphine in infants (Koren et al 1985b; Bhat et al 1990; Pokela et al 1993).

In this study, the CSF to plasma transfer ratio was increased in newborn piglets consistent with previous studies in monkeys (Lynn et al 1991). However, significant intersubject variability was observed in the transfer ratio due to morphine accumulation in CSF in two piglets in the 1-week age group. The CSF clearance at 1 week was relatively lower than at 6 weeks, which indicated that morphine was being cleared from the CSF at a much slower rate in younger piglets (Table 1). This could be attributed to variable rates of BBB development. Since morphine distributes into the CNS by passive diffusion (Letrent et al 1999), increased exposure of the CNS in newborns would be likely due to increased permeability of the BBB relative to older pigs. This permeability declines through postnatal development. In addition, the apparent clearance of morphine from the CSF is reduced in younger pigs and appears to increase with age. We propose that the mechanism of reduced morphine clearance from the CSF may be related to reduced efflux of morphine from the CNS. In adult rats, P-gp regulates morphine brain efflux (Letrent et al 1999). It has been shown that inhibition of brain P-gp resulted in a significant increase in the morphine brain-to-blood ratio and significantly increased morphine exposure and consequently morphine-induced analgesia (Letrent et al 1999). Given the immaturity of

**Table 1** Median (range) of morphine pharmacokinetic parameter estimates

| Parameters | One week | Three weeks | Six weeks | *P* value |
|---|---|---|---|---|
| $V_1$ ($L\,kg^{-1}$) | 0.5 (0.01–1.4) | 1.2 (0.06–1.8) | 0.2 (0.04–1.6) | 0.47 |
| CL ($mL\,min^{-1}\,kg^{-1}$) | 4.5 (3.8–8.6) | 30.0 (19.1–39.0) | 37.0 (29.7–82.8) | 0.001 |
| Q ($mL\,min^{-1}\,kg^{-1}$) | 0.2 (0.02–0.4) | 0.2 (0.1–0.2) | 0.1 (0.1–0.2) | 0.73 |
| $V_2$ ($L\,kg^{-1}$) | 3.0 (1.2–5.5) | 4.1 (3.2–5.7) | 2.7 (1.4–4.4) | 0.36 |
| $CL_{IN,CSF}$ ($mL\,min^{-1}\,kg^{-1}$) | 0.7 (0.01–6.9) | 4.5 (0.1–5.5) | 1.9 (0.09–36.1) | 0.53 |
| $CL_{OUT,CSF}$ ($mL\,min^{-1}\,kg^{-1}$) | 1.0 (0.2–9.0) | 6.2 (2.3–9.3) | 4.0 (1.3–85.7) | 0.45 |
| $V_{CSF}/f_{CSF}$ ($L\,kg^{-1}$) | 371.2 (6.8–1084.8) | 744.4 (27.2–1079.2) | 91.9 (25.8–862.0) | 0.43 |
| Plasma:CSF transfer ratio | 0.7 (0.6–0.8) | 0.6 (0.4–0.8) | 0.5 (0.3–0.6) | 0.07 |

the BBB, it is possible that deficiencies in P-gp in neonates may contribute to enhanced and sustained CNS exposure to morphine.

### Conclusions

Morphine disposition in plasma and CSF varied during postnatal development. These changes likely reflected immaturity of organ systems, including the liver, kidney and BBB. Changes in central exposure to morphine were due, in part, to changes in clearance over time, although this might not have been the only mechanism. It was likely that other mechanisms that influenced distribution of morphine across the BBB also influenced CNS exposure to morphine. Consequently, neonates were likely to have higher CNS morphine concentrations, which might have made them more sensitive to analgesic and adverse effects (Koren et al 1985b). Our results support the need for careful titration of morphine dosing in neonates (Olkkola et al 1995). It is necessary to explore mechanisms for variable CNS exposure to morphine during postnatal development. The disposition of morphine metabolites in the CSF and plasma of neonatal pigs and the role of P-gp in the transport of morphine across the BBB of neonatal pigs remain to be investigated.

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