Morphine and morphine-6-glucuronide concentrations and their correlation with pain responses

JOANNA RÓŻYCKA¹, JANUSZ GADZINOWSKI¹, DHARMAPURI VIDYASAGAR², MAREK CHUCHRACKI³

Abstract
The aim of the study was to assess morphine and its metabolite morphine-6-glucuronide (M6G) serum concentrations after continuous morphine infusion during first days of life, in preterm neonates requiring mechanical ventilation. We also examined correlation between morphine, its metabolite and pain scores. Fourteen preterm neonates with a mean birth weight of 1196 g (range 780-1760 g) and mean of 29 weeks (range 26-33 weeks) gestational age were randomly assigned to the study group. They received morphine for 1 to 5 days (100 mg/kg over 30 minutes followed by 20 mg/kg/h). Blood samples were obtained from neonates at 0, 30 minutes, 6 and 24 hours after the start of morphine infusion and 24 hours after discontinuation of infusion. The pain responses were assessed using two scales – Premature Infant Pain Profile (PIPP) and Comfort Scale (CS) at 6 and 24 hours. M6G was found in all samples, even after 30 minutes of morphine infusion. In most samples M6G concentration exceeded morphine concentration. Mean ± SD morphine clearance was 5.5 ± 3.0 ml/min/kg. There was a significant negative correlation between morphine plasma concentration and Comfort Scale scores at 6 hour of the study (r = – 0.72, p = 0.003). There was no correlation between M6G and pain scores. Clearance value of morphine was similar to values published by other authors. Finding correlation only between morphine concentration and CS at 6th hour of the study confirms complex problem of pain assessment.

Key words: morphine, morphine-6-glucuronide, pain

Introduction
Pain is an unpleasant sensory and emotional experience connected with actual or potential tissue damage [1]. Before mid-1980s it was believed that newborn infants did not feel pain and consequently the use of analgesics in neonatal units was limited. Although in 1985 intraoperative anesthesia was a routine in adults, only 23% of preterm infants undergoing patent ductus arteriosus ligation received adequate anesthesia [2]. It has taken scientists and doctors a long time to accept what parents have always known – that the infant can feel pain [3]. Preterm newborns and critically ill term newborns admitted to the intensive care unit are subjected to multiple diagnostic and therapeutic events that cause pain and discomfort. The younger the gestational age of the neonate, the more likely they are to have an increased number of procedures [4]. There are speculations that painful stimuli are followed for prolonged periods in which non noxious procedures (handling, physical examination, nursing procedures, etc.) may be perceived as chronic painful stimulation [5].

To obviate the effects of pain many analgesics have been used. Morphine is one of the most popular of them Morphine is widely in neonatal intensive care units now. There is, however, some concern regarding appropriate dosing, its analgesic effect and possible side effects in newborns [6-8]. Large variations in the pharmacokinetic properties of morphine have been found in term and preterm infants. That’s why recently more studies have concentrated on the pharmacokinetics of the opioid analgesics in infants and neonates [9-12]. Appropriate morphine doses and desired serum levels in preterm and newborn infants providing analgesia are still being investigated.

Because of its wide usage in the preterm and term infants the pharmacology and metabolic pathway need to be well understood. Morphine undergoes glucuronide conjugation in the liver to two metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), which are subsequently excreted by the kidney. Whilst M3G appears to be an opiate antagonist, M6G has potent analgesic properties [13, 14]. There is no information regarding the role of morphine and its components on the analgesic effects in the newborn

We conducted a study to assess morphine and its metabolite concentrations, to assess morphine clearance and to find correlation between morphine and its metabolite M6G and pain scores.

¹ Department of Neonatology, University of Medical Sciences, Poznań, Poland
² Division of Neonatology, University of Illinois at Chicago, USA
³ Department of Mother and Child Health, University of Medical Sciences, Poznań, Poland
Material

The study protocol was approved by the Ethics Committee of the University of Medical Sciences in Poznań. 14 preterm, mechanically ventilated newborns at first day of life, of gestational age 26 to 33 weeks (29 ± 2 SD) and birth weight 780 to 1760 grams (1196 ± 277 SD) were studied. All of them had respiratory distress and received surfactant.

Neonates born with major congenital anomalies, birth asphyxia (5 minute Apgar score < 4 points or umbilical vessels pH < 7.0) [15] maternal opioid addiction and neonates receiving muscle relaxants were excluded from the study.

Methods

After written informed consent from the parents, eligible infants received a loading dose of morphine of 100 μg/kg over 30 minutes, followed by a continuous infusion at a constant rate of 20 μg/kg/hour for at least 24 hours, up to 5 days. Morphine was diluted in 5% glucose and given at 0.5 ml/hour rate. Blood samples before morphine administration were obtained and 1 ml at 30 minutes and at 6 and 24 hours after morphine dose from umbilical catheter. Additional sample was obtained 24 hours after morphine discontinuation. Only 4 to 5 samples were taken from any one infant to minimize the loss of blood volume. Serum was separated and stored at -70°C for later analysis.

Level of sedation was assessed by the Comfort Scale – CS [16] and responses to pain were measured by the Premature Infant Pain Profile (PIPP) score [4,17]. These measurements were obtained before starting the study drug infusion, at 6 and 24 hours after morphine administration. All newborns received regular monitoring of blood pressure, heart rate, ventilator rate and diuresis.

Analytical methods

Morphine and morphine-6-glucuronide (M6G) were measured in plasma using modified radioimmunoassay (RIA) with the use of antibodies [18]. Lower limit of detection for morphine and M6G was 0.67 ng/ml and 0.13 ng/ml respectively. The coefficient of variation in the range of the analyses was for morphine 10.4% and 6.1% for M6G.

Statistical analysis

The data were calculated by means of a computer program STATISTICA v. 6.0. Data are presented as mean values±SD or as medians and interquartile ranges, when appropriate. The relationships between morphine clearance and gestational age and birthweight were analyzed with Pearson’s correlation coefficient. Relationship between morphine and M6G concentration pain scales were investigated using Spearman’s rank correlation analysis. A p value of < 0.05 was considered to be statistically significant.

Results

The median postnatal age of the studied patients was 4 hours (range 2-20) at the start of the loading dose, and the median duration of morphine administration was 1 day (range1 to 5 days). Mean (SD) plasma concentration of morphine and M6Gs are shown in Table 1 and Fig 1.

### Table 1. Mean ± SD plasma morphine and M6G concentrations at first day of life (at 0, 0.5, 6, 24 hours) after morphine infusion and 24 hours after discontinuation of morphine infusion

<table>
<thead>
<tr>
<th></th>
<th>Morphine (ng/ml)</th>
<th>M6G (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Median</td>
</tr>
<tr>
<td>0 hour</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5 hours</td>
<td>23.8 ± 25.7</td>
<td>12.5</td>
</tr>
<tr>
<td>6 hours</td>
<td>51.4 ± 30.2</td>
<td>55.3</td>
</tr>
<tr>
<td>24 hours</td>
<td>84.3 ± 55.4</td>
<td>73.7</td>
</tr>
<tr>
<td>24 hours after discontinuation</td>
<td>44.0 ± 12.0</td>
<td>32.0</td>
</tr>
<tr>
<td></td>
<td>47.4 ± 41.9</td>
<td>36.7</td>
</tr>
<tr>
<td>6 hours</td>
<td>53.6 ± 39.3</td>
<td>40.0</td>
</tr>
<tr>
<td>24 hours</td>
<td>96.8 ± 56.3</td>
<td>86.5</td>
</tr>
<tr>
<td>24 hours after discontinuation</td>
<td>87.0 ± 144.0</td>
<td>42.5</td>
</tr>
</tbody>
</table>
M6G was found in all samples, even after 30 minutes of morphine infusion. In most samples M6G concentration exceed morphine concentration.

Morphine clearance values for all infants are shown in Table 2. The values were calculated from morphine plasma concentration at 24 hours of study drug infusion. Mean clearance value for group was 5.5 ± 3.0 ml/min/kg. There was no statistical correlation between morphine clearance and week of gestation or birth weight (Spearman rank correlation, respectively $r = -0.09; r = -0.04$, $p > 0.05$)

The correlation between morphine and M6G concentration and PIPP and CS scores was analyzed. The only significant correlation found was a negative correlation between morphine concentration and CS scores at 6 hour of the study (Spearman’s correlation rate, $r = -0.72, p = 0.0032$) (Fig. 2).

**Discussion**

Morphine metabolism and pharmacokinetics have been widely studied in adults and children, but data on preterm newborns are limited [19]. Most studies were performed on a small number of newborns and few examined preterm newborns.

We tried to find correlation between morphine and M6G plasma concentrations and their effect on pain res-
The correlation between morphine concentration and pain scale scores was achieved only for Comfort Scale at 6th hour of morphine infusion. Studies performed in older children and adults did not show correlation between morphine concentration and pain responses [20, 21]. Scott et al. [9] analyzed the group of preterm newborns, requiring mechanical ventilation using Neonatal Facial Coding System. In their although morphine showed to lower the pain responses, no correlation between morphine concentration and changes in face mimic were found.

Chay et al. examined 19 term and preterm newborns and found that the sedative properties of morphine were achieved when morphine plasma concentration was 125 ng/ml [22]. Such a high level was found only in 2 newborns at 24 hours of drug infusion in our study. According to other studies examining morphine effect on lowering pain responses adequate morphine concentrations ranged between 20 to 65 ng/ml [22-24]. In our study 79% of newborns exceeded morphine concentration of 20 ng/ml at 6th hour of morphine infusion. It was assumed that analgesic effect of morphine is achieved with lower concentrations than Chay proved as causing sedation effect.

Analyzing therapeutic effect of morphine we have to take into consideration also its metabolites. In adults and children M6G concentration exceeds morphine concentration. Glucuronization is slower in preterm newborns, because of liver immaturity [25, 26]. In preterm neonates M3G levels were higher than M6G levels, and in some studies M6G wasn’t detected at all [22]. In our study M6G was detected in all samples, even after 30 minutes of morphine infusion. In most samples (57% of samples) M6G concentration exceeded morphine concentration. No correlation between M6G concentration and pain scales scores was found.

In this study mean morphine clearance value (mean ± SD) was 5.5 ± 3.0 ml/min/kg. It was calculated based on morphine concentration at 24 hour of morphine infusion. To minimize the blood volume requirement per patient and because of short time of morphine infusion (often 24 hours) it wasn’t possible to calculate morphine concentration at steady-state. It was assumed that steady-state was achieved at 24 hours of study drug infusion. According to Saarenmaa study, some newborns achieve steady-state morphine concentration on the second day of infusion [12]. Because of these limitations, clearance value is approximated. It is comparable to clearance values reported in earlier studies. The reported values of plasma clearance in preterm neonates range from 2.27 ml/kg/min [9] to 4.7 ml/kg/min [27] and were lower comparing with term newborns. In term neonates, the reported values range from 6.3 to 20.1 ml/kg/min [27, 28]. Our estimation of morphine clearance as 5.5 ml/kg/min supports the belief that the elimination rate of morphine is reduced in preterm infants.

Some studies showed correlation between morphine clearance and week of gestation and birth weight [12, 22, 29]. They showed that the more mature and higher the birth weight, the higher is morphine clearance. Probably the small number of patients and the range of gestational age of patients participating in our study, did not show such correlation with gestational age or weight. Barrett et al had similar problem in their study [30].

Unsatisfactory knowledge on morphine metabolism causes the risk of its side effects. Newborns are the only patients that don’t receive analgesia and sedation routinely after intubation. Systemic research investigations on large number of newborns assessing morphine and its metabolites concentrations and their influence on pain control and sedation are needed.

Finding correlation only between morphine concentration and CS at 6th hour of the study confirms complex problem of providing analgesia and pain assessment in preterm neonates. Our data suggest wide variability in the pharmacokinetic properties of morphine in preterm patients.

References


