I, Joshua C Euteneuer, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Large Variability of Morphine Exposure during Standard of Care Dosing in Critically Ill Neonates

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Large Variability in Morphine Exposure during Standard of Care Dosing in Critically Ill Neonates

A thesis submitted to the
Graduate School
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Master of Science
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by

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Abstract

Background: Pain control in neonates is an important clinical concern with potential long-term adverse neurodevelopmental effects. Intravenous morphine is routinely administered for pain management post-operatively, but the neonatal morphine dosing-concentration-response relationship is not well characterized. Neonatal pain is difficult to measure challenging the ability to titrate the drug effectively. The current literature provides dosing guidelines but also describes and fails to account for the large unexplained variability in morphine clearance and response. In addition, it is still unknown if these recommended neonatal dosing regimens lead to the analgesic morphine exposure suggested by the literature.

Objective: The purpose of this study was to evaluate morphine pharmacokinetics and exposure in post-operative critically ill neonates. We hypothesized that the inter-patient variability in morphine clearance would frequently result in morphine concentrations outside the tentative target analgesic range.

Design/Methods: This was an open label, prospective, opportunistic study using discarded blood samples in infants receiving morphine as part of their standard care from Sept 2014 to March 2015. Concentration data were analyzed using a pediatric population PK model with Bayesian estimation (MW/Pharm). PK model-based concentration-time profiles were predicted based on the measured morphine concentrations.

Results: Data on 20 patients who underwent 27 interventions with a total of 60 samples were available for analysis. Morphine concentrations ranged from 2.6-529.7 µg/L. Morphine clearance showed large inter-patient variability (4.28-205.3 L/h/(Wt/70 kg)0.75) with a 48-fold range. Of the morphine samples, 13 (21.7%) were in the target exposure range while 19 (31.7%) were below and 28 (46.7%) were above the target range. From the study population in only two (7.4%) cases was a steady-state morphine concentration in the target range within the first 24 hours post-operative period achieved. Both cases occurred in the same patient.
**Conclusion:** In critically ill neonates a large variability was noted in morphine concentrations which were frequently well outside of the goal target range. This large interpatient variability in morphine concentration suggests that dosing guidelines should be individualized in this population to optimize the response of morphine in neonates. Further pharmacometric analysis with PK-PD modeling and research to identify important predictive pharmacokinetic and pharmacogenetic factors to individualize morphine treatment is warranted.
Acknowledgements

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**Figure 1**: Morphine Clearance Plotted Across Postmenstrual Ages.
Introduction

Morphine is routinely used for post-operative pain control in the neonatal intensive care unit (NICU) but precision dosing schemes do not exist for neonates. The neonatal morphine pharmacokinetic (PK) literature describes considerable unexplained variation in morphine clearance but dosing recommendations are made from these clearance estimations. Treating neonatal pain is a humane and ethical concern but this unpredictability in morphine clearance leads to dosing designed for the average neonate without controlling for interpatient variability. Thus, pain may be inadequately treated or infants may be placed at higher risk for adverse effects. Increased morphine exposure is associated with prolonged ventilation, respiratory depression, hypotension, decreased gastrointestinal motility, and withdrawal while underdosing of morphine occurs because of concerns for these adverse effects.

Determining the right dose as quickly as possible is also important because of emerging literature that suggests negative long term consequences of neonatal pain that may be prevented with appropriate analgesia. For example, increased childhood pain sensitivity was reported in infants who underwent surgery in the first three months of life. In another study, adolescents born premature were more sensitive to painful stimuli than adolescent controls born at term. Moreover, compared to age-matched controls, children who underwent surgery in the first three months of life but received preemptive morphine showed no difference in behavioral or physiological responses to immunizations raising the possibility that preemptive morphine prevents the long-term impact of neonatal pain experiences.

Equipoise is needed because morphine exposure can have negative consequences, like respiratory depression, and has been associated with impaired cerebellar growth and poorer neurodevelopmental outcomes at 18 months corrected age.
A number of studies have been undertaken to characterize morphine pharmacokinetics but this has not translated to the clinical realm\textsuperscript{2,10,11}. Existing dosing regimens typically dose intravenous morphine per bodyweight and suggest titration of the medication to the desired clinical response. However, in neonates, whose weight can vary 10-fold (from less than 500 grams to more than 5 kilograms) dosing per bodyweight fails to take into consideration a number of clinically important factors that can influence morphine exposure and response. This is especially true in the most premature neonates with immature hepatic and renal systems\textsuperscript{12}. Concerning titration of morphine, pain in neonates is difficult to measure and even when protocols exist they are difficult to follow.

While a morphine exposure-response curve does not exist\textsuperscript{13} studies have identified a tentative target morphine concentration of 10-20 µg/L as the range for optimal analgesia in neonates with a low risk for adverse effects\textsuperscript{14}. Therapeutic drug monitoring of morphine is not performed and clinicians are left with minimal clinical information to measure effectiveness.

The purpose of this study was to evaluate morphine pharmacokinetics and exposure in post-operative critically ill neonates. We hypothesized that the inter-patient variability in morphine clearance would frequently result in morphine concentrations outside the tentative target analgesic range.

**Materials and Methods**

We conducted a prospective opportunistic study using discarded blood samples in infants in the receiving morphine as part of their standard care from Sept 2014 to March 2015. The Institutional Review Board at Cincinnati Children’s Hospital Medical Center (CCHMC) approved the study protocol. Informed consent was obtained from the legal guardians of all the enrolled subjects. All infants receiving intravenous morphine for at least 24 hours for analgesia in the CCHMC NICU were eligible except those...
with severe liver (aspartate aminotransferase (AST) or alkaline phosphatase >5 times the upper limit of normal for age) or kidney disease (creatinine >3 times the upper limit of normal for age), undergoing therapeutic hypothermia, receiving extracorporeal membrane oxygenation, or receiving other opiate medications. Infants receiving morphine for sedation were also excluded because target concentrations for sedation may differ than those for analgesia\textsuperscript{15}. From the medical record demographic information and clinical data collected included medical and surgical history, gestational age, postnatal age, weight, gender, race, serum creatinine, alkaline phosphatase, and AST, and time and dose of administered morphine.

Standard of Care Dosing
The clinical team decided when to initiate treatment with morphine and dosing. Clinical judgment was used to determine the need for a constant morphine infusion and frequency of intermittent bolus doses of morphine. Not all patients received a constant infusion. For most patients the administration of as needed intermittent bolus doses of morphine rests with the nursing staff. This is guided by the use of the Neonatal Infant Pain Scale\textsuperscript{16}, a validated measure of pain in infants. In general, hospital protocols dictate that infants scoring in the moderate (score 3-4) or severe (score > 4) range should undergo non-pharmacologic interventions first to differentiate pain from agitation but if the score remains elevated after reassessment then pharmacological interventions are pursued. If analgesia remains insufficient or there are other clinical concerns nursing notifies the clinical team. A typical starting infusion dose of morphine in our NICU is 0.05 mg/kg/hr and the usual initial intermittent or as needed intravenous dose is 0.05 mg/kg.

Morphine Concentration
Serum morphine concentration was quantified by a validated liquid chromatography analysis. Based on previous literature the therapeutic range for morphine was considered to be 10-20 ng/mL\textsuperscript{14}.

PK analysis and Simulation
Population PK analysis was performed by nonlinear mixed effects modeling. Concentration data were analyzed using a pediatric population PK model with Bayesian estimation (MW/Pharm Version 3.8). Population model parameter estimates and their distributions used as priors are based on pharmacokinetic data from Anand et al.\textsuperscript{10} Individual PK model-based concentration-time profiles were then estimated based on the measured morphine concentrations. To differentiate the effects of size and maturity on PK parameters clearance and volume were allometrically scaled:

\[ P_i = P_{\text{pop}} (W_{t_i}/W_{\text{standard}})^{\text{power}}, \]

where \( W_{t_i} \) is the individual weight scaled to a 70 kg person (\( W_{\text{standard}} \)) with allometry using a power coefficient of \( \frac{3}{4} \) for clearance and 1 for volume\textsuperscript{17}.

Statistical Analysis
Data are given as a range and median or mean. Linear regression was used to determine the relationship between morphine clearance and age.

Results
Data on 20 patients who underwent a combined 27 surgeries or procedures treated post-operatively with morphine for analgesia provided a total of 60 samples for analysis during the study period. The number of morphine concentration samples available for each patient varied from 1 to 6 samples with a
median of 2.5 samples per patient. The infants’ gestational age ranged between 25 to 41 completed weeks while post-natal age stretched from just hours after birth to 148 days of life. Seven of the 20 patients (35%) were female. Patient demographic and clinical data, including diagnosis, surgery or procedure, estimated individual morphine clearance and volume distribution, the success of clinical team in achieving a steady-state morphine concentration within the target range by 24 hours post-operatively, and in cases where the clinical team was unable to achieve the this, information about whether the morphine exposure was too high or too low are summarized in Table 1.

Morphine clearance was allometrically scaled to a 70 kg adult with a ¾ power model and showed a large inter-patient variability (4.28 to 205.3, mean 40.3 L/h/(Wt/70 kg)0.75) with a 48-fold range. This variability was reflected in the wide observed morphine concentrations ranging from 2.6-529.7 µg/L. Of the morphine samples, 13 (21.7%) were in the target exposure range while 19 (31.7%) were below and 28 (46.7%) were above the target range. Morphine volume of distribution also displayed substantial variability between patients (1.15 to 11.78, average 2.80 L/kg). Out of the 27 painful interventions only there were only two (7.4%) cases of reaching a steady-state morphine concentration in the target range within the first 24 hour post-operative period. Both of these times occurred in the same patient. In most cases (15/27, 55.6%) the morphine concentration was above the reported target range but in ten (37.0%) instances the morphine exposure was less than the target. The highest clearance was an outlier with the next greatest clearance estimated to be 92.5 L/h/(Wt/70 kg)0.75 which was less than half the maximum value.

Estimated morphine clearance was compared to gestational age, postnatal age, and postmenstrual age. Clearance correlated best with postmenstrual age (Figure 1). Although only a weak correlation (r² = 0.3992) it showed improved clearance with higher corrected gestational age.
Discussion

This study is the first to show that the current trial and error dosing paradigm frequently results in morphine concentrations outside the target range suggested by the literature. Because of the inter-individual variability in morphine clearance and challenge of assessing neonatal pain the clinical teams had a difficult time achieving and maintaining the appropriate morphine exposure. Variability in exposure can be related to illness, a decrease in hepatic or renal blood flow as seen in hypotension or mechanical ventilation\textsuperscript{18}, variation in gestational or postnatal age, fluid status, recent blood transfusion, or race\textsuperscript{19}. These factors were not accounted for in this study but underline the clinical importance of developing precision dosing guidelines to achieve effective pain control while decreasing the risk of adverse effects. Per weight dosing is typically used in neonates and, while some authors make further recommendations based on age\textsuperscript{2,10,11,18,20} this has not translated to changes in the clinical practice of dosing morphine. A strength of this study was the use of real life clinical patients and morphine dosing for post-operative analgesia. Only by studying patients as they actually receive morphine can the success or inadequacies of this dosing strategy can assessed.

While previous studies have demonstrated wide variations in morphine concentrations\textsuperscript{18} this is the only study that quantifies how often this variability leads to sub- or supratherapeutic morphine exposure. Subtherapeutic concentrations can lead to inadequate analgesia, which is both inhumane and can subsequently influence development leading to the adverse consequences of neonatal pain\textsuperscript{21}. Increased morphine exposure, on the other hand, can lead to the unnecessary risk of adverse effects.

In this study the estimated clearance of $40.3 \text{ L/hr/(Wt/70kg)}^{0.75}$ was in the previously published range of morphine clearance changes for infants suggesting our infants behave similarly to other studied groups.
Bouwmeester et al.\textsuperscript{11} reported a total morphine clearance of 14.5 L/hr/(Wt/70kg)\textsuperscript{0.75} at birth rising to 71 L/hr/(Wt/70kg)\textsuperscript{0.75} in adults. In their discussion reanalyzing clearance data by standardizing to a 70 kg person with an allometric ¾ power model similar trends in improving clearance with maturation was seen (From Lynn et al.\textsuperscript{22} and McRorie et al.\textsuperscript{23} clearance ranged from 18.7 and 10.6 L/hr/(Wt/70kg)\textsuperscript{0.75} in the first week of life to 94.5 and 51.6 L/hr/(Wt/70kg)\textsuperscript{0.75} at six months of age, respectively). It was anticipated that clearance would increase with age although there have been inconsistencies as to which measure of age is best. Our data showed clearance was most correlated with postmenstrual age which has previously been used\textsuperscript{10} but other work correlates it with postnatal age\textsuperscript{22-26} or gestational age\textsuperscript{4,27,28}.

The inability to assess the target morphine exposure range and the routine use of higher morphine doses than the literature recommends are limitations of the study. We are unable to differentiate if apparent subtherapeutic exposure provides adequate analgesia or if supratherapeutic dosing leads to increased risks of adverse effects. It is possible that patients may vary in the target exposure based on type of surgery, time from surgery, differences in pain processing, and mu opioid receptor genetics. Future studies incorporating morphine pharmacodynamics (PD) and pharmacogenetics to better define the exposure-response relationship are needed. Also, in this single NICU study the standard intravenous morphine dosing regimen of 0.5 mg/kg per dose or 0.5 mg/kg/hr if initiating an infusion may have resulted in the majority of infants with exposures to morphine greater than the target range because the doses used are greater than usually recommended (see Table 2). The higher doses are based on clinical experience in a busy surgical NICU further exemplifying the need for a more evidence based dosing regimen.
To achieve precision dosing for morphine in the NICU a new strategy must be pursued. One such strategy could include calculating an initial dose using available population based PK models and using a measured morphine concentration as feedback into the model to refine the dosing regimen\textsuperscript{29,30}. This requires a readily available means to measure morphine to use in real time to incorporate into the PK-PD model. A similar strategy has been pursued to effectively and safely dose sirolimus in our NICU\textsuperscript{31}.

Identifying useful pain biomarkers allowing for titration of morphine could also be done but measuring pain in infants is challenging. Over 40 behavioral and physiological scales exist to assess neonatal pain, however, there is no consensus as to which pain scale to use or when an analgesic intervention is warranted\textsuperscript{32}. Brain oriented approaches including near-infrared spectroscopy\textsuperscript{33}, functional magnetic resonance imaging\textsuperscript{34}, and electroencephalogram\textsuperscript{35,36}, show promise to measure pain but additional research is still needed before they are brought into clinical practice. Pain PD marker research may help establish a morphine exposure-response relationship to assist in precision dosing\textsuperscript{13,37}.

**Conclusion**

In critically ill neonates receiving standard of care morphine dosing a large variability was noted in morphine concentrations which were frequently well outside of the proposed target range. This is reflective of the wide range of morphine clearance observed which cannot be explained by clinical factors alone. The large interpatient variability in morphine concentration suggests that dosing guidelines should be individualized in this population to optimize the response of morphine in neonates. Further pharmacometric analysis with PK-PD modeling and research to identify important predictive PK and pharmacogenetic factors to individualize morphine treatment is warranted.
### Tables and Figures

**Table 1: Patient Demographics and Clinical Data.** “Age” is the age of life in days for the infant on the date of the surgery or procedure using the birth date as day of life 0. “SS at 24 hr” indicates if a steady-state morphine exposure in the target range was achieved by 24 hours after surgery. If not, then “Exposure at 24 hr” indicates whether the exposure was above or below the target range. (GA: Gestational age at birth, VD: Volume of distribution, SS: Steady-state, CDH: Congenital diaphragmatic hernia, TEF: Tracheoesophageal fistula)

<table>
<thead>
<tr>
<th>GA</th>
<th>Age (days)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Procedure/Surgery</th>
<th>Clearance (L/h/(Wt/70kg)$^{0.75}$)</th>
<th>VD (L/kg)</th>
<th>SS at 24 hr?</th>
<th>Exposure at 24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>42</td>
<td>M</td>
<td>Hirschsprung's disease</td>
<td>Laparoscopic G-tube, mucus fistula revision</td>
<td>47.55</td>
<td>1.19</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>39</td>
<td>0</td>
<td>F</td>
<td>Pneumothorax</td>
<td>Chest tube insertion</td>
<td>7.67</td>
<td>1.29</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>38</td>
<td>57</td>
<td>F</td>
<td>Left CDH, feeding difficulties, GERD</td>
<td>Open Nissen fundoplication, extensive lysis of adhesions</td>
<td>49.84</td>
<td>1.74</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>39</td>
<td>11</td>
<td>M</td>
<td>Hirschsprung's disease</td>
<td>Laparoscopic resection</td>
<td>43.17</td>
<td>1.75</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>37</td>
<td>0</td>
<td>M</td>
<td>Gastrochisis</td>
<td>Primary closure of abdominal wall</td>
<td>37.51</td>
<td>1.97</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>37</td>
<td>7</td>
<td>M</td>
<td>Gastrochisis</td>
<td>Lysis of adhesion, secondary closure of gastrochisis defect</td>
<td>37.51</td>
<td>1.97</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>39</td>
<td>1</td>
<td>F</td>
<td>Complex anorectal malformation</td>
<td>Placement vaginostomy drain, colostomy, mucus fistula</td>
<td>14.37</td>
<td>1.15</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>38</td>
<td>11</td>
<td>M</td>
<td>Left CDH</td>
<td>Exploratory laparotomy, wound closure, removal of duomesh patch, repair of enterotomy</td>
<td>45.82</td>
<td>3.75</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>37</td>
<td>0</td>
<td>M</td>
<td>Left CDH</td>
<td>Repair of left CDH with transversus abdominis muscle flap</td>
<td>16.91</td>
<td>1.55</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>37</td>
<td>15</td>
<td>M</td>
<td>Left CDH</td>
<td>Exploratory laparotomy, Ileo-colonic stricturoplasty</td>
<td>205.3</td>
<td>2.77</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>35</td>
<td>106</td>
<td>M</td>
<td>Gastrochisis, bowel dysmotility</td>
<td>Exploratory laparotomy, Ileo-colonic stricturoplasty</td>
<td>205.3</td>
<td>2.77</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>25</td>
<td>148</td>
<td>F</td>
<td>Subglottic stenosis</td>
<td>Laryngotraceoplasty</td>
<td>30.9</td>
<td>2.61</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>41</td>
<td>1</td>
<td>M</td>
<td>Ileal atresia with volvulus and perforation</td>
<td>Resection of ileal atresia</td>
<td>15.76</td>
<td>1.63</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>41</td>
<td>3</td>
<td>M</td>
<td>Bowel obstruction</td>
<td>Lysis of adhesions, placement of silo</td>
<td>15.76</td>
<td>1.63</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>41</td>
<td>6</td>
<td>M</td>
<td>Ileal atresia</td>
<td>Ex-laparotomy</td>
<td>15.76</td>
<td>1.63</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>37</td>
<td>2</td>
<td>M</td>
<td>Sacrococcygeal teratoma</td>
<td>Excision of sacrococcygeal teratoma</td>
<td>15.49</td>
<td>1.87</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>37</td>
<td>14</td>
<td>F</td>
<td>Left CDH</td>
<td>Repair of CDH with transversus abdominis muscle flap</td>
<td>8.08</td>
<td>1.8</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>M</td>
<td>Esophageal atresia with distal</td>
<td>Right thoracotomy with repair of esophageal atresia and TEF ligation</td>
<td>4.28</td>
<td>11.78</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>TEF</strong></td>
<td>Placement of chest tube</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
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<td></td>
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</tr>
<tr>
<td>17</td>
<td>Tracheal pouch</td>
<td>Cautery of tracheal pouch, tisseel injection of tracheal pouch</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>141</td>
<td>M</td>
<td>Distal TEF, tracheal stenosis</td>
<td>Tracheoesophageal fistula repair</td>
<td>92.5</td>
<td>1.74</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>37</td>
<td>1</td>
<td>M</td>
<td>TEF</td>
<td>TEF repair, open approach</td>
<td>18.3</td>
<td>3.41</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Pneumothorax</td>
<td>Chest tube insertion</td>
<td>No</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Pneumothorax</td>
<td>Chest tube insertion</td>
<td>No</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>26</td>
<td>80</td>
<td>M</td>
<td>Colonic strictures</td>
<td>Ex-lap with extended right hemicolecystomy</td>
<td>67.77</td>
<td>5.52</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>34</td>
<td>108</td>
<td>M</td>
<td>Pierre Robin syndrome</td>
<td>Bilateral mandibular osteotomies with placement of external distractors</td>
<td>45.52</td>
<td>1.74</td>
<td>No</td>
<td>High</td>
</tr>
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<td>34</td>
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<td>F</td>
<td>Gastroschisis</td>
<td>Gastroschisis closure</td>
<td>21.5</td>
<td>4.36</td>
<td>No</td>
<td>Low</td>
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</tbody>
</table>
Table 2: Neonatal Morphine Dosing Recommendations from the Literature. Recommended doses are typically less than the intermittent dose of 0.05 mg/kg or maintenance dose of 0.05 mg/kg/hr used in the study NICU.

<table>
<thead>
<tr>
<th>Study</th>
<th>Loading Dose (mg/kg)</th>
<th>Maintenance Dose (mg/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koren et al., (1985)³⁸</td>
<td>0.05-0.1</td>
<td>Not to exceed 0.015</td>
</tr>
<tr>
<td>Chay et al., (1992)¹⁵</td>
<td>0.25 over 100 min</td>
<td>0.0225</td>
</tr>
<tr>
<td>Saarenmaa et al., (2000)⁴</td>
<td>0.14 over 2hr</td>
<td>0.02</td>
</tr>
</tbody>
</table>
| Lynn et al., (2000)²⁵     |                      | Non-cardiac Cases: 0-7 days: 0.01  
                          |                      | 8-30 days: 0.015  
                          |                      | 31-90 days: 0.02  
                          |                      | 91-180 days: 0.025  
                          |                      | Cardiac surgery: 0-7 days: 0.005  
                          |                      | 8-30 days: 0.005  
                          |                      | 31-90 days: 0.01  
                          |                      | 91-180 days: 0.015  
| Bouwmeester et al. (2003)²⁰|                      | For non-cardiac cases:  
                          |                      | Birth: 0.007  
                          |                      | > 4wk: 0.01  
| Bouwmeester et al. (2003)¹⁸| For non-cardiac cases: < 7 days: 0.05  
                          | For non-cardiac cases: < 7 days: 0.005-0.01  
                          | For non-cardiac cases: > 7 days: 0.01  
| Bouwmeester et al. (2004)¹¹|                      | Birth: 0.005  
                          |                      | 1 month: 0.0085  
                          |                      | 3 months: 0.0135  
| Knibbe et al. (2009)²     | <10d: 0.05            | 0.01mg/kg¹⁵/hr              
                          | >10d: 0.1             |                             |
Figure 1: Morphine Clearance Plotted Across Postmenstrual Ages. A weak positive correlation is revealed when the allometrically scaled clearance is related to postmenstral age.
References


