Heart rate variability as an indicator for morphine pharmacokinetics and pharmacodynamics in critically ill newborn infants

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Abstract - **Morphine is the commonest drug used for analgesia in newborn infants. It is a natural opioid that acts as an agonist at the mu and kappa receptors, which are receptors for analgesia and sedation. Morphine pharmacokinetics and pharmacodynamics (PKPD) for the newborn infant population are not well understood. The objective of this study is to use morphine PKPD parameters to estimate morphine plasma concentrations to be correlated with heart rate variability in the neonatal population.**

I. Introduction

Morphine is one of the common opioids used in premature infants for management of pain. In 2006, the American Academy of Pediatrics and the Canadian Paediatric Society updated their statement "Prevention and Management of Pain in the Neonate" by recommending against the use of morphine, midazolam or fentanyl in chronically ventilated preterm neonates because of their short-term adverse effects and the lack of knowledge of long-term outcome data [1]. This lack of knowledge is not limited to the long-term outcome but also to the pharmacokinetics/pharmacodynamics phases of the drugs in the preterm infant.

The pharmacokinetics can be described as "what the body does to the drug" and Pharmacodynamics as "what the drug does to the body". There is still a lack of knowledge about the pharmacodynamics of morphine in the neonatal population and it is poorly described in the modern literature. Recently Anand et al used heart rate and the Premature Infant Pain Profile (PIPP) [2] in an attempt to describe the action of the drug in the body [3]. The study showed that pain was unrelated to morphine concentration when measured by PIPP and/or heart rate highlighting the relevance of a reliable pain score.

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An 'inappropriate' drug therapy could result in increased adverse effects and toxicity for the preterm infant. An inappropriate dose of morphine may inhibit breathing, depress the central nervous system, damage immature kidneys thus increasing the risk of renal failure in adulthood, and cause gastrointestinal immobility, urinary retention and seizures. The study of morphine's dynamics may provide a better understanding of the pain/stress scenario as well as a better approach for the titration of drugs to avoid overdoses, hyperalgesia episodes and irreversible neurological damage for the premature infant.

The object of this study is to use morphine PKPD parameters to estimate morphine plasma concentrations and correlate with heart rate variability in the neonatal population.

This manuscript is organized as follows: section II reviews pharmacokinetic and pharmacodynamic modeling and heart rate variability (HRV). Section III describes the methodology used to perform the experiment including: PKPD implementation; HRV; and nonparametric fitting methods. Section IV analyses the results of the findings and section V presents the conclusions based on the results.

II. Background

Scientists have been modeling morphine for the past 40 years. The neonatal population is one of the last groups to be studied as a result of the ethical issues surrounding the development of PKPD models.

Anand et al developed a morphine pharmacokinetic and pharmacodynamic model for preterm and term neonates [3]. The authors designed a two-compartment model (central and total body clearance) with a third compartment for effect-site concentration. Heart rate and the Premature Infant Pain Profile (PIPP) were used as pharmacodynamic markers. The results demonstrated that weight and age were the main covariates with maturational changes in the morphine clearance between 23 and 32 weeks of gestational age (GA) with a higher volume of distribution in preterm neonates than in term neonates. These findings placed age and weight as the two main covariates in the neonatal PKPD modelling. However, no correlation was found with heart rate and/or PIPP to characterize the biophase.

The most recent morphine model for neonates was written by Krekels [4]. The authors developed a four compartmental model composed of a central

compartment; a peripheral compartment; morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) compartments. The birth weight was considered the only covariant in the model. The results demonstrated that glucuronidation and elimination clearance of morphine glucuronides are well described by a bodyweight-based model. The authors highlighted that dosing of morphine could be made based on its effective target and its metabolic concentration.

Considering Anand's and Krekels' recent findings this study will use a four-compartment model to estimate morphine concentrations in the neonatal population. The central nervous system (CNS) represents the effect-site organ for opioids and the effect-site concentration describes the clinical effect of the drug in the PKPD model.

The common use of morphine in Neonatal Intensive Care Units (NICU) is due to its analgesic action. The modern multidimensional pain scores PIPP [2], the Bernese Pain Scale (BPSN) [5], and CRIES (C-crying; R-requires increase oxygen administration; I-Increased vital signs; E-expression; S-sleeplessness) [6] among several others scores use heart rate as the main physiological indicator to describe pain.

Anand et al.'s pharmacodynamic study considered heart rate as the immediate surrogate for the clinical effect of morphine. However, the author did not consider morphine metabolites separately. M6G is a potent opioid agonist contributing in morphine pharmacodynamics and sub consequently analgesic effects, while M3G is the antagonist of some effects of morphine may leading to hyperalgesia [7]. A recent study from Araout et al. hypothesized that M3G hyperalgesia is distinct from the morphine-induced phenomenon in mice. The results demonstrated CNS locus for M3G activity [8].

The present study will benefit from Krekels et al.'s pharmacologic model with compartments for M6G and M3G and will analyze the biophase by exploring the correlation between the morphine metabolites' compartments and heart rate.

Heart rate will be analyzed applying McGregor et al.'s heart rate variability method [9]. McGregor studied the correlation between heart rate and late onset neonatal sepsis (LONS) applying the variability calculation used in stream computing programming. The results demonstrated that low HRV is correlated with LONS. However, the authors showed that low HRV alone was inadequate to distinguish patients with infection or patients receiving analgesics.

The primary objective of this study is to evaluate the relationship between estimated morphine plasma concentrations and heart rate in the neonatal population. The better understanding of morphine's dynamics may lead to significant changes in dosing recommendation for newborn infants and thus significant improvements in patient care and safety.

III. Methods

A. Pharmacokinetics/Pharmacodynamics Modeling

A four compartmental model structure was used to implement Krekels et al.'s pharmacokinetic parameters for morphine [4]. Volume 1 represents the central compartment; volume 2 represents the peripheral compartment; volume 3 represents M3G and morphine antagonizing effect; and volume 4 represents M6G and the pain-relieving effect of morphine. The concentration in the fourth compartment is used for correlation with HRV. The PKPD model was programmed with differential equations in discrete time. The four compartmental model can be described by the following differential equations (1, 2, 3, 4):

$$\frac{\partial \mathrm{M_1(t)}}{\partial \mathrm{t}} = -(k_{12} + k_{13} + k_{14}) \cdot M_1(t) + k_{21} \cdot M_2(t) + I(t) \quad (1)$$

$$\frac{\partial \mathrm{M_2(t)}}{\partial \mathrm{t}} = k_{12} \cdot M_1(t) - k_{21} \cdot M_2(t) \quad (2)$$

$$\frac{\partial \mathrm{M_{3G}(t)}}{\partial \mathrm{t}} = k_{13} \cdot M_1(t) - k_{30} \cdot M_{3G}(t) \quad (3)$$

$$\frac{\partial \mathrm{M_{6G}(t)}}{\partial \mathrm{t}} = k_{14} \cdot M_1(t) - k_{40} \cdot M_{6G}(t) \quad (4)$$

System 1 – PKPD differential equations.

M1, M2, M3G and M6G are the mass in the respective compartments described by Krekels et al., where k_{ij} are model parameters, and I is the infusion rate in ml/h.

Based on these equations the system was modeled by state space method, as follows:

$$\frac{\partial X(t)}{\partial t} = A \cdot X(t) + B \cdot I(t) \quad (5)$$

$$C_p(t) = C \cdot X(t) \quad (6)$$

$$C_e(t) = C_p(t) \cdot (1 - e^{-k_{e0} \cdot t}) \quad (7)$$

Where:

$$A = \begin{bmatrix} -(k_{12} + k_{13} + k_{14}) & k_{21} & 0 & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{30} & 0 \\ k_{14} & 0 & 0 & -k_{40} \end{bmatrix} \quad (8)$$

$$B = \begin{bmatrix} \frac{1}{V_1} \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (9) \qquad C = [1 \quad 0 \quad 0 \quad 0] \quad (10)$$

$$D = \begin{bmatrix} C_1(t) \\ C_2(t) \\ C_3(t) \\ C_4(t) \end{bmatrix} \quad (11)$$

Where C_p is plasma concentration and C_e is the effect-site concentration.

The algorithm considers model parameters in a discrete time system. The Zero-Order-Hold method was used as the continuous-discrete conversion. The output of the discrete state space function is used to estimate concentrations every 10 seconds. In this study the input is a constant infusion and no titration scheme was used.

The bodyweight and clearances were calculated using an allometric equation with a scaling factor (K) of 1.44. This study used GA and postnatal age (PNA) to establish the premature infant weight in the allometric equation to be used in the PKPD model as shown in Figure 1.

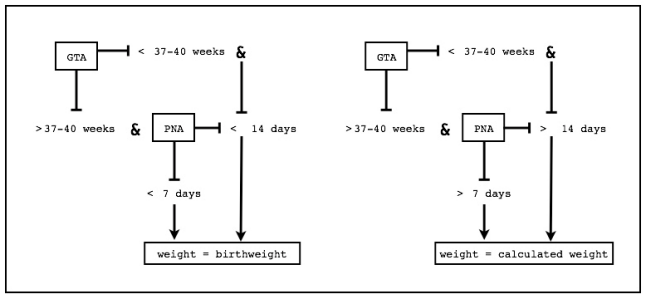

Figure 1 – Gestational Age Algorithm diagram

PKPD data was synchronized with physiological data acquired through an intelligent data environment, known as Artemis. Artemis is a computational platform operational in the NICU at The Hospital for Sick Children, Toronto, Canada since August 2009 [10]. This platform acquires real-time data from multiple bedside monitors such as heart rate (HR), blood oxygen saturation (SpO_2), electrocardiogram (ECG) and respiratory rate (RR). The PKPD algorithm was implemented using IBM® Streams Processing Language (SPL) in Artemis. The PKPD model is a sub-entity of Artemis's deployed as a simulator tool.

B. Heart Rate Variability

McGregor et al. developed a method to quantify HRV deployed in Artemis for the detection of late onset neonatal sepsis. The HRV is calculated by taking the absolute value of the difference between two consecutive minute spot reading time points minute by minute and summarizing this behavior in hourly abstractions. When the threshold is increased, the number of minutes of low variability will increase, as this corresponds to a looser criterion for variability. The threshold used in this study was determined via statistical analysis in that prior study. HRV was calculated based on the number of minutes of high variability per hour for the entire duration of the patient's NICU duration [9].

C. Nonparametric Fitting

A biharmonic-type interpolation method was performed using MatLab® to solve a 3D scattered data interpolation problem. The biharmonic spline interpolation is based on Green's function commonly used for its high precision, simplicity and flexibility [11]. Green's function is an integral kernel used to solve inhomogeneous differential equations with boundary conditions.

This study considers estimated morphine concentration, GA, weight and HRV as the scattered data. Two groups with 12 subjects each were used to design the curve response.

One group was used to design the fitting curve that estimates the values as part of the exploratory data mining phase to describe the correlation between morphine concentration, GA and HRV. A second group was used as validation data group as part of the explanatory/confirmation data mining phase.

Newborn infants admitted to the Neonatal Intensive Care Unit (NICU) at The Hospital for Sick Children, Toronto, Canada, who were enrolled in an institutional Research Ethics Board approved study of neonatal infection and who received morphine for analgesia were enrolled in this study.

IV. Results

Twenty-four newborn infants admitted to the NICU, gestational age 24-41 completed weeks (mean ± SD: 33.25 ± 5.42) and birth weight 700-3300 grams (mean ± SD: 2440 ± 910), were studied under morphine concentrations at 100ug/ml, 80ug/ml, 40ug/ml, 20ug/ml. Figure 2 shows mean HRV and estimated morphine concentration of the population in this study.

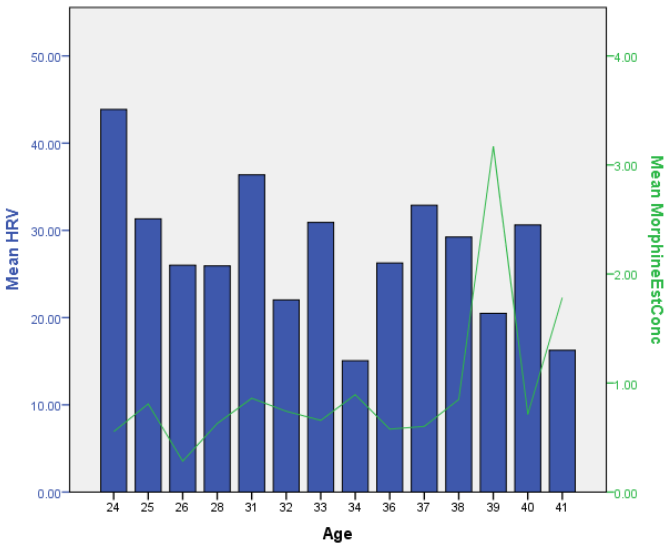

Figure 2 – HRV vs. Morphine Estimated Concentration vs. Neonatal Gestational Age Range

In the first analysis estimated morphine concentration, weight and HRV were considered as scattered data. The results demonstrated correlation between estimated morphine concentration and weight, validating Krekels et al.'s findings. Analyzing the surface in figure 3, the higher the morphine estimated concentration the lower the HRV. This result may suggest cardiovascular depression with higher morphine doses.

In figure 3, moderate to late preterm neonates [12] (GA: 32-36 weeks) represented by black dots, were described by the surface, while extremely and very preterm neonates (GA: 23-31) represented by green dots, were represented outside of the surface.

In the second analysis estimated morphine concentration, GA and HRV were considered as scattered data, as follows in figure 4. The results demonstrated a correlation between GA and estimated morphine concentration. However, when the GA range was between 28 and 24 weeks the result did not presented a surface to describe the correlation. Considering GA, the results demonstrated that the higher the estimated morphine concentration the lower the HRV.

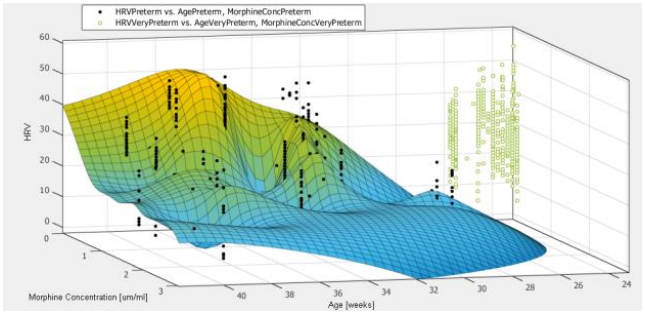

Figure 3 – HRV vs. estimated morphine concentration vs. weight

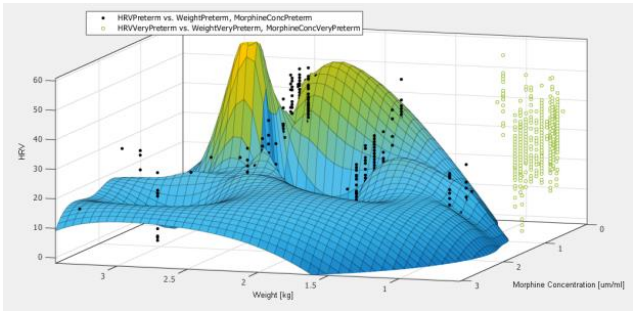

Figure 4 – HRV vs. estimated morphine concentration vs. Gestational Age

V. Discussion

This study questioned the hypothesis of heart rate being an immediate surrogate for the clinical effect of morphine in the neonatal population.

The parameter set from Krekels et al.'s model was considered in a four compartmental model. Estimated morphine concentration by the M6G compartment was used in the analysis of heart rate variability using the method by McGregor et al [9].

The results demonstrated that a correlation between HRV and estimated morphine concentration could be described by a surface designed by the biharmonic interpolation method. Age and weight proved to be the most reliable covariates for a future PD model.

The subjects considered moderate to late preterm were described by a biharmonic surface while the extreme and very preterm subjects could not be described by the model. However it is important to highlight that the extreme and very preterm subjects were represented in their own cluster. This pattern suggests that a specific model and/or surface for extreme and very preterm neonates must be explored.

This study aimed to explore the relationship between physiological variables, drug dosing and clinical effect, however, only a properly designed PD experiment will finally elucidate and overcome the questions about morphine's dynamic behavior in the neonatal population. Further studies are required. In future work we will report on studies we have commented in this area.

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