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Pharmacokinetic models of morphine and its metabolites in neonates: Systematic comparisons of models from the literature, and development of a new meta-model

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ABSTRACT

Morphine is commonly used for pain management in preterm neonates. The aims of this study were to compare published models of neonatal pharmacokinetics of morphine and its metabolites with a new dataset, and to combine the characteristics of the best predictive models to design a meta-model for morphine and its metabolites in preterm neonates. Moreover, the concentration-analgesia relationship for morphine in this clinical setting was also investigated.

A population of 30 preterm neonates (gestational age: 23–32 weeks) received a loading dose of morphine (50–100 μg/kg), followed by a continuous infusion (5–10 μg/kg/h) until analgesia was no longer required. Pain was assessed using the *Premature Infant Pain Profile*. Five published population models were compared using numerical and graphical tests of goodness-of-fit and predictive performance. Population modelling was conducted using NONMEM® and the $PRIOR subroutine to describe the time-course of plasma concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide, and the concentration-analgesia relationship for morphine.

No published model adequately described morphine concentrations in this new dataset. Previously published population pharmacokinetic models of morphine, morphine-3-glucuronide, and morphine-6-glucuronide were combined into a meta-model. The meta-model provided an adequate description of the time-course of morphine and the concentrations of its metabolites in preterm neonates. Allometric weight scaling was applied to all clearance and volume terms. Maturation of morphine clearance was described as a function of postmenstrual age, while maturation of metabolite elimination was described as a function of postnatal age. A clear relationship between morphine concentrations and pain score was not established.

1. Introduction

Preterm neonates of low birth weight experience significant pain and stress during their stay in the neonatal intensive care unit (Canadian Paediatric Society, 2000; Johnston and Stevens, 1996; Simons et al., 2003). The physiological instability and underlying diseases of these infants necessitates advanced perinatal care. Different factors such as mechanical ventilation, invasive procedures, postoperative issues, and acute medical illness due to prematurity (Bhalla et al., 2014) may be responsible for pain in this vulnerable population. Morphine is the main analgesic used for pharmacological pain relief in preterm neonates (Chay et al., 1992). However, the response to morphine is highly variable and difficult to predict, so optimal analgesia remains a challenge (Carbajal et al., 2005; Tibboel et al., 2005).

Neonatal pharmacokinetics is affected by developmental aspects of morphine metabolism and excretion, particularly maturation of organ function, and variability in body size (Alcorn and McNamara, 2002; de Wildt et al., 1999; van den Anker, 1996). The major metabolic pathway of morphine is the formation of morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Changes in enzyme systems and decreased hepatic function causes a reduced glucuronidation capability

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in preterm neonates (Choonara et al., 1989). Reduced glomerular filtration rate and impaired renal function also affects morphine pharmacokinetics and especially the excretion of metabolites (Choonara et al., 1989). These rapid changes in body composition and renal function results in extensive inter-individual and intra-individual variability in morphine exposure. This makes the prediction of morphine concentrations after a given dose a challenge, and therefore makes it difficult to achieve a desired target concentration.

The effects observed after morphine administration are primarily due to μ-opioid receptor activation. The active morphine metabolite, M6G, is also a μ-opioid receptor agonist and is believed to contribute to analgesia (Kilpatrick and Smith, 2005). No significant signs of pharmacological activity have been shown for M3G in humans (Penson et al., 2001). The concentration-response relationship for morphine used in acute pain in preterm and term neonates is however still not characterised (Anand et al., 2008; Anderson and van den Anker, 2014; Tibboel et al., 2005).

In recent years, several studies have examined variability and maturational effects to increase our understanding of morphine pharmacokinetics in paediatrics (Anand et al., 2008; Bouwmeester et al., 2004; Knibbe et al., 2009; Wang et al., 2013). However, as far as we know there are currently no models that capture the antenatal maturation of morphine clearance separated from size-related factors, and describe metabolite pharmacokinetics in preterm neonates at the same time. Based on a new dataset from preterm neonates receiving morphine on clinical indication, collected in two neonatal intensive care units (NICU) over 5 years, the aims of the current study were to compare the observed concentrations of morphine and its metabolites with the predictions based on the currently existing published models, to investigate if the new data would result in an update of currently described parameters, and to combine the characteristics of the best models to propose a meta-model that is able to describe the new data. Moreover an attempt to describe the analgesia-concentration relationship for morphine was planned.

2. Methods

2.1. Study design

The current study used data from a clinical trial conducted at the Children's National Health System, Washington DC, and the Kosair Children's Hospital, Louisville, KY, USA. Thirty preterm neonates were enrolled in the study from December 2005 to June 2009. The original proposal was designed with the goal to enroll 60 neonates but despite multiple efforts including adding other clinical site, only 30 neonates were enrolled. Subjects received morphine as part of their routine medical management of pain. The inclusion criteria were neonates with a gestational age (GA) at birth from 22 to <32 weeks, a postnatal age (PNA) of <30 days, an indwelling arterial line already in place for clinical purposes, and a clinical indication for receiving intravenous (IV) morphine with an anticipated therapy for at least 24 h. Neonates who received morphine prior to the study were eligible for enrolment. The exclusion criteria were neonates with severe asphyxia, serious intraventricular haemorrhage, major congenital/facial malformations, neurological disorders, and neonates with clinical or biochemical evidence of hepatic and/or renal failure. Neonates who were receiving continuous or intermittent neuromuscular blockers and had received drugs that were UGT2B7 substrates were also excluded.

2.1.1. Study medication

The study drug was morphine sulphate. Neonates with a gestational age of <29 weeks received a 30-minute IV loading infusion of 50 μg/kg at time of study enrolment. This loading dose was immediately followed by a continuous IV infusion of 5 μg/kg/h as a maintenance dose. Neonates with a gestational age of 29 weeks or more received a 100 μg/kg loading infusion and a continuous infusion of 10 μg/kg/h as a maintenance dose. Decisions to administer additional breakthrough doses of morphine (30-minute IV bolus dose of 50 μg/kg) or to discontinue the morphine infusion were made at the neonatologist's discretion. The total duration of the study for each infant was dependent on the duration of the continuous infusion.

2.1.2. Blood samples

Sampling started at time of enrolment, and 200 μL blood was drawn at each predetermined blood sampling time point. The first PK sample was drawn just before the administration of a loading dose, and subsequent PK samples were scheduled at 1, 4, 8, 12, 24, 48, 72, and 96 h after study enrolment. One additional sample was collected 24 h after morphine discontinuation. If doses for breakthrough pain were given, an additional PK sample was collected just before the additional morphine administration. Morphine, M3G, and M6G were quantitated in plasma, using a validated HPLC-MS/MS method (Meng et al., 2000). The analysis of the samples was carried out at the Paediatric Pharmacology Research Unit of the University of Utah.

2.1.3. Pain assessment

At each of the scheduled blood sampling time points (t = baseline, 1, 4, 8, 12, 24, 48, 72, and 96 h), each subject was videotaped by a whole-body camera and a separate camera focused on their face. Neonatologists scored each patient's pain using the videotapes and the *Premature Infant Pain Profile* (PIPP; Stevens et al., 1996). Each infant had continuous monitoring of vital signs, such as temperature, respiratory rate, blood pressure, heart rate, and oxygen saturation (SaO_2). The PK/PD analysis was performed on the PIPP score, and other components of the study will not be discussed.

2.2. Pharmacokinetic-pharmacodynamic modelling

An overview of the full modelling process can be found in Fig. 1. All steps in the modelling analysis are explained in detail in the following sections.

2.2.1. Software

The PK/PD analysis was performed using nonlinear mixed effects modelling. The population modelling process, simulations, and bootstraps were performed with NONMEM version VII, level 3.0 (Beal et al., 2009) using the Wings for NONMEM interface (http://wfn.sourceforge.net/) and Intel Fortran compiler. The first-order conditional estimation with interaction (FOCE-I) method in NONMEM was used for estimation of the population parameters. Individual parameter estimates were obtained using the Bayesian POSTHOC functionality of NONMEM. The ADVAN 13 subroutine in NONMEM was used for the PK/PD modelling. Raw data manipulation, processing of NONMEM output, visual representation of the data, and graphical outputs were performed using the R data analysis language, version 3.1.1 (R Development Core Team, 2014), with the ggplot2 (Wickham, 2009), doBy (Søren Højsgaard et al., 2014), plyr (Wickham, 2011), reshape2 (Wickham, 2007) and the npde (Comets et al., 2008) packages. Morphine sulphate doses and metabolite concentrations were converted to their morphine base equivalent after fitting in NONMEM using a conversion factor of 0.752 for morphine sulphate, and 0.618 for the two morphine glucuronides. Missing concentrations and pain score data were omitted from the analyses.

2.2.2. Literature models

Four previously published reports of population PK analyses of morphine in neonates (Anand et al., 2008; Bouwmeester et al., 2004; Knibbe et al., 2009; Wang et al., 2013) were selected to provide the basis for a systematic model comparison. The models were selected based upon a literature search, and by scanning reference lists of relevant articles for additional studies. The performance of these models and their suitability for simulation purposes was assessed in the current