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Systematic evaluation of pain in neonates: effect on the number
of intravenous analgesics prescribed

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Abstract Objective: To document the effect of systematic evaluation of pain in neonates on prescription of intravenous analgesics in a level-III neonatal intensive care unit (NICU) as a marker of increased awareness of treating and preventing pain.

Methods: Retrospective analysis of the number of yearly prescribed vials of intravenous analgesics in a level-III NICU during a period before (1996-1999) and after (2000 to August 2002) introduction of a multidimensional pain scale. Correction was carried out by multiple regression analysis for clinical co-variables (admissions, days on parenteral nutrition, days on respiratory support, surgical procedures), which also might explain changes in prescription of analgesics. Postoperative length (hours) of administration of analgesics was calculated in a group of infants (1996-2001) who all received cryotherapy for threshold retinopathy of prematurity (ROP) before (1996-1999) and since (2000-2001) introduction of pain evaluation.

Results: The number of yearly prescribed vials increased from $3140 \pm 619$ (mean $\pm$ SD) to $5915 \pm 675$ ($P < 0.005$).

There is also a significant increase in the number of surgical interventions ($P < 0.05$) but not in days on respiratory support, days on parenteral nutrition or in number of admissions. After correction for the number of surgical procedures, the increase in prescribed vials remained significant ($P < 0.05$). In infants who received cryotherapy, a significant increase in length of postoperative analgesia (65-107 h, $P < 0.01$) was documented. Even after correction for the increased postoperative length of ventilation, duration of postoperative analgesia remained significantly ($P < 0.05$) longer.

Conclusions: Systematic evaluation of pain increased awareness of treating and preventing pain in neonates, even after correction for clinical co-variables. This increase was not associated with an increase in potential side-effects (length of respiratory support, length of parenteral nutrition).

Keywords Analgesia · Assessment · Intensive care units

Introduction

Recognition and treatment of pain is an important indicator of quality of care delivered to patients [1]. Since the landmark publications of Anand in the late 1980s, the impact of adequate treatment of pain in neonates has also been well acknowledged [2, 3, 4, 5].

Systematic evaluation of pain likely improves awareness of the medical and nursing staff in optimising treatment, but a specific problem in neonates is objective assessment. We share this challenge in preverbal infants, with professionals taking care of severely mentally retarded, handicapped or comatose patients. Different pain scales have been developed and validated for the neonatal population as reviewed recently by us [6, 7].

To the best of our knowledge, this is the first study to examine the impact of the implementation of systematic evaluation of pain on prescriptive behaviour of analgesics in a level-III neonatal intensive care unit (NICU).
Changes in intravenous analgesics (number of vials) and prescription behaviour after cryotherapy (length of postoperative analgesia) before and after the implementation of a pain scale were used as quantitative markers.

Methods

Data collection

The NICU Gasthuisberg is a tertiary neonatal intensive and high care unit, taking care of both premature infants and infants with congenital malformations. Perinatal data of all infants admitted in the unit since 1 January 1996 were available in a prospectively collected database. Clinical variables (total number of admissions, number of extreme low birth weight (ELBW, i.e. <1000 g) infants, days of parenteral nutrition, days on respiratory support and number of surgical interventions) that might influence consumption of analgesics were extracted from this database. Days of respiratory support and days on parenteral nutrition were used as markers of severity of medical disease, at the same time serving as markers of potential side-effects of opioids. Data on the number and type of drugs administered were extracted from the hospital pharmacy database. Intravenous analgesics used and studied during this period (1996 to August 2002) were fentanyl, tramadol, piritramide and propacetamol. There were no major changes in the medical or nursing staff during this period, nor were there changes in the composition of the vials. Data were reported on a yearly basis after extrapolation of the data for 2002 based on the first 8 months.

We also investigated prescription (postoperative hours) of analgesics in a cohort of infants who received cryotherapy for threshold retinopathy of prematurity (ROP) before and since systematic pain evaluation became the standard of care. Data on relevant co-variables (birth weight, weight at surgery, postoperative ventilation) were collected. Since laser therapy was introduced as the preferred treatment for retinal surgery in January 2002, only the period from 1996 to the end of 2001 was analysed [8].

Development and implementation of the Leuven neonatal pain scale

Based on literature and after discussion within the medical and nursing staff, a multi-dimensional pain scale was developed with seven items (sleep, facial appearance, crying, heart rate, motor tone, movement and consolability). Each variable was graded 0, 1 or 2 points, resulting in a maximal score of 14. After a preliminary trial during the direct postoperative period (n = 10), infants admitted to the NICU were scored simultaneously by two caregivers (n = 628 observations), blinded for each other. A strong inter-observer correlation (r = 0.88) was observed with a cut-off point of 6 or above for infants in pain as used in the algorithm. We further validated this pain score during endotracheal aspiration (n = 10), where we could demonstrate marked correlation (r = 0.8) between increase in pain score and increase in serum catecholamines. Implementation in daily nursing care was achieved after all caregivers attended a training session during which the pain scale was introduced together with observations in the unit [9].

Standard analgesia protocol (therapeutic algorithm)

Analgesic treatment in post-surgical, ventilated infants was provided by continuous intravenous administration of fentanyl, 3 μg/kg/h (0.3 mL/h) after a loading dose (3-5 mg/kg IV bolus) was administered before transfer to the unit. Within 24 h, treatment with intravenous tramadol (5 mg/kg per day; 0.3 mL/h) in combination with propacetamol (4×10–20 mg/kg per day) was initiated to decrease fentanyl needs and to enable weaning. In post-surgical, non-ventilated infants, analgesia was provided by continuous administration of tramadol (5 mg/kg per day; 0.3 mL/h), while propacetamol (an intravenous pro-drug of paracetamol) (4×10–20 mg/kg per day) was administered as additional treatment. Continuous perusions were increased by 0.1 mL/h if the pain scale was above 5 and decreased by 0.1 mL/h if the pain scale remained below 4 for at least 6 h. All continuous perusions were changed every 24 h. In non-surgical infants, treatment was initiated if the pain score was above 5 by continuous fentanyl or tramadol administration in the same dose as mentioned above. Perusions were adapted based on the same step-up/step-down as in surgical infants. The initial dose of fentanyl and propacetamol used in our study were in line with reports in literature while tramadol administration was extrapolated from data in infants and children [5, 10, 11, 12, 13]. Before introduction of the pain scale, administration and adaptation of analgesics were based on the subjective impression of the attending physician, but the same medications were used.

Statistics

All variables are reported on a yearly basis by mean and standard deviation (SD) in the period before (1996-1999) and since (2000 to August 2002) implementation. The student t-test was used in a univariate approach to compare both periods. ANOVA (MedCalc) was used for all clinical variables studied with an additional variable (pain score used or not during a given year) as factor. All significant co-variables were entered in a multiple regression model (MedCalc) to correct the trend in the number of prescribed vials of analgesics. The same approach was used to study prescriptive behaviour after cryotherapy (1996-2001).

Results

The mean number of yearly prescribed vials of intravenous analgesics before implementation (1996-1999) was 3140±619 (mean ± SD). Since introduction of the pain scale, mean number of yearly prescribed vials increased to 5915±675 (P<0.005). Mean yearly number of opioid vials prescribed increased from 1473±395 to 2819±534 (P<0.05), while mean number of propacetamol vials increased from 1667±294 to 3096±434 (P<0.05).

Mean yearly number of fentanyl vials increased from 908±241 to 1394±345 (P<0.05). There was no significant increase in days on respiratory support, in the number of admissions or in the number of ELBW infants admitted or in days of parenteral nutrition. There was a significant increase in the number of surgical procedures (P<0.05, Table 1).

Table 1 Mean and standard deviation of all variables studied. Data are reported on a yearly basis. Data for 2002 were extrapolated based on the first 8 months

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Total number of vials</td>
<td>3140 (619)</td>
<td>5915 (675)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Vials of opioids</td>
<td>1477 (398)</td>
<td>2483 (748)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vials of fentanyl</td>
<td>608 (241)</td>
<td>1294 (345)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vials of propacetamol</td>
<td>1663 (290)</td>
<td>3096 (722)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Number of admissions</td>
<td>532 (6)</td>
<td>596 (56)</td>
<td>NS</td>
</tr>
<tr>
<td>ELBW infants (&lt;1000 g)</td>
<td>40 (2)</td>
<td>40 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Surgical interventions</td>
<td>128 (15)</td>
<td>149 (6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Days on parenteral nutrition</td>
<td>1389 (530)</td>
<td>7331 (297)</td>
<td>NS</td>
</tr>
<tr>
<td>Days respiratory support</td>
<td>5073 (594)</td>
<td>3548 (406)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 2: Clinical characteristics in infants who received cryotherapy for retinopathy of prematurity in two consecutive periods: before (1996–1999) and since (2000–2001) introduction of systematic evaluation by pain scale. Results expressed by mean and standard deviation or incidence.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of infants</td>
<td>30</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>25.1 (1.3)</td>
<td>25.9 (2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight at birth (g)</td>
<td>764 (188)</td>
<td>686 (185)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Postnatal age at surgery (days)</td>
<td>62.5 (14.5)</td>
<td>63.1 (18)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight at surgery (g)</td>
<td>1703 (340)</td>
<td>1393 (239)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Duration of postoperative analgesia</td>
<td>65 (19)</td>
<td>107 (32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of postoperative opioids</td>
<td>50.5 (32)</td>
<td>71 (30)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Duration of ventilation (h)</td>
<td>25 (17)</td>
<td>35 (20)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Using ANOVA, with presence or absence of the pain scale in a given year as factor, the number of vials (P = 0.005) and the number of surgical procedures (P = 0.05) were significantly higher during the second period, while all other clinical variables were not. Even after correction for the increase in surgical procedures, the increase in the number of vials prescribed remained significant (P < 0.05).

Cryotherapy for threshold ROP was performed in 42 infants during the studied period (1996–1999 = 30 and 2000–2001 = 12). Length of postoperative analgesia was 65 ± 19 h and increased to 107 ± 32 h (P < 0.01) after systematic pain evaluation was introduced. The same trend was documented if only opioids were considered: 71 ± 30 h versus 50.5 ± 32 h (P < 0.005). There were no significant differences in gestational age at birth and postconceptional age at surgery. Weight at birth (P < 0.01) and weight at surgery (P < 0.03) were significantly lower, and postoperative ventilation was significantly longer in the second group (P < 0.005, Table 2). Using ANOVA, with presence or absence of pain score as factor, length of any analgesic treatment and opioids administered (both P = 0.001) and length of postoperative ventilation (P = 0.005) increased significantly. After correction for ventilation, weight at surgery and birth weight, pain score remained a significant independent variable (P < 0.05) to explain the trend in the number of prescribed vials.

Discussion

To the best of our knowledge, this is the first study to examine the impact of the implementation of systematic evaluation of pain on prescriptive behaviour of analgesics in a level-III neonatal intensive unit.

Change in the number of analgesics prescribed was used as marker of improved awareness to treat and prevent pain. A significant increase in the vials used after introduction of systematic evaluation was documented. This increase was significant for all opioid vials, for fentanyl vials and also for propacetamol vials, reflecting an overall increase in consumption of intravenous analgesics. This change in prescriptive behaviour was also documented in a cohort of infants after a specific surgical procedure (cryotherapy), where a significant increase in duration of postoperative analgesia was documented.

There are overwhelming data in the literature supporting the relevance of adequate analgesia after surgery in neonates [2, 3, 4, 5]. Adequate postoperative analgesia is mandatory, even if this might prolong ventilation while in non-surgical, mostly premature infants, there is still debate whether adequate analgesia and/or sedation are mandatory [12, 13, 14, 15]. In the NOPAIN trial, pre-emptive analgesia by continuous low-dose morphine infusion (loading dose 100 μg/kg, maintenance dose 10–30 μg/kg/h) was well tolerated in ventilated pre-terms [14]. There was a (non-significant) trend in reduction of the incidence of poor neurological outcome in infants on morphine, likely based on reduction of fluctuations of blood pressure, decreased stress hormones, improved oxygenation and improved ventilator synchrony. The same trend was documented in a randomised placebo-controlled trial of fentanyl (0.5–2 μg/kg/h) infusion in pre-term infants with hyaline membrane disease [15]. Based on these and other studies, pre-emptive analgesia in ventilated infants is considered the standard of care in most neonatal units [5]. In this study, we could illustrate that systematic evaluation increased consumption of analgesics, without significant increase in respiratory support, in line with reports in the literature [14, 15]. Systematic evaluation by validated pain scale is mandatory in order to objectify the prescriptive behaviour. In addition to making prescriptions more objective, it might also improve awareness to treat and prevent pain as we illustrated in this study. This might not only be relevant in neonates and infants, but also in other groups of non-verbal (comatose, severely mentally retarded) patients. The risk of undertreatment of pain in non-verbal patients was recently illustrated in an adult intensive care population [16]. If pain is not measured, it’s easy to ignore it.

Propacetamol is an intravenous pro-drug of paracetamol. There are still very few data of this specific drug in neonates. Although paracetamol itself is frequently used for neonatal analgesia, especially after surgery [17]. During the period studied, doses administered were based on the report of Autret et al. [10]. Bypassing drug absorption variability and better accuracy of dose using an intravenous formula when compared with rectal or oral administration might improve effectiveness and predictability of its effects in ill neonates. Therefore, pharmacokinetics and dynamics of the specific intravenous formula should be studied in neonates.

Although prescription of intravenous analgesics was used as marker in this study, we wish to stress that pharmacological treatment is only part of a more extensive approach of comfort in neonates. An environment that reduces noicceptive stimuli and that enhances comfort is equally important in contemporary neonatal care. The switch in retinal surgery, from cryo- to less
invasive laser therapy is an illustration of this integrated approach [6].

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References

Cryotherapy for Threshold Retinopathy: Perioperative Management in a Single Center

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ABSTRACT

Perioperative management and complications during and after surgery were reviewed in a population of premature infants who received cryotherapy because of threshold retinopathy by retrospective analysis of medical, anaesthetic, and ophthalmologic files. Infants (n = 31) who received cryotherapy between January 1, 1996 and January 1, 2001 and were treated during the neonatal period in the unit were included in the study. Cryotherapy was performed under general anesthesia on the neonatal ward. Neonatal and preoperative characteristics of this cohort point to a vulnerable group of infants with a preoperative weight of 1622 g (1519 to 1862 g), bronchopulmonary dysplasia criteria applying in 29 of 31 patients and methylanthins prescribed in 26 of 31 patients. No single cryotherapy session had to be interrupted because of systemic complications. Still marked cardiopulmonary instability was documented until 36 hours postoperative in 8 patients. Performing surgical procedures on the neonatal ward is a feasible option. Perioperative management in infants who received cryotherapy is used as an illustration of this approach.

KEYWORDS: Threshold retinopathy, cryotherapy, general anesthesia, surgery on the neonatal ward

Cryotherapy for retinopathy of prematurity (ROP) is a well-established surgical technique to treat threshold retinopathy in premature infants to prevent either progression to blindness or major visual impairment. In the design of the Multicenter trial of Cryotherapy (Cryo-ROP) uniformity on ophthalmologic management was emphasized, but local caregivers were given freeway on perioperative anaesthetic management and there is still variability on perioperative management in these patients. In the Cryo-ROP trial general anesthesia was provided in only 27.5% of cases and local anesthesia in the

American Journal of Perinatology, Volume 20, Number 5, 2003. Address correspondence and reprint requests: K. Allegaert, M.D., Department of Pediatrics, Neonatal Intensive Care Unit, University Hospitals, Gasthuisberg, KU Leuven, Herestraat 49, 3000 Leuven, Belgium. 1Department of Pediatrics, Neonatal Intensive Care Unit, 2Department of Anesthesiology, and 3Department of Ophthalmology, University Hospitals, Gasthuisberg, KU Leuven, Belgium. Copyright © 2003 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662. 0735-1631/2003/20,05,219,226.fsb.enjip37950c.
majority. Perioperative nonophthalmologic complications were recorded in 21 of 157 treatments, which led the authors to conclude that while the surgery was stressful, no unexpected complications occurred during or shortly after surgery.\(^1\) Since the original trial in the 1980s, neonatology itself has also changed. Epidemiological data on the incidence of retinopathy point a more vulnerable group of very-low-birth-weight (VLBW) infants who develop retinopathy as a major complication of extreme prematurity, while the importance of adequate pain relief in neonates was highlighted by Anand and others.\(^2\)\(^3\) Moreover, these infants may not only have nonophthalmologic complications during, but also after surgery.\(^4\) It is well known that premature and former premature infants display more respiratory and cardiorespiratory instability after surgery than their full-term peers.\(^5\) Improved stability is documented when infants had the surgical intervention performed on the ward by minimizing stress, hypothermia, and risk of deterioration during transfer to the operating room.\(^6\) We report on a homogeneous-treated cohort of infants who received cryotherapy in a tertiary care center between January 1, 1996 and January 6, 2001. Surgery was performed in the neonatal intensive care unit (NICU) under general anesthesia after elective endotracheal intubation and with short-term postoperative ventilation to prevent or minimize systemic complication during and after surgery. This option also enabled us to provide adequate analgesia during and after surgery.

**MATERIALS AND METHODS**

All infants who received cryotherapy for threshold retinopathy and were treated during the neonatal period in the unit between January 1, 1996 and January 6, 2001 were included. Since January 6, 2001, laser therapy is preferred approach in threshold retinopathy. The unit serves as a tertiary NICU with 35 beds and on average 540 IC-admission each year. All infants admitted during this period with a birth weight < 2000 g or a gestational age < 35 weeks after screened for retinopathy of prematurity starting at the postnatal age of 4 weeks. After first screening, follow-up was continued at least every second week until retinal vascularization was completed or screening was done more frequent when retinopathy was documented according to the attending ophthalmologist. All infants fulfilled Cryo-ROP criteria at the time of surgery, that is, threshold disease (at least five contiguous or eight cumulative clock hours of stage 3 ROP in zone 1 or 2 in the presence of plus disease). The incidence of threshold retinopathy in our population is 6.4% in survivors with a birth weight < 1500 g. General anesthesia was provided on the neonatal ward by a certified anesthesiologist. Anesthesia was induced using 3 to 5 \(\mu\)g/kg fentanyl and 3 mg/kg propofol. Muscle relaxation was achieved using pancuronium bromide, 0.2 mg/kg. Following induction of anesthesia, ventilation was maintained by mask ventilation. After 2 minutes, endotracheal intubation was performed and pressure controlled ventilation with Babyleg 2000 (Dräger Medizintechnik, Lübeck, Germany) system was instituted. Anesthesia was maintained using intravenous propofol and additional fentanyl as judged by the anesthesiologist. Monitoring consisted of pulse oximetry, ventilatory rate, and heart rate registration during and also after surgery. The infants were placed in an open-type incubator (Air Shields, Vickers, Denver, CO) with temperature control and heater. After surgery, the infants were ventilated by conventional pressure-control ventilation and were weaned according to the clinical judgement of the attending neonatologist. Cryotherapy was performed after preoperative dilation with atropine and phenylephrine. After incision of the conjunctiva, the avascular retina anterior to the edge of the ridge was treated with a contiguous single or double row of cryo-points over 360 degrees. In the postoperative period, all infants were treated with local steroids and atropine 0.5% tapered over 1 week.

Pre- and postoperative rectal temperature was recorded as part of routine nursing care. Neonatal characteristics of this population [birth weight, ges-
tational age, Apgar score, Clinical Risk Index for Babies (CRIB) score, incidence of neonatal hypotension, length of artificial ventilation, length of respiratory support, length of extra oxygen, and length of stay] and preoperative condition (weight at surgery, incidence of bronchopulmonary dysplasia, prescribed medications, cardiorespiratory instability in the days before cryotherapy, the level of respiratory support, and previous surgery) were collected from an available neonatal database (Epi Info, World Health Organization) or from the medical files and daily nursing progress reports, as appropriate. Ophthalmologic data were collected from the ophthalmologic files. To evaluate postoperative instability, the scoring system as described by Haigh et al was used for a total period of 48 hours after surgery. The characteristics of this score are illustrated in Table 1. All results are expressed by mean and interquartile range or by (percentual) incidence as appropriate.

RESULTS

Thirty-two sessions of cryotherapy in 31 inborn infants were performed. In addition, 3 infants were referred by other units to perform cryotherapy during this period. Because we do not have all perinatal data in these 3 infants, they were left out of the study but the same peroperative approach was used in these infants. Neonatal and preoperative characteristics of the cohort are summarized in Table 2.

Neonatal Characteristics

Mean birth weight in this cohort was 760 g (616 to 907 g). The highest birth weight in the cohort was 1205 g. Five infants were born at a gestational age of 24 weeks, 11 were 25 weeks, 4 were 26 weeks, 4 were 27 weeks, 5 were 28 weeks, and only 2 were 29 gestational weeks at birth. Fourteen of 31 infants were part of a multiple pregnancy. All but one infant needed intubation at birth or shortly afterward and artificial ventilation was provided by either conventional techniques or by high frequency oscillation. Mean Apgar scores in this cohort were 6 (4 to 8) and 8 (8 to 9) at 1 and 5 minutes. Highest mean airway pressure (MAP) in this cohort during the first 24 hours was 13 (12 to 15) and mean oxygenation index at the highest MAP was 14.2 (9 to 18). Mean total length of ventilation during the total neonatal stay was 27 days (10 to 39 days), mean total length of respiratory support was 55 days (41 to 64 days), and mean total length of extra oxygen was 64 days (42 to 77 days). Mean CRIB score was 7.6 (5 to 10). Twenty-seven infants received at least one medication, that is, dopamine, for hypotension. Mean length of stay (LOS) was 99 days (86 to 120 days).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cardiorespiratory Stability Scoring</th>
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<tbody>
<tr>
<td>Score 0: Improved from baseline. Decreased oxygen requirement (&gt;20% relative change in FiO2)</td>
<td></td>
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<tr>
<td>Score 1: No change from baseline</td>
<td></td>
</tr>
<tr>
<td>Score 2: Mild instability. Increased oxygen requirement (20–50% relative change in FiO2), more apneas and/or bradycardias responding to gentle stimulation</td>
<td></td>
</tr>
<tr>
<td>Score 3: Marked instability. Increased oxygen requirement (&gt;50% relative change in FiO2), more apneas and/or bradycardias responding to vigorous stimulation (100% increase or 5 if none before), higher ventilation requirement</td>
<td></td>
</tr>
<tr>
<td>Score 4: Life threatening event. Requiring emergency resuscitation (e.g., intubation, suction/bag and mask oxygen, or cardiac massage)</td>
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</tbody>
</table>

Data from Haigh et al.
Table 2 Neonatal and Preoperative Characteristics of this Cohort

<table>
<thead>
<tr>
<th>Neonatal</th>
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<tbody>
<tr>
<td>Birth weight</td>
<td>760</td>
<td>615-907 g</td>
</tr>
<tr>
<td>Gestational age</td>
<td>25</td>
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</tr>
<tr>
<td>Apgar score 1 min</td>
<td>6</td>
<td>4-8</td>
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<tr>
<td>Apgar score 5 min</td>
<td>8</td>
<td>8-9</td>
</tr>
<tr>
<td>Highest MAP first 24 h</td>
<td>13</td>
<td>12-15 cm H₂O</td>
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<tr>
<td>Oxygenation index at highest MAP</td>
<td>14.2</td>
<td>9-18</td>
</tr>
<tr>
<td>Length of artificial ventilation</td>
<td>27</td>
<td>10-30 days</td>
</tr>
<tr>
<td>Length of respiratory support</td>
<td>55</td>
<td>41-64 days</td>
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<td>Length of extra oxygen</td>
<td>64</td>
<td>42-77 days</td>
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<td>76</td>
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<td>86-120 days</td>
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<table>
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<tbody>
<tr>
<td>Postnatal age at surgery</td>
<td>66</td>
<td>60-71 days</td>
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<tr>
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<td>34</td>
<td>34-36 weeks</td>
</tr>
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<td>1622</td>
<td>1519-1662 g</td>
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<td>BPD 28 days</td>
<td>93%</td>
<td>29/31</td>
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<tr>
<td>BPD 36 postmenstrual weeks</td>
<td>58%</td>
<td>18/31</td>
</tr>
<tr>
<td>Receiving respiratory support</td>
<td>32%</td>
<td>10/31</td>
</tr>
<tr>
<td>Receiving extra oxygen</td>
<td>52%</td>
<td>16/31</td>
</tr>
<tr>
<td>Receiving methylxanthins</td>
<td>89%</td>
<td>26/31</td>
</tr>
<tr>
<td>Receiving corticoids</td>
<td>55%</td>
<td>17/31</td>
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<tr>
<td>History of previous surgery</td>
<td>25%</td>
<td>6/31</td>
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</tbody>
</table>

Results are expressed as mean with interquartile range or as (percentual) incidence as appropriate.

Preoperative Characteristics

Mean postnatal age at time of surgery was 65 days (60 to 71 days) or more relevant, mean gestational age at time of intervention was 34 weeks (34 to 36 weeks). The oldest infant at time of surgery was 39 weeks' gestational age. Mean weight at time of surgery was 1622 g (1519 to 1862 g). Only two infants had a weight > 2500 g at time of surgery. According to the bronchopulmonary dysplasia criteria applied, 29 of 31 received either respiratory support or extra oxygen on postnatal day 28 and 18 still received either respiratory support or extra oxygen at 36 weeks' postmenstrual age. Ten infants still had respiratory support; 2 received conventional ventilation and 8 had nasal continuous positive airway pressure (CPAP). Sixteen infants still received extra oxygen. Twenty-two were on diuretics, 26 received methylxanthins for apnea of prematurity, and 17 were on corticoids (oral or inhalation) in the days before surgery. Eight infants had a history of surgical intervention before cryotherapy (ductus, abdominal, neurosurgical, or ophthalmologic).

No single cryotherapy session had to be interrupted because of systemic complications and hemodynamics remained stable. Feeding was stopped 4 hours prior to the intervention and a nasogastric tube was placed either before or after surgery. Mean temperature before surgery was 36.8°C, mean temperature postsurgery was 36.4°C. In 9 of 32 sessions, postoperative temperature was below 36°C.

Postoperative Characteristics

Mean postoperative length of ventilation was 22 hours (15 to 38 hours) in infants (n = 30) who were not already ventilated before surgery. Full enteral
feeding was reestablished within (mean) 72 hours (52 to 112 hours) in infants who were already on full enteral feeding before surgery. Postoperative analgesia was provided by opioids (fentanyl, tramadol, piratramide) in 19 of 32 sessions and by paracetamol in 27 of 32 sessions. Mean length of opioid therapy was 24 hours (0 to 48 hours) while mean length of paracetamol therapy was 60 hours (48 to 72 hours). In all sessions, at least one analgesic medication was prescribed. Mean postoperative LOS was 40 days (23 to 58 days).

Cardiorespiratory stability scores were calculated for the first 48 hours after surgery (n = 32). Sixteen patients showed no increase in instability during the postoperative period. Marked instability (score = 3) was documented during 8 periods in 8 patients. No marked instability events were documented after 36 hours postoperative. Mild instability (score = 2) was documented during 25 periods in 14 patients. The results of the instability score in this cohort are illustrated in Figure 1.

**DISCUSSION**

We describe our experience in a cohort of 31 infants and 32 interventions who all received a homogeneous approach by general anesthesia and endotracheal intubation on the NICU to perform cryotherapy with short-term postoperative ventilation. As expertise in management of VLBW infants increased and the technical equipment in the NICUs improved, surgical procedures under general anesthesia on the neonatal ward became a feasible option. We described our experience with ventriculoperitoneal drainage on ward and others used an equivalent approach for cardiac, abdominal, or thoracic surgery.9-11 Surgical interventions on ward make it possible to avoid hypothermia or suboptimal monitoring during transportation and ventilator modes designed for these infants are also available.6 By describing this retrospective cohort, we have the ability to document the effect of new anaesthetic techniques (inhalation anaesthesia, newer opioids,

![Postoperative stability score](image)

**Figure 1** Cardiorespiratory stability scores. Stability score was calculated after 32 procedures in 31 infants for 5 consecutive time intervals (0-6, 6-12, 12-24, 24-36, and 36-48 hours) after surgery. Marked instability (score = 3) was documented during 8 periods in 8 patients. Mild instability (score = 2) was documented during 25 periods in 14 patients. Postoperative stability score remained stable (score = 1) during all periods after 16 (50%) interventions. (x-axis: consecutive time intervals, y-axis: number of patients).
or short-acting muscle relaxants) or of new surgical techniques (laser therapy) by comparing the effects with this historical control group.

Neonatal Characteristics

Neonatal characteristics were documented to stress the vulnerability of the cohort. Mean birth weight was 760 g. Mean gestational age at birth was 25 weeks. All infants who needed cryotherapy had a birth weight < 1250 g. These findings are slightly below the original Cryo-ROP trial and are in line with the more recent cohorts of Sullivan and Haigh, pointing to a shift to a more vulnerable younger population.

Highest MAP, Oxygenation Index, CRIB score, and the incidence of hypotension were calculated to document perinatal intensity of disease.

PRE- AND PERIOPERATIVE CHARACTERISTICS

Mean weight at surgery was 1622 g and surgery was performed at a mean gestational age of 34 weeks. This is 200 g below the mean weight mentioned in the Cryo-ROP and in line with the more recent cohort of Haigh, pointing to a trend to perform this procedure on an even more vulnerable population. The choice to provide general anesthesia was made to avoid deterioration during surgery. It enabled the surgeon to document the retinopathy and to perform cryotherapy in the most controllable way. There is still debate in literature about whether or not intubation is necessary in these infants and if sedation might be preferred, considered to be less aggressive. Schulenburg documented the different approaches of different NICUs in the United Kingdom and other authors also commented on this controversial issue. We stress the fact that we could not see any deterioration during surgery in this cohort and that we could complete all surgical procedures without interruption. Brown et al documented 3 respiratory arrests and 1 cardiorespiratory arrest during cryotherapy in 75 patients who only received local anesthetics for cryotherapy. Haigh et al described systemic complications associated with different anaesthetic techniques after switch from local to general anesthesia in a unit. Life-threatening events, that is, severe bradycardia or cyanosis for which the procedure was interrupted and mask ventilation was provided during treatment, were only observed during procedures under local anesthesia. An anaesthetic approach with nasal ketamine and midazolam associated with local anesthesia was described in a single case report. Conditions were said to be excellent although two periods of desaturation during surgery were reported. Surgery needed to be interrupted and oxygen was provided. In the Cryo-ROP study, no guidelines on anaesthetic management were provided. Nonophthalmologic complications (bradycardia, arrhythmia, or asystole, acquired or increased cyanosis) were documented during 21 of 157 (13%) sessions. Data on postoperative cardiorespiratory instability are not available for the Cryo-ROP. No deaths from treatment were recorded. Relevant hypothermia, that is, rectal temperature below 36°C should be avoided although we still documented hypothermia after 9 sessions.

POSTOPERATIVE CHARACTERISTICS

Marked increase in instability (score = 3) was documented in 8 periods in 8 different patients within 36 hr after surgery and increase in instability (score = 2) in 25 periods in 14 different patients within 48 hours. No increase in instability was documented after 16 of 32 procedures (Fig. 1). Although we were able to achieve stability during surgery, this cohort still displayed significant instability after surgery. This stresses the relevance of postoperative monitoring in an intensive care setting. Although one could argue that general anesthesia or postoperative pain management itself might increase cardiorespiratory instability, we believe that prematurity and clinical conditions of these infants are more relevant factors in the postoperative evolution. The need to prescribed methylxanthines in 26 of 31 infants
before surgery illustrates this immaturity. Haigh\textsuperscript{5} still documented increased instability in the group who received general anesthesia, but patients who received general anesthesia were significantly more stable when compared with patients who received local anesthesia. The patient described by Louon\textsuperscript{16} also displayed instability after surgery with a single episode of bradycardia, resolved by bag ventilation.

Inadequate pain management itself might also cause cardiorespiratory instability. In this retrospective study, only prescribed analgesics (type, dose, and length) after surgery could be documented. Pain measurement instruments should enable caregivers to objectivize the prescription of analgesics. Short-term postoperative pain therapy with opioids or nonopioids after cryotherapy is quite logical when local edema and incision of the conjunctivae is considered.

Mean length of postoperative ventilation was 22 hours. These findings are in line with the cohort published by Haigh,\textsuperscript{1} but postoperative period of ventilation is shorter than the cohort described by Sullivan,\textsuperscript{12} where the infants were ventilated for (mean) 40 hours. Full enteral feedings were reestablished within (mean) 72 hours in our group. We could not find other reports to compare these data on enteral feeding.

**CONCLUSION**

General anesthesia and elective endotracheal intubation with postoperative ventilation for cryotherapy in the neonatal ward is a feasible and safe approach by which unexpected deterioration during surgery can be avoided. Increased cardiorespiratory instability is still documented in these VLBW infants after general anesthesia. Postoperative monitoring in an intensive care setting is necessary for at least 48 hours. Mean birth weight and weight at surgery point to a more vulnerable group of infants when compared with the Cryo-ROP trial. These data enable us to document the effect of future changes in surgical or anaesthetic management in these infants. Further study is still needed to document the optimal perioperative approach in these infants.

**ACKNOWLEDGMENTS**

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Intravenous paracetamol (propacetamol) pharmacokinetics in term and preterm neonates

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Abstract Background: The aim of this study was to describe propacetamol pharmacokinetics in term and preterm neonates to suggest dosing regimens. Methods: A population pharmacokinetic analysis of propacetamol (acetaminophen) time-concentration profiles in 48 neonates was undertaken using non-linear mixed-effects models. Neonates were given either single (n = 30) or multiple doses (n = 18) of propacetamol infusion over 15 min. Neonates had a median postnatal age of 1 day (range, 1–76 days), Median post-conceptual age (PCA) was 35 weeks (range, 27–42 weeks), and median weight was 2.4 kg (range, 0.51–4 kg). Results: The population volume of distribution estimate and between-subject variability (%) for a one-compartment model with zero-order input and first-order elimination was 70.4 l (30.7%)/70 kg. Clearance increased from 2.85 l/70 kg, CV 40.7% at 27 weeks PCA to reach 7.05 l/h per 70 kg by 42 weeks PCA (standardised to a 70-kg person using allometric “1/4-power” models). Between-occasion variability for volume of distribution and clearance were 17.4% and 26%, respectively. Conclusions: A mean paracetamol steady-state target concentration above 10 mg/l at trough can be achieved using a loading dose of 40 mg/kg and maintenance doses of 20 mg/kg 6 h in 28-week PCA neonates, 25 mg/kg 6 h at 32 weeks, 30 mg/kg 6 h at 36 weeks and 20 mg/kg 4 h at term (propacetamol doses). Since the role of the oxidative enzyme CYP2E1 and production of the hepatotoxic metabolite N-acetyl-p-benzoquinone-imine still is unknown in prematures, lower doses scaled by age-related clearance and centred on a daily dose of 60 mg/kg per day in a child of 6–8 years with a clearance of 0.25 l/h per kg (12.5 l/h per 70 kg) may be more appropriate.

Keywords Paracetamol · Propacetamol · Neonate

Introduction

Paracetamol (N-acetyl-p-aminophenol, acetaminophen, APAP) is the most commonly prescribed drug in infants and neonates to treat mild to moderate pain or to supplement opioid analgesia [1, 2]. This drug is usually administered enterally and, like many other drugs used in paediatric practice, remains unlicensed in the neonatal age group [1]. A parenteral formulation, propacetamol, is available, but there are limited pharmacokinetic data available for premature neonates [3, 4]. Propacetamol is a pro-drug of paracetamol and is hydrolysed by plasma esterases after intravenous administration such that 1 g of propacetamol is hydrolysed to 0.5 g of paracetamol [3, 5, 6]. Intravenous administration might improve prediction of concentration compared with enteral.
formulations by elimination of plasma variability due to absorption and relative bioavailability parameter variability.

We had the opportunity to examine propacetamol serum concentrations in neonates between 27 weeks and 42 weeks post-conceptual age (PCA) who received intravenous propacetamol for analgesia for up to 48 h. Data from these patients were combined with those from a published study of neonates given a single dose of propacetamol for analgesia in their first 24 h of life [4]. These pooled data were investigated using a population-based approach that included size as the primary covariate, with the intention to suggest a dosing regimen of intravenous propacetamol (propacetamol) in neonates. Age-appropriated dosing regimens for enteral propacetamol in premature neonates have been proposed, but there are few data on which to base intravenous propacetamol dosing regimens for term and preterm neonates [7].

This current study investigates pharmacokinetics only and does not consider pharmacodynamics. An effect-site target concentration of 10 mg/l has been suggested in children suffering tonsillectomy pain, but the target concentration required for different types of pain in the neonatal period remains undefined [8].

Materials and methods

Patients

In a previous single-dose study, propacetamol (either 20 mg/kg or 40 mg/kg) was administered to premature and term infants in the first 24 h of life [4]. The present multiple-dose study regimen was extrapolated from this single-dose study and used a loading dose of 30 mg/kg in all infants, followed by a maintenance dose of 20 mg/kg of propacetamol using a dosing interval based on PCA (PCA > 36 weeks: 6 h, PCA 32–36 weeks: 8 h, PCA < 32 weeks: 12 h). Propacetamol was administered as a 15-min intravenous infusion to avoid infusion site discomfort [5]. Both the current multiple-dose study and the single-dose study were approved by the local ethics committee (University Hospital, Gasthuisberg, Leuven, Belgium), and infants were only included after informed consent of the parents.

In the single-dose study, neonates admitted within the first 24 h of life in the neonatal intensive care unit and with an arterial line in place were considered for inclusion if propacetamol was administered. The decision to prescribe propacetamol was made by the attending neonatologist. Propacetamol was administered when infants underwent minor painful procedures or as additional treatment in infants on opioids. Blood samples were taken from an arterial line 30, 60, 90, 120, 180, 240 and 600 min after initiation of intravenous administration [4].

In the multiple-dose study, admission criteria were the same as those used in the single-dose study. The decision to prescribe propacetamol was made by the attending neonatologist and was based on standardised evaluation of pain and an analgesic algorithm after surgical interventions or during specific medical conditions in neonates [2]. Blood samples for propacetamol assay were taken from an indwelling arterial line during the first 48 h after the first dose of propacetamol. The total amount of blood collected from each single infant was limited to 1 ml/kg. Blood samples were collected every 3 h for the first 12 h and at 6-h intervals thereafter.

Assay

After centrifugation, plasma samples were stored at −20°C until analysis. In the single-dose study, APAP plasma concentrations were determined using fluorescence polarisation immunoassay (ADx system, Abbott Laboratories, North Chicago, IL). Determination limit was 1 mg/l, and precision was 7% [4, 9].

In the multiple-dose study, plasma samples were analysed using high-performance liquid chromatography [10, 11]. First, 10 μl of the standard APAP dilution, 10 μl of the internal standard solution (20 g/ml p-propiomandiphencol), 0.2 ml H2O, 0.2 ml 0.1 M potassium phosphate buffer pH 7.4 and 2 ml ethylacetate were added to 0.1 ml of plasma. After shaking for 10 min and centrifuging (1286 g) at 4°C, the organic layer was transferred to conical glass tubes. Following evaporation of ethylacetate in a water bath at 45°C with an air stream, the residues were dissolved in 180 μl of mobile phase and vortexed for 10 s. After addition of 20 μl of trichloroacetic acid 50%, mixtures were centrifuged again (8 min at 9300 g). The clear supernatants were pipetted into microvials (300 μl) used for automatic injection. A Waters 600E pump was used in combination with an UV detector SPD-6A (Shimadzu, Kyoto, Japan), set at 245 nm, and a Waters 717 plus autosampler. The column was a stainless-steel column, packed with Spherisorb hexyl 5 μ (Alltech Associates, Deerfield, Illinois, US). The mobile phase consisted of a mixture of acetonitrile and 50 mM acetate buffer pH 4 (2/98, v/v) and pumped at a flow rate of 1 ml/min. Linearity of the calibration curve in plasma was found in the range of 0.078–40 μg/ml (y = 0.003 + 0.707x, r = 0.99). The lower limit of quantification was 0.08 μg/ml, being the lowest concentration of the standard curve with a coefficient of variation lower than 20%. Analytical recovery (%) of APAP was 62.6% (SD 6.6%) (mean ± SD) and of the internal standard p-propiomandiphencol 77.0% (SD 8.3%). Variation coefficients in intra- and interday accuracy and precision were below 15%.

Pharmacokinetic analysis

Population parameter estimations

Population parameter estimates were obtained using a non-linear mixed-effects model (NONMEM) [12]. This
model accounts for population-parameter variability (PPV) (between and within subjects) and residual variability (random effects) as well as parameter differences predicted using covariates (fixed effects). The PPV in model parameters was modelled using a proportional variance model. An additive term characterised the residual unknown variability. This error model assumes that the residual variability is the same order of magnitude over the whole range of measurements. The population mean parameters, between subject variance and residual variance were estimated using the first-order conditional estimate method using ADVAN 1 TRANS 2 of NONMEM V. Convergence criterion was three significant digits. A Compaq Digital Fortran Version 6.6A compiler with Intel Celeron 333 MHz CPU (Intel Corp., Santa Clara, CA) under MS Windows XP (Microsoft Corp., Seattle, WA) was used to compile NONMEM.

The PPV is modelled in terms of random effect \( \eta \) variables. Each of these variables is assumed to have mean 0 and a variance denoted by \( \sigma_\eta^2 \), which is estimated. PPV for clearance and volume was partitioned into between-subject- (BSV) and between-occasion variability (BOV) because neonates received paracetamol on up to six different occasions.

The covariance between two elements of \( \eta \) (e.g. CL and \( V \)) is a measure of statistical association between these two variables. Their covariance is related to their correlation \( R \) i.e.

\[ R = \frac{\text{covariance}}{\sqrt{\sigma_{CL}^2 \times \sigma_V^2}} \]

The covariance of clearance and distribution volume variability was incorporated into the model. The between-occasion covariance of clearance and volume was also estimated. This covariance is effected by factors that alter both clearance and volume together (e.g. bioavailability, protein binding, total body water).

In addition, there were two sources of data for the population analysis—the single-dose and the multiple-dose study. This BSV was accounted for by giving each study a separate residual error.

Covariate analysis

The parameter values were standardised for a body weight of 70 kg using an allometric model \([13, 14]\)

\[ P_i = P_{\text{std}} \times \left( \frac{W_i}{W_{\text{std}}} \right)^{PWR} \]

where \( P_i \) is the parameter in the \( i \)th individual, \( W_i \) is the weight in the \( i \)th individual and \( P_{\text{std}} \) is the parameter in an individual with a weight \( W_{\text{std}} \) of 70 kg. This standardisation allows comparison of neonatal parameter estimates with those reported for adults. The \( PWR \) exponent was 0.75 for clearance and 1 for distribution volumes \([15, 16, 17, 18]\).

The quality of fit of the pharmacokinetic model to the data was sought using NONMEM’s objective function and using visual examination of plots of observed versus predicted concentrations. Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess significance, e.g. an objective function change of 3.84 is significant at \( x = 0.05 \).

Covariate analysis included a model investigating age-related changes for clearance and volume of distribution:

\[ CL (L/h) = (CL_{\text{std}} \times (W_i/70)^{0.75}) \times \exp(SLOPECL \times PCAGE - 27) \]

\[ V (L) = (V_{\text{std}} \times (W_i/70)) \times \exp(SLOPEV \times (PCAGE - 27) \]

where \( V_{\text{std}} \) and \( CL_{\text{std}} \) are the population estimates for \( V \) and \( CL \) at 27 weeks PCA, respectively, standardised to a 70-kg person using allometric models; \( PCAGE \) is the post-conceptual age in weeks; \( SLOPECL \) and \( SLOPEV \) are parameters describing changes of clearance and volume with age. The effect of postnatal age (\( PNAGE \)) rather than \( PCAGE \) was also investigated during model building.

Results

The pooled analysis comprised 48 subjects and 320 drug assay samples. Of neonates, 30 were given a single dose, and 18 received multiple doses of propacetamol. Median postnatal age (PNA) was 1 day (range, birth–76 days), median PCA was 35 weeks (range, 27–42 weeks) and median weight was 2.44 kg (range, 0.51–4 kg). Clinical characteristics and indications to administer analgesics are available in Table 1.

Parameter estimates for the analysis are shown in Table 2. Figure 1a, b demonstrates the quality of fit for pharmacokinetic data. Individual concentration predictions are based on values of maximum a posteriori Bayesian estimates of the parameters using the post-hoc option, while predicted typical (population) concentra-

<table>
<thead>
<tr>
<th>Clinical characteristics and indications to administer analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics (median and range)</strong></td>
</tr>
<tr>
<td>Weight at inclusion ( 2.44 ) Kg</td>
</tr>
<tr>
<td>Post-conceptual age ( 35 ) Weeks</td>
</tr>
<tr>
<td>Postnatal age ( 1 ) Days</td>
</tr>
<tr>
<td><strong>Indications to administer analgesics (absolute number)</strong></td>
</tr>
<tr>
<td>Surgical</td>
</tr>
<tr>
<td>Thoracic</td>
</tr>
<tr>
<td>Oesophageal</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Abdominal</td>
</tr>
<tr>
<td>Ophthalmological</td>
</tr>
<tr>
<td>Medical</td>
</tr>
<tr>
<td>Alloprostadiol (PGE(_i)) administration</td>
</tr>
<tr>
<td>Multiple bruising/cephal haematoma</td>
</tr>
<tr>
<td>Procedural interventions</td>
</tr>
<tr>
<td>Respiratory disease</td>
</tr>
</tbody>
</table>
Table 2 Standardised population pharmacokinetic parameter estimates. BSV between-subject variability, BOV between-occasion variability, SE standard error of the estimate, SLOPECL parameter describing changes of clearance with age.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>%BSV</th>
<th>%BOV</th>
<th>%SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{\text{ind}} )</td>
<td>1/70 kg</td>
<td>70.4</td>
<td>30.7</td>
<td>17.4</td>
</tr>
<tr>
<td>( \text{CL}_\text{ind} ) at 27 weeks</td>
<td>1/h/70 kg</td>
<td>2.85</td>
<td>40.7</td>
<td>25</td>
</tr>
<tr>
<td>SLOPECL</td>
<td>0.0604</td>
<td></td>
<td></td>
<td>22.4</td>
</tr>
</tbody>
</table>

Fig. 2 Individual predicted paracetamol clearances, standardised to a 70-kg person, from the non-linear mixed-effects models post-hoc step, are plotted against post-conceptional age. Estimates from premature neonates given single dose are shown as diamonds. Premature neonates given multiple doses have clearance estimates from each occasion (triangles) linked by a fine line. The solid line represents the non-linear relationship between clearance and age.

Fig. 3 Individual predicted paracetamol volumes of distribution \( (V) \), standardised to a 70-kg person, from the non-linear mixed-effects models post-hoc step, are plotted against post-conceptual age. Estimates from premature neonates given single dose are shown as diamonds. Those premature neonates given multiple doses have volume of distribution estimates (triangles) linked by a fine line. There is no relationship between volume of distribution and age.

The correlation of BSV for CL and \( V \) was 0.63, and for BOV it was 0.105. Changes in clearance and distribution volume with age are shown in Fig. 2 and Fig. 3. PCA, rather than PNA, fit best with clearance maturation. Clearance increased from 2.85 l/h per 70 kg at 27 weeks PCA to reach 7.05 l/h per 70 kg by 42 weeks. The addition of PNA to PCA clearance maturation did not improve fit. The volume of distribution did not alter with either PNA or PCA. Mean age-related clearance predictions based on the covariate model for clearance are shown in Table 3. This table also expresses clearance as per kilogram, based on an estimated weight for each PCA.

Table 2 shows the BSV for clearance and 17.4% for the apparent volume of distribution. This BOV can be seen in Fig. 2 and Fig. 3. The BSV for clearance and volume of distribution without covariates in the model were 86% and 65.3%, respectively. This difference between BSV without covariates and with covariates is a measure of the predictable decrease in BSV due to covariates. The relative estimates for the different components contributing to variability are shown in Table 4. The ratio of the BSV predictable from covariates to the total PPV obtained without covariate analysis gives an indication of how important covariate information is. For example, the ratio of 0.685 achieved for clearance in this current study indicates that 68.5% of the overall variability in clearance is predictable from covariate information. The residual errors (mg/l) for the two studies were 1.81 mg/l and 0.51 mg/l for the single-dose- and multiple-dose studies, respectively.

Figure 4a shows a simulated time-concentration profile for a 2.5-kg neonate (PCA 35 weeks) given
Table 3 Clearance maturation with post-conceptual age (PCA)

<table>
<thead>
<tr>
<th>PCA</th>
<th>Weight</th>
<th>CL l/h per kg</th>
<th>CLmtl l/h per 70 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>0.8</td>
<td>0.132</td>
<td>3.03</td>
</tr>
<tr>
<td>30</td>
<td>1.2</td>
<td>0.135</td>
<td>3.42</td>
</tr>
<tr>
<td>32</td>
<td>1.6</td>
<td>0.142</td>
<td>3.86</td>
</tr>
<tr>
<td>34</td>
<td>2.2</td>
<td>0.148</td>
<td>4.33</td>
</tr>
<tr>
<td>36</td>
<td>2.9</td>
<td>0.155</td>
<td>4.91</td>
</tr>
<tr>
<td>38</td>
<td>3.3</td>
<td>0.170</td>
<td>5.54</td>
</tr>
<tr>
<td>40</td>
<td>3.5</td>
<td>0.189</td>
<td>6.23</td>
</tr>
<tr>
<td>42</td>
<td>3.7</td>
<td>0.210</td>
<td>7.05</td>
</tr>
</tbody>
</table>

Table 4 Effect of covariate analysis on variance (σ²). PPVt total population parameter variability estimated without covariate analysis, BSVP between subject variability predictable from covariates, BSVR the random BSV estimated on a parameter when covariate analysis is included, BOV between-occasion variability (PPVt = BSVP + BSVR + BOV). The ratio of the BSVP predictable from covariates (BSVP) to the total population parameter variability obtained without covariate analysis (PPVt) (i.e. BSVP/PPVt) indicates the fraction of the total variability in the parameter that is predictable from covariates.

<table>
<thead>
<tr>
<th>PPVt</th>
<th>BSVP</th>
<th>BSVR</th>
<th>BOV</th>
<th>BSVP/PPVt</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>0.740</td>
<td>0.506</td>
<td>0.166</td>
<td>0.968</td>
</tr>
<tr>
<td>V</td>
<td>0.426</td>
<td>0.302</td>
<td>0.094</td>
<td>0.030</td>
</tr>
</tbody>
</table>

propacetamol 60 mg/kg (paracetamol 30 mg/kg) over 15 min. Predicted effect compartment concentrations were based on an equilibration half-time (Teq) of 0.9 h in a 70-kg person [19]. We predict a Teq of 0.38 h in a 2.5-kg infant by using allometric scaling with a power function of 0.25 [14, 18]. An effect, i.e. pain reduction, is also plotted on this graph. A concentration–response relationship has not been described for any pain stimulus in neonates. The Emax effect model used in this figure is based on tonsillectomy data in children and may not be applicable to neonates [14]. Simulated data are shown in Fig. 4b for a 2.5-kg neonate given paracetamol elixir 30 mg/kg orally. An absorption half-life of 2 h was used [8].

Table 4a shows predicted dosing regimens that achieve a trough target concentration of 10 mg/l, while Table 6 shows doses scaled for neonatal clearance based on a daily dose of 60 mg/kg per day in a child of 6–8 years with a clearance of 0.25 l/kg per h. Time-concentration profiles and time–effect profiles for a 2.5-kg, 35-week PCA neonate for both dosing regimens are shown in Fig. 5a, b. The higher-dose regimen that maintains a trough concentration above 10 mg/l achieves a mean pain reduction of 3/10. The lower-dose regimen, extrapolated from a child 6–8 years dosing regimen of 60 mg/kg per day by scaling to clearance, achieves a mean pain reduction of 2.6/10.

**Discussion**

This study is the first population analysis in preterm and term neonates exploring single and multiple doses of propacetamol, a prodrug of paracetamol. Pharmacokinetic studies using propacetamol enable "cleaner" predictions of pharmacokinetic parameters by removing variability associated with enteral paracetamol absorption parameters. The present study predicts a clearance of 3.42 l/h per 70 kg at 30 weeks and 6.25 l/h per 70 kg at 40 weeks PCA.

Clearance estimates are similar to those predicted using enteral formulations in neonates (2.1 l/h per 70 kg at 30 weeks and 6.8 l/h per 70 kg at 40 weeks) [7]. Volume of distribution is reported to decrease during infancy and to reach 86% of adult values (66.6 l/70 kg) by 60 weeks [7]. Neither PCA nor PNA had an effect on volume of distribution in this current study. The cause for this lack of effect of age on volume of distribution is unclear, but may be attributable to the pathology of the population studied that comprised neonates in intensive care from 27 weeks to 42 weeks only. Older infants that may accentuate age-related changes were not included in this study. However, the BOV was 17.4%, possibly reflecting extracellular fluid shifts during their stay in the intensive care unit.

Size was the first covariate used in our analysis of the effects of age and weight. This deliberate choice was based on known biological principles. A great many physiological, structural and time-related variables scale predictably within and between species with weight
order processes, which are common underlying mechanisms for time-related phenomena.

We have assumed all propacetamol is converted to paracetamol, based on adult literature [5]. There is bioavailability variability associated with this conversion, and the between-occasion covariance for clearance and volume of 10.5% supports this proposition. We suspect that a contributing factor for structural parameter BSV and BOV is attributable to systematic errors in dilution techniques. Propacetamol vials contain 1000 mg of propacetamol in 5 ml solvent marketed for use in adults. In neonates, doses of less than 10% of the initial vial content were administered.

A further large fraction of overall variability in clearance (68.5%) and volume of distribution (70.8%) in premature neonates and children is predictable from weight and PCA. Random BSV and BOV (Table 4) contributes the remainder. These findings support the use of weight and age to predict an appropriate dose. The random BSV contribution is low, and the measurement of drug concentration and target-concentration intervention would have limited merit [21]. In addition, a target concentration in this age group is undefined because of the still unknown contribution of oxidative metabolic pathways to hepatotoxicity [7].

In general, maturation of many enzyme systems involved in APAP metabolism, such as UDP-glucuronosyltransferase (UGT) or cytochrome P450 iso-enzymes, increases after birth. Krumbiegel et al. documented the additional effect of the PNA on UGT 1A6 activity in neonates of the same PCA using a single-dose N-acetyl urine test to describe the maturational aspects of cytochrome P450 iso-enzyme system [22]. PNA may also be a covariate for paracetamol clearance maturation, but the current study design was unable to estimate any effect because the median PNA was 1 day.

Taking all above-mentioned limitations into account, daily dose suggestions were calculated. The doses suggested in Table 5 are those predicted to maintain a trough plasma level of paracetamol of 10 mg/l [19]. These daily doses are higher than those given enterally in older children because there is no absorptive phase that blunts peaks and troughs with the intravenous formulation (Fig. 4a, b) [23]. Intravenous propacetamol has a more rapid onset of effect compared with an enteral formulation in children, while an enteral formulation sustains concentrations (and consequent effect) longer than an intravenous formulation.

Table 5 Propacetamol predicted dosing regimens that achieve a trough target concentration of 10 mg/l. Doses of propacetamol are reported as prodrug. 1 g of propacetamol equals 0.5 g of paracetamol. PCA post-conceptual age

<table>
<thead>
<tr>
<th>PCA weeks</th>
<th>Loading dose (mg/kg)</th>
<th>Maintenance dose (mg/kg)</th>
<th>Dose interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>40</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>32</td>
<td>40</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>36</td>
<td>40</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
<td>20</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 6 Propacetamol doses scaled for neonatal clearance based on a daily dose of paracetamol 60 mg/kg per day in a child of 6-8 years with a clearance of 0.251/kg per h. PCA post-conceptual age

<table>
<thead>
<tr>
<th>PCA weeks</th>
<th>Loading dose (mg/kg)</th>
<th>Maintenance dose (mg/kg)</th>
<th>Dose interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>40</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>32</td>
<td>40</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>36</td>
<td>40</td>
<td>12.5</td>
<td>4</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
<td>15</td>
<td>4</td>
</tr>
</tbody>
</table>
A continuous infusion (rate = target concentration x clearance) may be impractical because of fluid restriction or limited venous access in the neonatal intensive care patient. There are also limited data suggesting that immediate-release enteral paracetamol provides superior analgesia to sustained-release formulations and that the rate of increase in the plasma concentration of paracetamol might be important in the alleviation of acute pain [24]. Bolus dosing may provide better analgesia than infusion, but this is unproven, since concentrations were not reported in the paper by Nielsen et al., and the sustained release formulation may have only achieved low plasma paracetamol concentrations [24, 25].

Paracetamol hepatotoxicity is caused by N-acetyl-p-benzoquinone-imine (NAPQI), produced by the oxidative enzyme CYP2E1 and normally mopped up by glutathione reserves. Paracetamol concentrations associated with increased NAPQI are not reported in neonates, and the activity of CYP2E1 still is not quantified. Consequently, it is impossible to predict "safe" doses. Table 6 predicts maintenance doses scaled by neonatal clearance and based on a daily dose of 60 mg/kg per day paracetamol in a child of 6-8 years with a clearance of 0.25 l/kg per h [8, 25]. This reduced dose results in a mean reduction of 2.6/10 compared with 3/10 for the larger dose (Fig. 5a, b). The reduced dose has only slightly reduced analgesic effect because of the shape of the concentration-response relationship. However, such an assumption, based on tionsillectomy pain in children, remains speculative until a concentration-response relationship is described in neonates [19]. Future studies might focus on potential differences in pharmacodynamics of both dosing regimes. In the meanwhile, we personally tend to use the reduced dose in daily practice.

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References

Effects of Co-Administration of Ibuprofen-Lysine on the Pharmacokinetics of Amikacin in Preterm Infants during the First Days of Life

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Key Words
Ibuprofen-lysine co-administration • Preterm infants • Amikacin pharmacokinetics • Drug interactions

Abstract
The aim of this study was to assess the effects of intravenous co-administration of ibuprofen-lysine on the pharmacokinetics of amikacin during the first days of life in preterm infants. The pharmacokinetics of amikacin were retrospectively calculated in a cohort of 73 neonates (gestational age <31 weeks) who received either ibuprofen-lysine or placebo following inclusion in the multicentre ibuprofen prophylaxis study. Assuming a one-compartment model with instantaneous input and first-order output, there was no significant difference in the median distribution volume (0.63 vs. 0.59 liters/kg), but the median serum half-life (16.4 vs. 12.4 h) of amikacin was significantly longer (p < 0.02), and the clearance (0.36 vs. 0.6 ml/kg/min; p < 0.005) of amikacin was significantly lower in infants who received ibuprofen-lysine. We conclude that the time interval between consecutive amikacin administrations should be prolonged, if ibuprofen-lysine is co-administered.

Introduction
The bactericidal efficacy of amikacin relates to its peak serum concentration due to a concentration-dependent killing combined with a postantibiotic effect of the drug, while renal side effects and ototoxicity relate to the average plasma amikacin concentration, based on the saturation of the renal and cochlear cell-binding sites. The combination of efficacy and safety resulted in the concept of administration of relative larger doses of the drug with extended dosing intervals between consecutive administrations [1–6].

The interindividual variability in pharmacokinetics of amikacin makes it difficult to achieve an effective and safe administration in the individual preterm infant.
Based on differences in body composition and renal immaturity, marked differences in distribution volume (V_d, l/kg) and total body clearance (CL_r, ml/kg/min) of this hydrophilic drug have been observed. Since amikacin is cleared by renal elimination, co-administration of drugs with effects on the kidneys is likely to affect the pharmacokinetics of amikacin [3, 5–7].

Ibuprofen was reported to cause less renal side effects as compared with indomethacin when prescribed for therapeutic pharmacological closure of patent ductus arteriosus, but renal effects (lower urine output, increased creatininaemia) were still observed in therapeutic and prophylaetic trials [8–12]. We, therefore, wanted to assess the effects of intravenous co-administration of ibuprofen-lysoine on the pharmacokinetics of amikacin during the first days of life in a cohort of preterm infants [12].

**Patients and Methods**

**Patients**

In the multicentre ibuprofen prophylaxis study (MIPS), preterm infants with a gestational age (GA) <31 weeks at birth were randomised in a double-blind approach to receive either ibuprofen-lysoine or placebo (normal saline) during the first 3 days of life. The first dose of ibuprofen-lysoine (10 mg/kg and 1 ml/kg, respectively) was administered as an intravenous infusion of 15 min within the first 6 h of life. The two consecutive doses (5 mg/kg and 0.5 ml/kg, respectively) were administered 24 and 48 h after the first dose. Exclusion criteria for the MIPS were perinatal asphyxia (Apgar score at 5 min <5), serum creatininaemia >1.3 mg/dl, observed clinical bleeding tendency or thrombocytopenia (<60,000/mm^3), life-threatening septicemia, or documented intraventricular haemorrhage before inclusion. The neonatal characteristics (GA, birth weight, Apgar scores at 1 and 10 min, antenatal betamethasone, and antenatal indomethacin) were recorded. The MIPS was approved by the local ethical committee of the University Hospital Gasthuisberg, Leuven, like in all other centres of the MIPS, and the infants were included after informed consent of the parents was obtained [12]. In infants who entered the Leuven part of the MIPS and who also received amikacin during the first days of life, data on amikacin serum samples were retrospectively collected to calculate the pharmacokinetics of amikacin.

**Drug Administration and Sampling**

During the period the MIPS was conducted, combined administration of amikacin (20 mg/kg/36 h in infants with a GA <30 weeks and 20 mg/kg/24 h in those with a GA ≥30 weeks) and ampicillin (2 × 50 mg/kg/day) was the standard empiric treatment for suspected early-onset bacterial infection in the Gasthuisberg unit. Amikacin at a dose of 50 mg/ml (Amikin®; Bristol Myers Squibb Belgium) was given as an intravenous infusion of 20 min by syringe driver (Sims Graseby, Warford, UK). Administration was initiated shortly after admission. Blood samples were drawn by arterial line or by venous puncture just before C_min and 1 h after initiation or 40 min after completion of administration (C_max) of the second dose of amikacin.

**Analysis**

The amikacin serum concentrations were determined using a fluorescence polarization immunoassay (TDx, Abbott Laboratories, Abbott Park, Ill., USA) following sample collection and are expressed in milligrams per liter.

**Pharmacokinetics**

The pharmacokinetics (fig. 1) were calculated assuming a one-compartment model with instantaneous input and first-order output. For every single patient a logarithmic trend line was calculated based on C_max and C_min. C_max was calculated based on C_max = C_max - C_min. The slope of the curve (slope = (log C_min - log C_max) / (time interval)) was used to calculate the time constant K (slope × 2.303) and elimination half-life T_1/2 (0.693/K). The Y_0 (mg/kg) was calculated based on V_d = dose administered (mg/kg)/C_max. Therefore, C_min was calculated based on C_max and T_1/2. The clearance was calculated based on CL_r = K × V_d.

**Statistics**

Data are reported as mean values ± SD, if a normal distribution was documented, or as median and range, if a non-normal distribution was documented (Kolmogorov-Smirnov test). The chi-square test or the Mann-Whitney U test was used to study differences in clinical characteristics and pharmacokinetics of amikacin in infants who received either ibuprofen-lysoine or placebo. The correlations (Spearman rank) among GA, V_d, T_1/2, and CL_r were calculated using MedCalc® statistical software (MedCalc Software, Mariakerke, Belgium). p < 0.05 was considered significant.
Table 1. Clinical and pharmacokinetic data of preterm (GA <31 weeks) infants (mean ± SD, median and range in parentheses, or incidence)

<table>
<thead>
<tr>
<th>Pharmacokinetics of amikacin, available infants</th>
<th>Ibuprofen</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>982 ± 380</td>
<td>1,064 ± 390</td>
<td>NS</td>
</tr>
<tr>
<td>GA, weeks</td>
<td>27.4 ± 1.7</td>
<td>27.8 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar score 1 min</td>
<td>5 (1–9)</td>
<td>6 (1–9)</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar score 10 min</td>
<td>9 (7–10)</td>
<td>9 (7–10)</td>
<td>NS</td>
</tr>
<tr>
<td>Antenatal betamethasone, %</td>
<td>39</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Antenatal indomethacin, %</td>
<td>7</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>C_max, mg/l</td>
<td>46.7 (89–24.5)</td>
<td>40.9 (88.1–10.4)</td>
<td>NS</td>
</tr>
<tr>
<td>C_min, mg/l</td>
<td>9.9 (19–3.5)</td>
<td>6.2 (19–1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>V_d, V/kg</td>
<td>0.63 (0.27–3.1)</td>
<td>0.59 (0.19–1.24)</td>
<td>NS</td>
</tr>
<tr>
<td>T_1/2, h</td>
<td>16.4 (7.8–92.1)</td>
<td>12.4 (6.7–60.3)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>C_L, ml/kg/min</td>
<td>0.36 (0.14–0.84)</td>
<td>0.6 (0.03–2.6)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Results

As shown in Table 1, based on C_max (40) data of 76 infants and on C_min data of 84 infants, the pharmacokinetics could be calculated for 73 infants (34 ibuprofen, 39 placebo).

There were no significant differences in GA (27.4 ± 1.7 vs. 27.8 ± 2 weeks) or birth weight (982 ± 390 vs. 1,064 ± 380 g) between infants who received either ibuprofen or placebo. The antenatal use of indomethacin for tocolysis (7 vs. 10%) or betamethasone for antenatal lung maturation (39 vs. 34%) was not significantly different.

There was no significant difference between infants who received either ibuprofen-lysine or placebo in median C_max (40) (46.7 mg/l, range 89–24.5, vs. 40.9 mg/l, range 88.1–10.4) or V_d (0.63 liters/kg, range 0.27–3.1, vs. 0.59 liters/kg, range 0.19–1.24) of amikacin. The peak concentrations of amikacin were >20 mg/l in 70 out of 76 infants. We could not document a significant correlation of GA with C_L or T_1/2 of amikacin in this population. The trough concentrations of amikacin were >4 mg/l in 68 out of 84 infants (38 ibuprofen, 30 placebo) and >10 mg/l in 24 out of 84 infants (17 ibuprofen, 7 placebo). A significant difference in median C_min values (9.9 vs. 6.2 mg/l) of amikacin between both groups was documented (p < 0.01). The median T_1/2 values were significantly longer (16.4 h, range 7.8–92.1, vs. 12.4 h, range 6.7–60.3; p < 0.02), and the median C_L was significantly lower in infants who received ibuprofen (0.36 ml/kg/min, range 0.14–0.84, vs. 0.6 ml/kg/min, range 0.03–2.6; p < 0.005).

Discussion

Data on pharmacokinetics in neonates are still rare, leading to frequent off-label use of drugs in neonates [13]. The effects of co-administration of different drugs on pharmacokinetics are even less frequently studied. Using a retrospective study design, the pharmacokinetics of amikacin were studied in a selected cohort of extreme preterm infants (GA <31 weeks) included in the MIPS which is a prospective randomized, double-blind, placebo-controlled trial on the effects of prophylactic co-administration of ibuprofen-lysine during the first days of life [11].

Using this approach, two important results were documented. Firstly, the trough serum concentrations of amikacin in the placebo group as well as those in the ibuprofen group were too high, indicating that the intervals used between two administrations of amikacin during the study period (either 24 or 30 h) were still too short. Secondly, co-administration of ibuprofen-lysine still further increased the clearance of amikacin, resulting in a significant increase of the median T_1/2 of this drug.

There is still uncertainty about the most effective and safe way to administer any aminoglycoside in neonates. While still being off-label use in neonates, pulse administration seems to be a more promising approach. The transitory higher but less frequent maximum serum concentration allows an optimal C_max/minimal inhibitory concentration ratio, increasing the bactericidal efficacy and decreasing the risk of bacterial resistance [1–3]. In addition, due to a saturable process in binding of aminoglycosides on the renal proximal brush border membranes, pulse administration likely diminishes the risk of toxicity, provided that the trough concentration is low, although...
the nephrotoxicity of amikacin is lower in neonates, likely due to a reduced renal uptake capacity [14, 15].

Based on a relative higher water content, preterm infants have a higher V₀ for hydrophilic drugs. Therefore, a relatively higher dose of amikacin is necessary in more preterm infants to achieve a sufficient concentration at the site of infection. A loading dose of 20 mg/kg in this study resulted in an optimal median Cₘₐₓ₄₆ in both groups. Since life-threatening infection was an exclusion criterion for the MIPS, we are not able to provide additional data on efficacy.

The interindividual variability in elimination characteristics of amikacin makes it difficult to achieve safe trough serum levels in neonates. Since amikacin is cleared by renal elimination and since renal elimination has a maturational trend, more recent dosing charts frequently use a GA-based time interval [3, 5-7, 16, 17]. The need for a longer time interval between consecutive administrations in extremely preterm infants is demonstrated in this study. This is in line with results of several reports, suggesting a time interval of 42–48 h. Therefore, a more elaborated GA-based dosing chart with additional lengthening of interval has in the meanwhile been implemented in the Gashuisberg unit, with additional adaptations, if there are associated cardiovascular instability, hypoxic episodes, or asphyxia at birth. In the same paper and evaluating a more heterogeneous cohort of infants, Langhendries et al. [3] also suggested to increase the interval by 6 h during co-administration of indomethacin.

We observed a significant increase in the serum half life (16.4 vs. 12.4 h) of amikacin and a significant decrease in the clearance (0.36 vs. 0.6 ml/kg/min) of amikacin in preterm infants who received ibuprofen during the first days of life. Since this cohort is a more homogeneous group of preterm infants, excluding those with renal failure or birth asphyxia, we believe the observed differences in pharmacokinetics are causally linked with the co-administration of ibuprofen-lysine. When ibuprofen-lysine is co-administered within the first days of life, the dose interval of amikacin should be increased by at least 6–8 h.

These findings underscore the relevant effect of ibuprofen on the renal function, at least in preterm infants (GA <31 weeks) during their first days of life. These findings are in line with the observations of Hartmann et al. [18] who reported on the renal effects in another part of the MIPS. These authors documented a significant decrease in the mean urine output on day 1 (1.36 vs. 2.2 ml/kg/h) and a significant increase in mean creatininaemia on day 3 (1.1 vs. 0.9 mg/dl).

Actually, renal side effects of either indomethacin or ibuprofen in preterm infants in prophylactic trials seem to be equally prominent, in contrast to their use in therapeutic trials where ibuprofen was associated with lesser renal side effects as compared with indomethacin [8–11]. In the TIPPI trial [10], more infants who received indomethacin (3 × 0.1 mg/kg) developed oliguria (<0.5 mg/kg/h), and there was also a trend to a higher incidence of oliguria as compared with control infants in the study performed by Ment et al. [11]. These clinical observations in human neonates correlate well with recently reported renal effects of either indomethacin or ibuprofen in newborn rabbits and are based on a reduced glomerular filtration rate due to a reduced renal blood flow [19, 20]. This observation re-emphasizes the effect of any non-selective cyclooxygenase inhibitor on the perinatal renal function. Perinatal renal maturation processes with a progressive reduction of the impact of prostaglandins on renal function might at least partially explain the differences in impact of renal side effects in prophylactic as compared with therapeutic trials [7–13].

To conclude, it seems appropriate to further increase the GA-based interval between consecutive administrations of amikacin during co-administration of ibuprofen-lysine. This study further is a particular illustration of need and relevance of the systematic evaluation of co-administration of different drugs and their interactions in neonates.

Acknowledgment

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Ibuprofen and Pharmacokinetics of Anikacin

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Cerebrospinal fluid pharmacokinetics of paracetamol after intravenous propacetamol in a preterm infant

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Anderson et al. illustrated that the pharmacokinetics (PK) of cerebrospinal fluid (CSF) approximate closer to the analgesic effect compartment than those of plasma after enteral administration of paracetamol in children. Peak plasma concentrations were reached at 90–120 min after enteral administration in children, with maximal analgesia occurring 1 h later [1].

We recently reported data on the plasma pharmacokinetics of propacetamol in neonates [2]. Propacetamol is a pro-drug of paracetamol designed to allow intravenous (i.v.) administration [2]. In addition, we had the opportunity to study the CSF pharmacokinetics of propacetamol in a former preterm infant who already had a ventriculo-external drain (enabling continuous drainage of fluid from the lateral ventricle) inserted because of posthaemorrhagic hydrocephalus [3].

After undergoing retinal surgery, the infant who had a postconception age of 39 weeks, received i.v. tramadol. In addition, and after parental consent, a single i.v. dose of propacetamol (20 mg kg\(^{-1}\)) was administered over 20 min. A sample of CSF was collected before propacetamol was administered, and then hourly for the first 12 h after dosing. This protocol was approved by the local ethics committee of the University Hospitals, Gasthuisberg, Leuven, Belgium.

The median rate CSF production was 0.7 ml h\(^{-1}\). Analysis of the CSF sample immediately before drug administration showed no red or white blood cells to be present. Protein content was 1917 mg l\(^{-1}\). CSF paracetamol concentrations were determined using high-performance liquid chromatography. After correction for the volume of the ventriculo-external drain (3 ml), maximum CSF paracetamol concentration was 5.8 mg l\(^{-1}\) and was reached 150 min after drug administration (Figure 1). Assuming first-order pharmacokinetics, the terminal elimination half-life of paracetamol in the CSF in this infant was estimated to be 182 min, which is comparable to its plasma half-life (172 ± 59 min, mean ± SD) after single-dose i.v. administration of propacetamol to full-term infants [2].

Although the maximum CSF paracetamol concentration after single-dose i.v. administration occurs sooner than after other routes of administration, the passage of paracetamol across the blood–brain barrier causes a lag time between maximum plasma and CSF concentrations, whereas drug clearance from the CSF is based on bulk flow back to plasma [1, 4].

This present finding is relevant, since the CSF paracetamol concentration profile approximates more closely
to the analgesic effect compartment than does that of plasma. Effective analgesia will be reached sooner after i.v. administration of propacetamol compared with other routes.

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Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial

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Summary
Background Ibuprofen is used for treatment and prevention of patent ductus arteriosus in low-birthweight infants. Its effects on regional circulations differ from those of indomethacin. Because prophylactic indomethacin reduces the frequency of severe intraventricular haemorrhage and patent ductus arteriosus, we aimed to study the efficacy of early ibuprofen in reducing these outcomes in a double-blind, multicentre trial.

Methods Within 6 h after birth, 415 low-birthweight infants (gestational age <31 weeks) were randomly allocated ibuprofen-lysine (10 mg/kg then two doses of 5 mg/kg after 24 h and 48 h) or placebo intravenously. The primary outcome was occurrence of severe intraventricular haemorrhage; secondary outcomes were occurrence of patent ductus arteriosus and possible adverse effects of ibuprofen. Analysis was by intention to treat.

Findings 17 (8%) of 205 infants assigned ibuprofen and 18 (9%) of 210 assigned placebo developed severe intraventricular haemorrhage (relative risk 0.97 [95% CI 0.51–1.82]). In 172 (84%) infants of the ibuprofen group, the ductus was closed on day 3 compared with 126 (60%) of the placebo group (relative risk 1.40 [1.23–1.59]). No important differences in other outcomes or side-effects were noted; however, urine production was significantly lower on day 1 and concentration of creatinine in serum was significantly higher on day 3 after ibuprofen.

Interpretation Ibuprofen prophylaxis in preterm infants does not reduce the frequency of intraventricular haemorrhage, but does decrease occurrence of patent ductus arteriosus.

Introduction
Ibuprofen, a non-steroidal anti-inflammatory drug, is used in premature infants to induce closure of patent ductus arteriosus. Compared with indomethacin, it causes fewer side effects and has different effects on the cerebral circulation of such infants. Prophylactic administration of indomethacin in very-low-birthweight infants reduces both symptomatic patent ductus arteriosus and intraventricular haemorrhage. This strategy, however, has not improved outcome at age 18 months. The explanation for this lack of improvement is not completely understood. Results of studies in animals and people have shown that indomethacin has vasoconstrictive effects in the brain, and decreases cerebral blood flow and cerebral oxygen delivery interfering with oxygen use in the brain, and disturbs mesenteric and renal circulations. Ibuprofen is not known to cause these effects.

Because ibuprofen seemed to be effective in previous studies for early pharmacological closure of patent ductus arteriosus and had fewer side-effects than indomethacin, and because it does not affect cerebral oxygenation, we theorised that it could be used as prophylactic treatment in preterm infants. Our primary aim was to investigate whether ibuprofen would prevent development of severe intraventricular haemorrhage. Other endpoints were effect on patent ductus arteriosus and occurrence and severity of adverse reactions.

Methods
Participants Infants were eligible for inclusion within 6 h of birth in one of the neonatal intensive care units of the seven participating hospitals. Infants had to have a gestational age of 24–30 weeks and written informed consent had to be obtained from their parents before enrolment. Infants were excluded if they had a major congenital malformation or chromosomal anomaly, intraventricular haemorrhage higher than grade 1 already detected during baseline cranial ultrasonography, an Apgar score at 5 minutes of less than 5, signs of congenital infection or life-threatening sepsis, uncontrollable hypertension, or contraindications for administration of ibuprofen (eg, serum creatinine greater than 115 μmol/L or serum bilirubin more than 85 μmol/L, platelet count less than 60×10^9/L, tendency to bleed as revealed by haematuria, blood in the endotracheal or gastric aspirate or stools, or oozing from puncture sites). The study was approved by the independent medical ethics committee at each hospital (Antwerp University Hospital, Ghent University Hospital, University Hospital Leuven, Cliniques Universitaires Saint-Luc, Sint-Jan Ziekenhuis, Queen Paola Children's Hospital, and the CHC Clinique Saint-Vincent). Enrollment started on a different date at each site.

Procedures The study was a double-blind, randomised, multicentre trial. Randomisation was done independently by the...
Articles

Season pharmacist at each hospital in a 1 to 1 ratio between ibuprofen and placebo, in blocks of ten. Infants received intravenously either three doses of ibuprofen-lysine as an initial dose of 10 mg/kg within the first 6 h of life, followed by two doses of 5 mg/kg after 24 h and 48 h, or three doses of saline as an initial dose of 1 mL/kg, followed by 0.5 mL/kg after 24 h and 48 h. The doses and intervals for ibuprofen were based on earlier pharmacokinetic data. The study preparations were delivered in 2-mL glass vials containing either 20 mg ibuprofen with 14 mg lysine in water or normal saline. Ibuprofen-lysine is a clear and colourless solution and was prepared by the same method as described in our earlier trial. Ibuprofen-lysine or placebo was infused over 15 minutes. The attending and consulting physicians, nurses, study collaborators, and parents were unaware of treatment allocation. Fluid was given according to standard guidelines.

The primary outcome was the occurrence of severe intraventricular haemorrhage. Baseline cranial ultrasonography was done on every infant enrolled before the first dose of study drug was given. The examination was repeated on days 2, 3, 7, 14, and 28 of life, or before discharge. Intraventricular haemorrhage was graded from 1 to 4 according to the standard classification systems, and the highest grade was recorded in cases of increasing severity. The presence of cystic periventricular leucomalacia after age 2 weeks was recorded.

Secondary outcomes were: presence of echocardiographically confirmed open ductus arteriosus after day 1 of life and the need for its pharmacological rescue treatment or surgical ligation; occurrence of renal dysfunction as measured by urine production; necrotising enterocolitis; and death. Cardiac ultrasonography was recommended at baseline and an echocardiographic assessment was done after the third dose of study drug. Shunting through the ductus was graded as minor, moderate, or severe as described previously. If the ductus was still patent with moderate to severe left-to-right shunt in patients receiving ventilatory support after administration of propylthiouracil, a non-randomised intravenous pharmacological rescue treatment was given with either indomethacin (three doses of 0.2 mg/kg with 12-h intervals) or ibuprofen-lysine (first dose of 10 mg/kg followed by two doses of 5 mg/kg at 24 h and 48 h). If the infant was still on mechanical ventilation without decrease of the ductal shunt after rescue intervention, the ductus was surgically ligated. Data were obtained on the mother, antenatal medication, infants' baseline characteristics, ventilatory support, administration of dopamine for hypotension, and clinical courses.

Statistical analysis
Sample size was calculated to detect a possible difference in the occurrence of intraventricular haemorrhage of 10 percentage points between groups with 95% confidence and a power of 80%, on the assumption of a baseline of 15% in the study population. Interim analyses were done at 50% recruitment for primary and secondary outcome measures. We planned to stop the trial if we measured a difference of 15% in the primary outcome, or a significant increase for the secondary outcome of the composite variable death or ligation. Data were analysed by intention to treat. The primary outcome was severe haemorrhage (grade 3-4) by contrast with minor or no haemorrhage. Distributions of continuous data were tested for normality by Shapiro-Wilk's W test. Differences between groups were tested by t test for normally distributed data, and by Mann-Whitney U test when the distribution was not normal. Differences in the distributions of categorical data were tested by Mantel-Haenszel test, $\chi^2$, or by Fisher's exact test when
appropriate. To check for confounding factors, logistic regression analyses were done separately for severe haemorrhage and patent ductus arteriosus. We used SPSS software (version 10.0).

Results
Between Feb 1, 1999, and Sept 30, 2001, 775 infants were screened (figure). 415 were randomly assigned treatment and analyzed. Mean birthweight and gestational age were similar for infants who were and were not included (data not shown). Infants in the placebo group were born at a mean gestational age of 28-1 weeks (SD 1-6) with a mean birthweight of 1065 g (324), and those in the ibuprofen group had a mean gestational age of 28-8 weeks (1-7) and a mean birthweight of 1048 g (315). The following rates were recorded in the placebo and ibuprofen groups, respectively: antenatal steroid use 180 (86%) and 169 (82%); non-steroidal anti-inflammatory diclofenac 47 (22%) and 40 (20%); chronic clinical jaundice 45 (21%) and 42 (20%), and prolonged rupture of membranes 69 (33%) and 72 (35%). 177 (84%) infants in the placebo group and 174 (85%) in the ibuprofen group were ventilated from birth with either conventional or high-frequency ventilation. 116 (55%) and 123 (60%) were receiving surfactant treatment. Baseline echocardiography was done in 199 infants in the placebo group and 110 in the ibuprofen group, identifying two and three closed ducts, respectively. The median time after birth of the first dose of study preparation was 280 minutes in the placebo group and 290 minutes in the ibuprofen group (p=0.75). Eight infants in each group did not receive a complete course of three doses (figure).

The frequency of severe intraventricular haemorrhage did not differ between the groups (table 1). Multiple logistic regression identified no confounding by birthweight, gestational age, centre, or other factor (data not shown). Significantly more infants had a closed ductus arteriosus after the third day of life in the ibuprofen group than in the placebo group, a difference that remained significant within each gestational-age category and in the three lowest birthweight categories (table 2). Again, multiple regression analysis identified no major confounding. In infants whose ductus reopened after it had been closed on day 3, two of seven in the placebo group and one of five in the ibuprofen group received rescue treatment. In total, 42 infants received rescue treatment in the placebo group (27 indomethacin, 15 ibuprofen), as did 13 in the ibuprofen group (five indomethacin, eight ibuprofen). The rate of ductal closure after rescue interventions did not differ between the groups (24 of 42 [57%] and seven of 13 [54%], p=0.83). The ductus closed in 20 of 32 infants given indomethacin rescue treatment and in 11 of 23 given ibuprofen rescue treatment (p=0.28).

During the first 2 weeks of life, 17 infants died in the placebo group versus ten in the ibuprofen group. At the end of the second week, after final rescue treatment and final surgical treatment, the proportion of surviving infants with a persisting ductus not requiring any further treatment differed between groups 67 (35%) in the placebo group and 80 (34%) in the ibuprofen group (p=0.001). The outcome and occurrence of major complications did not differ between groups. However, infants who were allocated placebo treatment had significantly higher urine production on day 1 and a significantly lower concentration of creatinine in serum on the third day of life (table 3).

Discussion
This study provided no evidence for a preventive effect of ibuprofen on the occurrence of severe intraventricular haemorrhage, but the drug did induce closure of patent ductus arteriosus in low-birthweight infants. However, because of the large CIs for severe intraventricular

<table>
<thead>
<tr>
<th>Placebo (n=245)</th>
<th>Ibuprofen (n=265)</th>
<th>p</th>
<th>Treatment effect* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>25 (13%)</td>
<td>23 (14%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Necrotizing enterocolitis stage 3</td>
<td>12 (5%)</td>
<td>4 (2%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cystic pericarditis</td>
<td>5 (2%)</td>
<td>10 (5%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Days on ventilat</td>
<td>4 (0-8)</td>
<td>6 (0-10)</td>
<td>0.40</td>
</tr>
<tr>
<td>Days on oxygen</td>
<td>24 (10-44)</td>
<td>25 (10-12)</td>
<td>0.36</td>
</tr>
<tr>
<td>Brochoesophageal fistula</td>
<td>97 (46%)</td>
<td>93 (50%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Chronic lung disease or death</td>
<td>52 (24%)</td>
<td>50 (25%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Renal effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine production (ml/kg/h)'r'</td>
<td>23 (14-4)</td>
<td>14 (11-17)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Oliguria&lt;0.5 ml/kg/h'c'</td>
<td>30 (14%)</td>
<td>25 (11%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Serum creatinine (umol/L)'s'</td>
<td>69 (16)</td>
<td>72 (19)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Data are as number (%), unless otherwise specified. *Defined as relative in categorical data and mean difference for continuous data. Median (IQR). Defined as supplemental oxygen beyond 18 days of life. Defined as supplemental oxygen beyond 18 weeks of postmenstrual age. Mean (SD).
haemorrhage, a small effect cannot be excluded. Other studies have reported a pronounced and significant reduction of severe haemorrhage after early indomethacin administration. However, there is some overlap between the CIs from our report and those from these others. A significant reduction in the frequency of grade 3 or 4 intraventricular haemorrhage after prophylactic administration of indomethacin was reported in the Cochrane Review by Fowlie and Davis (pooled relative risk 0.66 [95% CI 0.53-0.82]).

Although both ibuprofen and indomethacin are non-selective cyclo-oxygenase inhibitors, they have been reported to have different effects on cerebral circulation. Indomethacin causes vasoconstriction of cerebral blood vessels with a rapid reduction in cerebral blood flow and blood volume. These effects took place before changes in cerebral prostaglandin concentrations. Infusion of ibuprofen did not cause such a reduction in studies with the doppler technique and near-infrared spectroscopy. Although the exact mechanisms have not yet been ascertained, the different effects of these drugs on cerebral haemodynamics are probably not related mainly to inhibition of prostaglandin synthesis. Our study seems to emphasise that the different cerebrovascular effects of the drugs are associated with different clinical consequences, although a causal relation is only speculative.

Indomethacin has been suggested to exert its stabilising effect on cerebral circulation indirectly by closing the ductus arteriosus. Because the rate of ductal closure was significantly higher in our ibuprofen group than the placebo group, this mechanism does not seem to have played an important part in prevention of haemorrhage. However, various other processes have a role in intraventricular haemorrhage in preterm infants. The fall in cerebral blood flow after indomethacin is accompanied by a decline in cerebral oxygen delivery and the concentration of oxidised cytochrome oxidase in the brain, indicating reduced cerebral intracellular oxygenation. These effects are cause for concern. In terms of long-term effects, the lack of effect of ibuprofen in intraventricular haemorrhage is disappointing. However, many other factors affect later neurodevelopmental outcome, and severe bleeding might not be the most important one. The absence of declining cerebral oxygen availability after ibuprofen could possibly be beneficial. Long-term studies of neurodevelopmental outcome after ibuprofen use in preterm infants are warranted.

In accordance with earlier reports, our results confirm that ibuprofen is effective in inducing closure of a patent ductus arteriosus. In particular, our data show that ibuprofen prophylaxis was also effective in inducing ductal closure in infants of birthweight less than 1000 g and in those born at 24 to 26 weeks of gestation. Although efficacy differed significantly between our two treatment groups, the difference was smaller than in other reports. In an unmasked comparative study of 46 infants, the ductal closure rate was 87% in the ibuprofen prophylaxis group but only 30% in the control group, and in a study comparing early versus late ibuprofen treatment in 80 infants, the ductus was closed in 93% after early ibuprofen but in only 8% of those who did not receive early treatment. Ductal closure rates with prophylaxis are higher than those after therapeutic use, which seems to parallel neonatal experience with indomethacin. Many antenatal and postnatal factors are known to affect closure of ductus arteriosus in preterm infants; the variation in proportions with closure among trials could be related to these factors.

The need for subsequent rescue treatment of the patent ductus and the number of infants with a persistent ductus at the end of 2 weeks were lower with ibuprofen than with placebo. The frequency of major complications did not differ between the two groups, and no other benefits were evident. Although more ducts were closed at 2 weeks of life in the ibuprofen group many infants would have had spontaneous closure of the ductus so were exposed to the drug unnecessarily. 218 treatments (205 prophylactic and 13 rescue) were given in the ibuprofen group compared with 42 (all rescue) in the placebo group.

Ibuprofen seemed to be safe. The same formulation of ibuprofen-lysine was used in this trial as in all previous ones. The occurrence of severe hypoxaemic events was reported after early administration of an ibuprofen solution buffered with THAM (tris(hydroxymethyl) aminomethane), leading to early closure of that trial. We could not attribute such acute hypoxaemic events to ibuprofen in our trial, and these effects were not reported by others. On the third day of life, ibuprofen induced less oliguria than indomethacin. When given within the first 6 h after birth, ibuprofen significantly decreased urine production on the first day compared with placebo, possibly contributing to a raised concentration of creatinine in serum on day 3. This finding is not unexpected because all non-steroidal anti-inflammatory drugs can have some effect on renal function. The reduced urine production was, however, short lasting, and the difference between the groups was no longer significant on day 3. None of the 205 infants who received ibuprofen in our trial developed renal failure. The occurrence of oliguria in the control group is noteworthy. By comparison with our previous report, gestational ages and birthweights were lower and ibuprofen was administered earlier. Although accurate and detailed assessment of renal function (eg, by measurement of inulin clearance) was not possible, our results suggest that at least some renal effects can be expected after ibuprofen prophylaxis in preterm infants, as suggested in studies of newborn rabbits. Ibuprofen carries the theoretical risk of increasing bilirubin encephalopathy by displacing bilirubin from albumin binding sites. An increase of four times in unbound bilirubin has been reported with concentrations of ibuprofen in serum of 150 mg/L. Although the peak concentrations of ibuprofen in plasma that we measured
in 77 preterm infants on day 3 (33.5 mg/L [SD 8.5]) and day 5 (28.4 mg/L [SD 9.2]) were much lower. "We have to exercise caution when using ibuprofen in preterm infants with jaundice until more data become available.

In conclusion, prophylactic administration of ibuprofen in very-low-birthweight infants did not seem to prevent occurrence of severe intraventricular haemorrhage, but it was associated with a significantly lower frequency of persistent ductus arteriosus and subsequent need for pharmacological rescue treatment. No side-effects could be attributed to ibuprofen prophylaxis, except a significant but transient decrease in urine production on the first day of life. Because the effects of ibuprofen on long-term outcomes are unknown, further trials that deal with these features in particular are warranted.

Contributors
The study was designed, planned, and coordinated by B Van Overmeire and J P Langendries with the support of the other authors. All authors participated in data collection, data review, and interpretation of results. J Weyer helped with data analysis and statistics. B Van Overmeire wrote the paper with the assistance of J P Langendries. All authors reviewed the final version of the report.

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Conflict of interest statement
We declare that we have no conflict of interest.

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References
Pharmacokinetics of single dose intravenous propacetamol in neonates: effect of gestational age

K Allegaert, C D Van der Marel, A Debeer, M A L Pluim, R A Van Lingen, C Vanholec, D Tibboel, H Devlieger

Aim: To investigate the pharmacokinetics and pharmacodynamics of single dose propacetamol in preterm and term infants on the first day of life.

Methods: Neonates were stratified by gestational age. Preterm (< 37 weeks) and term (37-41 weeks) infants received a single dose of propacetamol in the first 24 hours of life when they had minor, painful procedures or as additional treatment in infants receiving opioids. Blood samples were taken from an arterial line, and pain was evaluated by a multidimensional pain scale. Results were reported as mean (SD). Student's t and Wilcoxon tests were used to compare the groups.

Results: Thirty neonates were included, 10 of which were term infants. Serum half life was 277 (143) minutes in the preterm infants and 172 (59) minutes in the term infants (p < 0.05). Clearance was 0.116 (0.08) litre/kg/h in the preterm infants and 0.170 (0.06) litre/kg/h in the term infants (p < 0.05). Gestational age correlated with serum half life (r = 0.46). No effect of sex or administration of prenatal steroids was found on the pharmacokinetics of propacetamol. In neonates who only received propacetamol (n = 13), the level of analgesia seemed to be associated with the therapeutic (≥ 5 mg/l) level.

Conclusions: A correlation was found between gestational age and the serum half life of propacetamol. The maturational trend of clearance and half life in preterm and term neonates is in line with data on the pharmacokinetics of propacetamol beyond the newborn period.

PATIENTS AND METHODS

All neonates admitted within the first 24 hours of life to the neonatal intensive care unit and with an arterial line in place were considered for inclusion if propacetamol was administered. The decision to prescribe propacetamol or any other analgesic was made by the attending neonatologist. Propacetamol was administered when minor, painful procedures were carried out, such as insertion of a peripheral arterial or venous line, insertion of a central venous line, or placement of a chest tube, or as additional treatment in infants receiving opioids. Exclusion criteria were major congenital malformations and severe birth asphyxia (Apgar score < 4 at five minutes) in line with other studies performed on neonates. The initial dose (20 mg (10 mg propacetamol)/kg) was based on literature data, with the intention to change this dose if interim analysis of the propacetamol levels in the first 15 infants was inadequate (plasma levels < 5 mg/l within 8-10 hours of administration). Maternal use of analgesics (besides propacetamol) was not an exclusion criterion in this single-dose pharmacokinetic study.

As part of standard nursing care in the neonatal intensive care unit, a multidimensional pain scale was used to document pain/confort. With this pain scale (Leuven neonatal pain scale), three different levels can be discriminated: level 1, 0-4/10 (no pain); level 2, 4-6/10 (mild discomfort); level 3, 6/10 (pain). An algorithm is used within the unit to administer and adapt analgesics based on this pain scale.

The number and dose of other analgesics or sedatives prescribed in the first day of life were recorded. Birth weight data were available for all patients.
was documented on admission to the unit. GA was estimated by routine ultrasound examination before 20 weeks of gestation if available, or was based on the last menstrual period of the mother and postnatal physical characteristics.

Propacetacon was administered as a 15 minute infusion to avoid local discomfort. Blood samples (0.2 ml) were taken from an arterial line 30, 60, 90, 120, 180, 240, and 600 minutes after the start of intravenous administration. The maximum total amount of blood allowed to be collected in a single neonate was 1 ml/kg. After centrifugation, samples were stored at −20°C until analysis. Plasma paracetamol concentrations were determined using fluorescence polarisation: immunnassay (ADX system; Abbott Laboratories, North Chicago, IL, USA). The determination limit was 1 ng/ml, and the precision was 7%.

Pharmacokinetics were calculated assuming a linear one compartment model with instantaneous input and first order output. For every patient, a logarithmic trend line (y = a ln(x) + b) was calculated based on at least three plasma samples. The relative distribution volume (lites/kg) (Vd) and concentration at t = 0 (Cmax) were calculated. The slope of the curve (slope = (logCl2 − logCl1)/(t2 − t1)) was used to calculate the time constant K (slope < 2.303), elimination half life (0.693/K) (t1/2), and total clearance (K x Vd) (CL/A). Results are expressed as mean (SD) and range.

Students' t test (normal distribution) or the Wilcoxon test was used to compare clinical and pharmacokinetic findings in preterm (< 37 weeks GA) and term (> 37 weeks GA) infants. Linear regression analysis of the effect of GA and birth weight on V1 and Cl were calculated (MedCalc, MedSoftware, Mariakerke, Belgium). The protocol was approved by the local ethics committee (Gasthuisberg, Leuven, Belgium), and infants were only included after written informed consent had been obtained from the parents.

RESULTS

Thirty neonates of variable GA were included in this single-dose study. Fifteen received the 20 mg (10 mg paracetamol)/kg dose, and the remaining 15 received a 40 mg (20 mg paracetamol)/kg dose. Table 1 summarises the clinical characteristics. The overall mean (SD) birth weight was 2311 (605 g) g, and GA at inclusion was 33.8 (3.9) weeks. Postnatal age at inclusion was 12.7 (6.4) hours. Ten infants had a GA of > 37 weeks. Twenty infants were preterm (< 37 weeks GA), 10 of whom were younger than 32 weeks GA. Twenty-six infants received respiratory support, 16 of whom (53%) were ventilated. Fifteen (50%) received other analgesics in the first 24 hours of life.

In total, 213 blood samples were collected and analysed. Figure 1 gives the results for all the plasma samples: great variability can be observed.

Table 1 summarises the pharmacokinetic characteristics. No significant difference in relative V1 (lites/kg) between preterm and term infants was found, t1/2 and Cl were significantly (both p < 0.05) different between preterm and term infants. Mean t1/2 was 277 minutes in preterm infants and 172 minutes in term infants. Mean Cl was significantly lower in preterm than term infants (0.116 ± 0.170 lites/kg/h). In infants of < 32 weeks GA, mean t1/2 was 290 minutes, whereas in more mature infants (32–36 weeks GA) it was 265 minutes. Correlation of GA with t1/2 (r = -0.46) was stronger than birth weight with t1/2 (r = -0.39). Figure 2 shows linear regression analysis of the effect of GA on t1/2 with 95% confidence intervals. We found no difference in t1/2 or other clinical characteristics (birth weight, GA) between preterms (< 35 weeks GA) who received (n = 13) and preterms who did not receive (n = 6) perinatal steroids (betamethasone) for lung maturation. Neither did we find any sex related differences.

As this is a single-dose study, other analgesics were allowed. Half of the infants received at least one other analgesic (fentanyl, tramadol, ibuprofen, etc.) during the first 24 hours based on the standardised evaluation by pain score (Leuven neonatal pain scale). Level 1 pain (pain scale < 4) was documented in 26/30 infants in the hours before paracetamol administration, in 30/30 infants during the period when a therapeutic level (> 5 mg/l) of paracetamol had been reached, and 24/30 infants afterwards. If we consider only infants (n = 15) who did not receive any analgesic besides paracetamol in the first 24 hours, level 1 analgesia was documented in 14/15 infants before administration, in 13/15 infants in the period when a therapeutic level had been reached, and in 12/15 infants after this period.

DISCUSSION

The serum half life was 277 (143) minutes in preterm infants and 172 (59) minutes in term infants (p < 0.03). Clearance was 0.116 (0.08) lites/kg/h in preterm infants and 0.170 (0.06) lites/kg/h in term infants (p < 0.05). The pharmacokinetics and pharmacodynamics of paracetamol are well documented in adults and children, but there is only one study on its pharmacokinetics in infants younger than 1 year (n = 12, of which five were < 10 postnatal days), and there are no data on propacetamol in preterm neonates. The pharmacokinetics of paracetamol in this study were compared with the pharmacokinetics of paracetamol and propacetamol in other cohorts described in the literature.

Term neonates

Our findings in term infants are in line with the single study on intravenous propacetamol. Arnet et al. documented the pharmacokinetics in 12 infants, five of whom were less than 10 days old. The serum half life in these five neonates was 218 (30) minutes. Clr, was 0.149 (0.067) lites/kg/h, and Vd was 0.7 (0.2) (table 3). Pharmacokinetics after rectal
administration of paracetamol in term neonates were studied by Van Lingen et al. and Hopkins et al. Van Lingen et al. found a \( t_{1/2} \) of 162 (94) minutes (n = 10), and Hopkins et al. found a \( t_{1/2} \) of 228 minutes (n = 9). There are no studies on the pharmacokinetics of paracetamol after nasogastric administration in the first day of life. Studies in neonates by Hopkins et al. (n = 3) and Anderson et al. (n = 16) after nasogastric administration found a serum \( t_{1/2} \) of 168 minutes and 576 minutes respectively. Co-administration of opioids and its effect on gastric motility may, at least partially, explain these differences. There is a recent report on unintentional intramuscular administration of paracetamol in one term neonate; in that single case, the calculated serum half life was 210 minutes.

Preterm infants

Mean \( t_{1/2} \) (<37 weeks GA; n = 20) and \( C_L \) after a single dose were 277 minutes and 0.116 litre/kg/h in preterm infants, and the relative \( V_d \) was 0.61 litre/kg. In infants of <32 weeks GA, mean \( t_{1/2} \) was 290 minutes, and in more mature infants (32–36 weeks GA), it was 265 minutes. Data on the pharmacokinetics of paracetamol in preterm neonates are only available after rectal administration. Van Lingen et al. studied pharmacokinetics after rectal administration of paracetamol in 26 preterm neonates in the first day of life (28–36 weeks GA). \( t_{1/2} \) was 640 (342) minutes in the 28–32 week GA group and 490 (240) minutes in the 32–36 week GA group. Mean maximum concentration was 12.5 and 7.5 mg/l, and mean time to reach maximal concentration was 234 and 306 minutes (28–32 and 32–36 weeks). Lin et al. found a mean (SD) maximum concentration of 8.38 (3.9) mg/l and a mean (SD) time to reach maximum concentration of 78 (48) minutes after rectal administration of 20 mg/kg in five preterm neonates. These findings are formulation specific, but may be relevant in clinical care as therapeutic drug concentration after intravenous administration will be reached sooner.

Combining pharmacokinetic data in term and preterm neonates in our population with the findings of Auer et al. in neonates and infants, a maturational trend during the first year of life is observed (table 3). This is in line with the developmental pharmacokinetics described after oral or rectal administration of paracetamol.

Although we observed a maturational trend in the pharmacokinetics of paracetamol after intravenous administration, overall correlation \((r = 0.46)\) between GA and \( t_{1/2} \) is still weak. In contrast with rectal and oral administration, differences in bioavailability (versus rectal drainage, gastrointestinal motility) cannot explain this variability. Further study of other variables potentially responsible for this variability is needed. Prenatal administration of betamethasone for lung maturation had no maturational effect on \( t_{1/2} \) in this study. We did not find any sex related differences, in contrast with the findings reported after rectal administration.

Pharmacodynamic data suggest an analgesic effect of intravenous paracetamol in this population. The design of this study (not blinded, other analgesics allowed) does not allow us to draw conclusions other than that multiple dose administration of intravenous paracetamol should be adjusted for GA. Based on the longer \( t_{1/2} \) in preterm infants, either the interval should be longer or the dose should be lower, in line with reported regimens for rectal and oral administration.

Because of the major interindividual variability of the pharmacokinetics in preterm infants, we believe it is too early to make any multiple dose recommendations. In term

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### Table 2

| Pharmacokinetics of paracetamol in preterm (<37 weeks) and term (37-41 weeks) infants |
|---------------------------------|---|---|
| **Number of infants** | 20 | 10 |
| **Rel. \( V_d \) (litre/kg)** | 0.61 (0.15) | 0.64 (0.25) |
| **Mean \( t_{1/2} \) (min)** | 277 (143) | 172 (57) |
| **Range** | 87–690 | 195–369 |
| **Clearance (litre/kg/h)** | 0.116 (0.04) | 0.170 (0.06) |

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**Figure 2** Linear regression analysis (with 95% confidence intervals) of the effect of gestational age on serum half life \((r = 0.46)\).
Table 3  Mortality trend (mean) of serum half life ($t_1/2$) and relative distribution volume ($V_d$) in the first year of life after intravenous administration of propacental, based on this population* and on the study of Auftet et al. **

<table>
<thead>
<tr>
<th>Propranolol</th>
<th>Propranolol</th>
<th>Term day 1*</th>
<th>Term (&lt; 10 days)</th>
<th>&lt; 1 year (10-365 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number infants</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>$t_1/2$ (min)</td>
<td>2.79</td>
<td>2.66</td>
<td>1.72</td>
<td>2.10</td>
</tr>
<tr>
<td>Relative $V_d$ (l/mg/kg)</td>
<td>0.66</td>
<td>0.66</td>
<td>0.61</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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These results were partially presented at the biannual congress of the European Society of Developmental Pharmacology (ESDP) Liège, 25-28 October 2002.

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