Clinical pharmacology of analgesics in infants and the pharmacologic management of pain in neonates

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OBJECTIVES: The objectives of this study are to describe (1) the clinical pharmacology of analgesics in infants and (2) the pharmacologic management of pain in neonates.

METHODS: The bibliographic search was performed using PubMed and EMBASE databases as search engines.

RESULTS: Opioid analgesics are the most commonly used analgesics for acute pain and they include intravenous morphine (50 to 200 μg/kg), oral methadone (50 to 200 μg/kg), intravenous fentanyl (0.5 to 4 μg/kg), alfentanyl (10 to 20 μg/kg), sufentanil (10 to 15 μg/kg), and remifentanil (5 μg/kg). Fentanyl, alfentanyl, sufentanil and remifentanil are short-action opioid analgesics. Non-opioid analgesics can be used for moderate pain; they include oral paracetamol (acetaminophen, 12 to 15 mg/kg), the intravenous benzodiazepine midazolam (50 to 150 μg/kg) which is not recommended in neonates, intravenous propofol (2.5 mg/kg) which is used for induction of general anaesthesia, and ketamine, (2 mg/kg intravenously or 4 mg/kg intramuscularly) which produces a short-lasting, trance-like state with profound analgesia and amnesia.

CONCLUSION: The use of non-opioid analgesics has increased in the last years for the management of non-acute pain. If prevention or elimination of pain is not possible, a more realistic goal may be to aggressively intervene to minimize pain and its effects.

KEYWORDS: analgesia; analgesics; management of pain; neonate; pain; pharmacokinetics.

■ INTRODUCTION

The mainstay of systematic analgesia for moderate to severe pain is the use of opioid therapy. Opioids provide both sedation and analgesia, have a wide therapeutic window, and decrease hemodynamic and moderate stress response. The opioids include: morphine, methadone, fentanyl, alfentanyl, sufentanil, and remifentanil. Morphine and fentanyl are the most commonly used analgesic opioids in the "neonatal intensive care unit" (NICU).[1]

The non opioid analgesics comprise the non-steroidal anti-inflammatory drug paracetamol (acetaminophen), the benzodiazepine midazolam, which is not recommended in neonates, and the anaesthetics propofol and ketamine. Ketamine produces a trance-like state with profound analgesia and amnesia. In recent years, the use of non-opioid analgesics for the management of non-acute pain has increased.[2]

Neonates were believed to be unable to experience pain until late 1980s.[3] Several studies have changed our understanding of pain,[1] pain assessment and analgesia in newborn infants.[4-7] As a consequence, the importance of antinociceptive therapy in newborn infants has been increasingly acknowledged, leading to a burst of pain research in newborn neonates. Rational drug therapy in newborns requires the knowledge of drug pharmacokinetics and pharmacodynamics in infants, which are different from the adult parameters. Research has concentrated on the development of pain assessment instruments and clinical trials investigating the effectiveness and safety of a variety of analgesics in infants.[8]

In order to assess the painfulness of a procedure and then the effectiveness of a treatment, there is the obvious need to measure and quantify the pain.[9] The main goal of pain assessment is to identify an infant's potentially painful condition, quantify the pain level, and to predict the need for an intervention.[9]

Many factors, such as the gestational and postnatal ages, neurobehavioral state, and prior experience in the NICU can affect the newborn's responsiveness to pain.[10-13] In neonates, pain is mainly based on the behavioural response and physiological consequences of nociception, resulting in the concept of "multimodal" pain scales. These pain scales quantify aspects of "behavioural indicators" of pain that include facial action, body movements, tone, cry, state, or consolability, and "physiological indicators" of pain, which

include increased heart rate, respiratory rate, blood pressure, decreased heart rate variability, or oxygen desaturation. An example of such a multimodal pain scale is the "Echelle Douleur Inconfort Nouveau-Né" (EDIN) scale.[14]

According to the "International Association for the Study of Pain" (IASP), pain is an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage. In situations associated with persistent pain or discomfort, an attempt should be made to assess its intensity and the effectiveness of analgesic treatment using a validated measure for pain such as the EDIN or the "Neonatal Pain Agitation and Sedation" scale (NPAS).

Pharmacokinetics are dependent on the maturation of enzymes and physiological processes responsible for absorption, distribution and elimination of drugs. The expression of drug metabolizing enzymes and the processes of absorption, distribution and elimination of drugs are different in neonates, compared to adults. Therefore, the doses and the interval between doses are different in neonates and adults.

■ BIBLIOGRAPHIC SEARCH

The bibliographic search was performed using PubMed and EMBASE databases as search engines. The cutoff point was November 2013. The following key words were used: "pharmacological pain management in neonates." Articles were read carefully, and the selected ones were examined. In addition, the books "Neofax: a Manual of Drugs Used in the Neonatal Care" by Young and Mangum[15] and the "Neonatal Formulary"[16] were consulted.

■ RESULTS

This review reports 127 studies. The kinetic parameters of morphine are summarized in Table 1. Table 2 summarizes the pharmacokinetic parameters of fentanyl, alfentanil, sufentanil and remifentanil. The kinetic parameters of paracetamol (acetaminophen), midazolam and propofol are summarized in Tables 3, 4 and 5, respectively. Table 6 provides the therapeutic regimens and the monitoring of the various analgesics in neonates.

DRUGS FOR THE MANAGEMENT OF PAIN IN NEONATES

Opioids

Opioids include morphine, methadone, fentanyl, alfentanil, sufentanil, and remifentanil.

Morphine

Morphine is the most commonly used opiate for analgesia, although a wide variability occurs in clinical dosages.[17] This drug has an onset of action of 5 min; the time of peak of effect and the duration of action are 45 to 90 min and 4 to 5 hours, respectively.[18] The analgesic effects of morphine are caused mainly by an activation of μ-receptors, although it can also act on k-opioid receptors subtypes.[18]

After major surgery, continuous morphine doses of 10 to 40 μg/kg have been shown to be effective in alleviating pain in infants and children between 0 and 14 years of age.[19-23] No difference in analgesic effect was found between continuous and intermittent dosing.[19]

Morphine causes histamine release and may lead to hypotension, bradycardia, and bronchospasm, especially in infants with chronic lung disease.[24-27] Caution should be used when prescribing morphine to infants with asthma or bronchopulmonary dysplasia, because of the risk of histamine-induced bronchospasm.[28]

Chay et al.[29] suggest that the mean morphine concentration required to produce adequate sedation in 50% of infants was found to be 125 ng/ml. Concentrations of morphine above 300 ng/ml may be associated with adverse effects, which include effects on the gastrointestinal tract and possibly on the neurologic system.[9,29]

Lynn and Slattery[30] studied the morphine pharmacokinetics in 10 infants ≤ 10 weeks of age. Infants 1 to 4 days of age showed longer elimination half-lives than the older infants (6.8 versus 3.9 hours). Clearance in newborns ranged from 2.1 and 15.5 ml/kg/min, and it was lower than in adults.[34] The lower clearance and the longer elimination half-life in newborns (0 to 7 days of life) explain the prolonged duration of the action of morphine in very young infants.

The pharmacokinetics of morphine have been studied by various authors and the kinetic parameters are summarised in Table 1. Pokela et al.[31] studied the pharmacokinetics of morphine (100 μg/kg) in 27 infants. The clearance and the half-life varied considerably with postnatal age. The kinetic parameters obtained in 10 neonates younger than 1 week are summarised in Table 1. In 10 infants aged between 1 week to 2 months, the half-life and the clearance were 2.6 + 1.7 hours and 11.9 + 5.1 ml/kg/min, respectively.

Bhat et al.[32] studied the pharmacokinetics of morphine in 20 newborn infants aged from 26 to 40 weeks of gestation. Ten infants had a gestational age ≤ 30 weeks and the kinetic parameters are summarised in Table 1. A trend of decreasing distribution volume and elimination half-lives was increasing with gestation age, but a considerable degree of variation

Table 1 - Pharmacokinetic parameters of morphine in neonates. Figures are the mean + SD

Development stage	Number of infants	Dose (μg/kg)	$t_{1/2}$ (hours)	Cl (ml/kg/min)	Vd (l/kg)	Reference
Preterm and term	19	10 to 100	2.2 ± 1.6	2.1 ± 1.2	2.0 ± 1.0	29
Preterm	10	100	10 ± 3.7	3.4 + 3.3	1.8 + 0.8	32
Preterm	26	Note A	8.9 ± 3.3	3.6 ± 0.9	2.7 ± 1.0	33
Term	10	100	8.1 ± 8.1	8.7 ± 5.8	1.3 ± 0.4	31
Term	20	Note B	6.6 ± 2.9	5.5 ± 12.4	5.0 ± 6.8	22
Term	3	100	6.7 ± 4.6	15.5 ± 10.0	2.9 ± 2.1	32
Adults	–	–	1.9 ± 0.5	24 ± 10	3.3 ± 0.9	34

Note A = loading dose of 50 μg/kg of diamorphine followed by an intravenous infusion of 15 μg/kg/h of diamorphine. **Note B** = loading dose of 50 μg/kg of morphine, followed by a continuous infusion of 15 μg/kg/h of morphine; $t_{1/2}$ = β-phase elimination; Cl = clearance; Vd = apparent volume of distribution.

Table 2 - Pharmacokinetic parameters of fentanyl, alfentanyl, sufentanil and remifentanil in neonates. Figures are the mean + SD or median or range

Drug	Development stage	Number of infants	Dose (μg/kg)	$t_{1/2}$ (hours)	Cl (ml/kg/min)	Vd (l/kg)	Reference
Fentanyl	Preterm	6	30	8.7 ± 5.1	2.2 ± 2.4	1.0 ± 0.4	56
Fentanyl	Preterm	5	25	7.6 ± 1.8	1.3 ± 0.7	0.8 ± 0.5	57
Fentanyl	Term	5	25	5.5 ± 0.8	1.7 ± 0.5	0.8 ± 0.3	57
Fentanyl	Preterm	7	25	9.5 ± 2.6	19.2 ± 8.2	17.2 ± 9.0	59
Fentanyl	1 to 71 days	14	Note A	3.1 to 13.5	9.0 to 32.8	5.4 to 11.9	58
Fentanyl	Adults	–	–	3.7 ± 0.4	13.0 ± 2.0	4.0 ± 0.4	34
Alfentanyl	Preterm	13	Note B	4.1 ± 2.6	3.2 ± 2.2	0.5 ± 0.2	69
Alfentanyl	Preterm	5	25	7.6 ± 1.8	1.3 ± 0.7	0.8 ± 0.5	57
Alfentanyl	Term	5	25	5.5 ± 0.8	1.7 ± 0.5	0.8 ± 0.3	57
Alfentanyl	Preterm	22	20	5.3	0.9	0.8	70
Alfentanyl	Adult	–	–	1.6 ± 0.2	6.7 ± 2.4	0.8 ± 0.3	34
Sufentanil	0 days to 1 month	9	10 to 15	13.0 ± 5.8	6.7 ± 6.1	4.1 ± 1.0	74
Sufentanil	1 to 7 days	3	10	10.5 ± 7.4	4.3 ± 2.5	2.7 ± 0.1	115
Sufentanil	20 to 28 days	3	10	4.0 ± 1.3	17.0 ± 3.5	3.4 ± 0.2	115
Sufentanil	Adults	–	–	2.7 ± 0.4	12.7 ± 0.8	1.7 ± 0.2	116
Remifentanil	0 to 2 months	8	5	5.4 ± 1.8 (min)	90.5 ± 36.8	0.4 ± 0.3	79
Remifentanil	Adult	–	–	18 to 24 (min)	40 to 60	0.3 to 0.4	34

Note A = a loading dose of 5 μg/kg fentanyl was followed by a constant infusion ranging from 0.57 to 10.3 μg/kg/h. The rate and duration of fentanyl infusion were determined by the patient's attending physician; **Note B** = a loading dose of 8 μg/kg of alfentanil was followed by a variable-rate continuous infusion from 2.5 to 10 μg/kg/h fentanyl. $t_{1/2}$ = β-phase elimination; Cl = clearance; Vd = apparent volume of distribution.

was seen. The morphine clearance increased as a function of gestational age at a rate of 0.9 ml/kg/min per week of gestation. During the first week of life, adequate blood levels can be maintained by administering 100 μg/kg morphine at 4 to 6 hour intervals in term infants, and in prematures, the frequency of morphine administration must be less frequent. Morphine binds to plasma protein at a percentage between 18 and 22.[32]

Barrett et al.[33] reports that the administration of 50 μg/kg of diamorphine, followed by an intravenous infusion of 15 μg/kg/h to 26 prematures aged from 26 to 38 weeks, produced a steady-state plasma concentration of morphine of 62.5 + 22.8 ng/ml. Table 1 summarizes the morphine pharmacokinetic parameters. Gestational age correlated with infant clearance (r^2 = 0.31; p = 0.003) and half-life (r^2 = 0.35; p = 0.01) of morphine.[33] The currently used dosing regimen of diamorphine achieves an effective morphine concentration in infants, but the loading dose could be modified to achieve a more rapid onset of analgesia.[33]

An intravenous loading dose of morphine (100 μg/kg) followed by an infusion of 10 μg/kg/h was administered to infants with a postmenstrual age of 23 to 26 weeks.

An infusion of 20 or 30 μg/kg/h of morphine was administered to infants with postmenstrual age of 27 to 29 or 30 to 32 weeks, respectively.[33] The total number of infants was 449. The clearance was 50% of the mature value at 54.2 weeks of postmenstrual age, and increased from 0.5 ml/kg/min at 24 weeks of postmenstrual age to 1.5 ml/kg/min at 32 weeks of postmenstrual age. The volume of distribution (Table 1) did not change with age.

Morphine metabolism was studied in 12 children and 9 prematures maintained on a continuous infusion of morphine ranging from 10 to 360 μg/kg/h.[35] All neonates and children had detectable concentrations of morphine-3-glucuronide (M3G) in plasma. Five neonates and all children had detectable concentrations of morphine-6-glucuronide (M6G) in plasma and urine. The M3G/morphine ratios in plasma and urine, and M6G/morphine ratios in urine, were significantly higher in children than neonates (p < 0.01), suggesting that morphine glucuronidation capacity is enhanced after the neonatal period.

Methadone

Methadone is a synthetic μ-agonist with long duration of action because it is eliminated slowly.[6] Methadone causes a

Table 3 - Pharmacokinetic parameters of paracetamol (acetaminophen) in neonates. Figures are the mean or the mean + SD

Development stage	Number of infants	Dose (mg/kg)	$t_{1/2}$ (hours)	Cl (ml/kg/min)	Vd (l/kg)	Reference
Preterm	21	20 Rectally	11.0 ± 5.7	1.7 ± 0.7	na	4
Preterm	7	20 Rectally	4.8 ± 1.2	0.7 ± 11	na	
Note A	283	Note B	6.1	3.0 (44%)*	0.9 (20%)*	90
Preterm	48	Note C	na	Note D	1.0 l/kg (30)*	87
Preterm	50	Note E	na	1.2 (30.5)*	1.1 l/kg (29.6)*	91
Adults	–	–	2.0 ± 0.4	5.0 ± 1.4 l/kg	0.9 ± 0.1 l/kg	34

na = not available; **Note A** = median postconceptional age was 40 weeks (range was 28 to 64 weeks); **Note B** = infants were given either single or multiple doses of four different formulations of paracetamol; **Note C** = paracetamol was given intravenously in either single (n = 30) or multiple (n = 18) doses. A loading dose of 30 mg/kg was followed by a maintenance dose of 20 mg/kg every 6 to 12 hours. **Note D** = clearance increased from 0.7 ml/min/mg at 27 postconceptional weeks to reach 1.7 ml/kg/min by 42 weeks. **Note E** = infants received intravenously paracetamol adjusted every 6 hours according to the following dosing regimens for 4 days. The dose was 10 mg/kg for infants aged between 28 to <32 weeks, 12.5 mg/kg for infants aged between 32 to <36 weeks and 15 mg/kg for infants aged ≥ 36 weeks. *The values in brackets indicate the percent variability. $t_{1/2}$ = β-phase elimination; Cl = clearance; Vd = apparent volume of distribution.

Table 4 - Pharmacokinetic parameters of midazolam in neonates and children. Figures are the median or the mean $+$ SD

Comments	Development stage	Number of infants	Dose (μg/kg)	$t_{1/2}$ (hours)	Cl (ml/kg/min)	Vd (l/kg)	Reference
Healthy neonates							
Intravenous administration	Preterm	24	100	6.3	1.8	1.1	117
Population pharmacokinetics of midazolam in neonates and children							
Note A	Preterm	187	Note B	9.9	1.2 $\pm$ 0.2	1.0 $\pm$ 0.2	118
Note C	Preterm	60	100	14.1	0.94	1.15	119
Age ranged from 2 days to 17 years	–	18	50 to 400 μg/kg/h Infusion	5.5 $\pm$ 3.5	5.0 $\pm$ 3.9	1.7 $\pm$ 1.1	92
Adult subjects							
Adults	–	–	–	1.9 $\pm$ 0.6	6.6 $\pm$ 1.8	1.1 $\pm$ 0.6	34

Note A $=$ all neonates received midazolam during artificial ventilation; **Note B** $=$ midazolam was administered as a continuous infusion to 109 infants, as a bolus dose to 22 infants, and as a combination of both to 56 infants. **Note C** $=$ neonates undergoing mechanical ventilation had a body weight $< 1,500$ g; $t_{1/2} = \beta$-phase elimination; Cl = clearance; Vd = apparent volume of distribution.

desensitization of delta-opioid receptors involved in pain sensitization. The action on the delta-opioid receptors reverses the tolerance that occurs with morphine and, as a NMDA receptor antagonist, methadone produces additive analgesia and delayed development of tolerance.[9,28] Its potency is similar to that of morphine but has a more rapid distribution and a slower elimination. Methadone has a slow onset of action of about 20 min after intravenous administration and 30 to 60 min after oral administration;[28] it has a bioavailability of 75 to 85% and a prolonged elimination half-life of 41 hours in neonates.[37] The volume of distribution of methadone is 7.1 $+$ 2.5 l/kg in children and 6.1 $+$ 2.4 l/kg in adults[36]. In adult liver microsomes, methadone is N-demethylated by CYP2B6 and CYP3A4,[37] and these enzymes undergo a considerable interindividual variability in human adult liver microsomes.[37]

Few data on the efficacy, safety and pharmacokinetics of methadone are available in neonates. A study on the pharmacokinetics of methadone in neonates is lacking and should be performed. Methadone is widely used for the treatment of opioid withdrawal in neonates and children.[38,39] Intravenous methadone has been shown to be an effective analgesic for postoperative pain relief[40] and it has been recommended as the first-line opioid for severe and persistent pain in children.[41] Chana and Anand[42] suggested using oral methadone as the first-line opioid for severe and persistent pain in children.

Maternal methadone is transferred across the placenta and can induce significant withdrawal symptomatology in newborns.[43] The relationship between a maternal dose of methadone and the incidence and severity of neonatal signs of withdrawal were studied in 30 mothers and their infants. The ratio of neonatal to maternal plasma concentrations of methadone was 2.2:1. At methadone plasma levels greater than or equal to 0.06 μg/ml, symptomatic patients appeared to be protected from withdrawal. The apparent excretory half-life of methadone in the neonate was 32.5 hours.[44]

Fentanyl

Fentanyl is a synthetic opioid that acts as a "morphine-like" agonist. Fentanyl crosses the blood-barrier more rapidly than morphine.[16] Its potency is 50 to 100-fold that of morphine on a weight basis.[15] Fentanyl has an onset of action of 3 min and a duration of effect of 0.5 hours.[18] It maintains hemodynamic stability, blocks endocrine stress responses, and prevents pain-induced responses and increases pulmonary vascular resistance.[5,45] This drug causes less histamine release than morphine and decreases the heart rate and mildly decreases blood pressure.[16] It is commonly used for patients undergoing cardiovascular surgery or for patients with poor cardiac function.[16] It has been used in neonates under artificial ventilation, with bronchopulmonary dysplasia, pulmonary hypertension and/or diaphragmatic hernia.[46] In neonates, the continuous fentanyl infusion should be reduced by 25% to 50% when compared with older infants.[47]

Fentanyl is widely distributed in tissues. Hepatic clearance is linked to the ontogeny of the unbound fraction to α_1-acid glycoprotein. It binds to 77% and 70% to the plasma proteins of preterm and term neonates, respectively.[48] The clearance of fentanyl is immature at birth but it increases dramatically after birth and reaches the adult values within 2 weeks of life.[7,49] Fentanyl is metabolized into the inactive norfentanyl by CYP3A4[15,50] and this enzyme appears during the first week of life.[51,52,53]

The clearance of fentanyl, after a loading dose of 10.5 μg/kg followed by a continuous infusion of 1.5 μg/kg/h, was

Table 5 - Pharmacokinetic parameters of propofol in neonates and children. The figures are the median or the mean $+$ SD

Development stage	Number of infants	Dose (mg/kg)	$t_{1/2}$ (hours)	Cl (ml/kg/min)	Vd (l/kg)	Reference
Preterm	9	3	12.8	13.6[a]	3.7[b]	110
Preterm	25	3	na	28.0 ml/min (32)*	1.3 l (19)*	109
Preterm	25	3	na	29.0 ml/min	1.3 l	112
1 to 3 years	12	4	1.6 (0.01)*	53.0 $\pm$ 13.0	9.5	120
4 to 7 years	10	2.5	na	30.0 $\pm$ 2.9	0.7 $\pm$ 0.1	121
1 week to 12 years	21	4 mg/kg/h	na	30.2	1.4	107
4 to 12 years	12	2.5	4.8 $\pm$ 0.5	40.0 $\pm$ 3.6	5.0 $\pm$ 2.7	108
Adults	–	–	3.5 $\pm$ 0.7	27.0 $\pm$ 5.0	1.7 $\pm$ 0.7	34

na = not available; *The values in brackets indicate the percent variability; [a]the range was 3.7 to 78.2 ml/min/kg;[b] the range was 1.33 to 7.96 l/kg; $t_{1/2} = \beta$-phase elimination; Cl = clearance; Vd = apparent volume of distribution.

Table 6 - Analgesic dosing regimens for neonates and monitoring of the various analgesics in infants.

Drug	Sedation and analgesia	Infusion rate (µg/kg/h)	Anaesthesias	Monitoring	Reference
Morphine	50 to 200 (µg/kg) IV or IM	10 to 20 IV	Not applicable	Monitor respiratory and cardio-vascular status closely. Observe for abdominal distension. Consider urine retention.	15
Methadone	50 to 200 µg/kg PO	Not applicable	Not applicable	Monitor respiratory and cardiac status closely. A 12-lead ECG should be obtained. Assess for gastric residual, abdominal distension, and loss of bowel sounds.	15
Fentanyl	0.5 to 4 (µg/kg) IV	1 to 5 IV	5 to 50 µg/kg/dose IV	Monitor respiratory and cardio-vascular status closely. Observe for abdominal distension, loss of bowel sounds, and muscle rigidity	15
Alfentanyl	10 to 20 µg/kg IV	Loading dose of 8 µg/kg, followed by an infusion of 2.5 to 10 IV	400 ng/ml IV	High incidence of chest wall rigidity with doses above 20 µg/kg	65, 66, 69, 76
Sufentanil	10 to 15 µg/kg IV	0.41 IV	No data available	No data available	74, 75
Remifentanil	5 µg/kg IV	0.25 µg/kg/min IV	No data available	No data available	79, 122, 123
Paracetamol (Acetaminophen)	20 to 25 mg/kg Loading dose (PO) 12 to 15 mg/kg Maintenance dose (PO)	Not applicable	Not applicable	Assess for signs of pain. Monitor temperature. Administration. Asses liver functions. Liver toxicity occurs with prolonged administration >48 hours.	15
Midazolam	It is not recommended in neonates 50 to 150 µg/kg IV or IM 200 µg/kg (PO) 200 to 300 µg/kg/dose intranasally.	10 to 60 µg/kg/h IV Maintenance infusion 60 to 400 µg/kg/h IV	Not applicable	Follow respiratory status and blood pressure closely, especially when used concurrently with narcotics. Assess hepatic function. Observe for signs of withdrawal after discontinuation of prolonged therapy.	15
	For anticonvulsant activity, the loading dose is 150 µg/kg and the maintenance dose is 60 to 400 µg/kg/h.				
Propofol	Use during neonatal intubation 2.5 mg/kg IV Do not use for prolonged period in children <3 years	Prolonged sedation: used to provide sustained sedation for patients requiring intensive care. Do not use in children less than 3 years.	Maintenance anaesthesia: give IV less than 4 mg/kg/h in children less than 3 years	Must be supervised by an experienced intensivist and recovery monitored until it is complete. Can cause respiratory depression and hypotension.	9, 16
Ketamine	0.5 to 2 mg/kg (IV) 2 to 5 mg/kg PR	Sustained IV administration: 1 mg/kg loading dose followed by 0.5 mg/kg/h. 4 mg/kg IM	2 mg/kg (IV) 4 mg/kg (IM)	Stridor and laryngospasm can be encountered. Prolonged apnea may be encountered. Increased production of salivary secretion.	9, 16

IV = intravenously; IM = intramuscularly; PO = by mouth; PR = rectally.

studied by Saarenmaa et al.[54] in the first days of life. The infants (n = 38) had a gestational age from 26 to 42 weeks. The clearance of fentanyl was 11.5 ± 4.0 ml/kg/min, correlated with the gestational age (r = 0.46; p < 0.01) and body weight (r = 0.48; p < 0.01).

Collins et al.[55] administered a bolus dose of 30 μg/kg to 9 preterm infants with a gestational age of 31.8 ± 4.7 weeks for induction of anaesthesia for ligation of the patent ductus arteriosus. Fentanyl plasma concentrations ranged between 7.7 and 13.6 ng/ml in the 30 min after administration. Elimination half-life was 14.7 ± 9.3 hours. Systolic blood pressure remained stable throughout surgery. There was a gradual increase in heart rate from 159 ± 12 beats/min at the time of skin incision to 173 ± 15 beats/min at the time of skin closure (p < 0.05). Fentanyl plasma concentrations remained similar between 30 (10.6 ± 1.9 ng/ml) and 120 min (9.6 ± 1.6 ng/ml) after administration.

The pharmacokinetics of fentanyl were studied in neonates by different authors and the pharmacokinetic parameters are summarized in Table 2. The clearance of fentanyl exhibits a highly interindividual variability in neonates.[58] A significant correlation was observed between postnatal age and total body clearance (r = 0.80; p = 0.03) in 7 newborns undergoing mechanical ventilation.[59] The kinetic parameters are reported in Table 2.

Fentanyl is frequently used as a continuous infusion in neonates with pulmonary hypertension or in those requiring extracorporeal membrane oxygenation (ECMO). Muscle rigidity appears after high doses of fentanyl used in anaesthetic induction.[60-62] Chest wall rigidity and respiratory depression can be treated with naloxone (10 μg/kg)[15].

The pathology and/or the surgical lesion lengthen $t_{1/2}$ of fentanyl in neonates. In infants undergoing surgical operation, the half-life of fentanyl was 463 and 750 min, whereas the population mean of fentanyl half-life in healthy neonates is 317 min.[49]

When administered intranasally (1 to 2 μg/kg), the bioavailability of Fentanyl is 89%, with a lag of approximately 5 min and a half-life of about 6.5 min. Intranasal versus intravenous administration of fentanyl leads to a delay in the mean fentanyl time to a maximum concentration (13 versus 6 min) and lower maximum concentration (1.2 versus 2.0 ng/ml).[63]

Alfentanyl

Alfentanyl is a short synthetic opioid that is a chemical derivative of fentanyl. The kinetic parameters of alfentanyl are summarised in Table 2. This drug causes less histamine release than fentanyl.[64] Ten to 20 μg/kg alfentanyl are sufficient for analgesia during endotracheal intubation and suctioning in preterm neonates.[65-67] A target plasma concentration of 400 ng/ml is used in anaesthesia. Alfentanyl binds to plasma protein at percentages of 67.2% and 88.2% in neonates and in their mothers, respectively.[68] A significant negative correlation was found between alfentanyl plasma concentration and total-body clearance (r = -0.75; p = 0.02[69]). Alfentanyl undergoes extensive metabolism by CYP3A4, CYP3A5 and CYP3A7.[71]

Sufentanil

Sufentanil is one of the most potent synthetic opioids available. Its use is primarily for deep anaesthesia in patients undergoing cardiac surgery. The clearance, expressed as per kg of body weight, is increased in children compared to adults[72]. Sulfentanil binds to α1-acid glycoprotein. The fraction of sulfentanil bound to plasma protein is 0.79 in neonates and 0.91 in their mothers.[72] The free fraction of sufentanil is negatively correlated with α_1-acid glycoprotein plasma concentration (r = -0.73; p < 0.001), whereas there was a weak correlation with plasma albumin concentration (r = -0.34; p < 0.05).[73]

The pharmacokinetic parameters of sufentanil are summarised in Table 2. The half-life (hours) of sulfentanil was 13.0 ± 5.8 in neonates, 3.6 ± 0.7 in children (p < 0.01) and 2.3 ± 0.5 in adolescents (p < 0.01).[74] The clearance (ml/kg/min) was 6.7 ± 6.1 (neonates), 18.1 ± 2.7 (infants), 16.9 ± 3.2 (children), and 16.9 ± 3.2 (adolescents) and 13.1 ± 3.6 (adults; p < 0.01).[74] The volume of distribution (l/kg) was 4.1 ± 1.0 in neonates, 2.7 ± 0.5 in infants, and 2.5 ± 0.5 in children (p < 0.05).[74]

Remifentanil

Remifentanil is a μ-opioid receptor agonist characterized by a fast onset and by a short time of action. It is rapidly degraded in blood and other tissues by esterases.[77] The overall median degradation half-life of remifentanil was 143 min (2.4 hours) and ranged from 76 and 221 min.[78] Remifentanil is rapidly metabolised by preterm infants and does not accumulate in infants.[80] The pharmacokinetic parameters of remifentanil[79] are summarized in Table 2. Remifentanil is a good option to attenuate the hemodynamic/endocrine markers of stress related to surgery.[81] Hypotension may become significant when the remifentanil is associated to other drugs like sevoflurane.

Non-opioid analgesics

Non-opioid analgesics can be used to treat mild to moderate pain, either alone or in combination with opioid analgesics to increase their efficacy and decrease the risk of adverse effects in neonates with severe pain. The non-opioid analgesics are paracetamol (acetaminophen), a non-steroidal anti-inflammatory drug, the benzodiazepine midazolam, and the anaesthetics ketamine and propofol. Among the non-opioid analgesics, paracetamol (acetaminophen) is the drug most often used. It also has good antipyretic activity. Midazolam is a commonly used hypnosedative but it is not recommended in neonates. Ketamine is commonly used for analgosedation in children, with only very rare complications. Besides parenteral administration (intravenous or intramuscular) oral administration of ketamine can be used, despite a low bioavailability of 15 to 20%.[82] Propofol has a low clearance capacity at birth with consequent postnatal related increase.[83]

Paracetamol (Acetaminophen)

Paracetamol is safe and effective in preterm and term neonates with mild to moderate pain, but it is ineffective for acute pain[10,84]. Paracetamol is the only agent recommended for use as an antipyretic in newborns and recently has been proposed as a supplement therapy to opioids for post-operative analgesia.[85]

There is a significant inverse correlation between paracetamol Cmax and gestational age (r = -0.50; p = 0.007[4]). The recommended doses for oral or rectal paracetamol administration are 25 to 30 mg/kg/day in preterm neonates of 30 weeks' gestation, 45 mg/kg/day in preterm neonates of 34 weeks' gestation, and 60 mg/kg/day in term neonates.[86] Allegaert et al.[86] suggest an intravenous

loading dose of 20 mg/kg followed by 10 mg/kg every 6 hours to achieve a concentration of 11 µg/ml in neonates.

Prenatal and infant paracetamol exposure has been associated with an increased risk of childhood asthma phenotypes.[88] Risk of asthma was higher when maternal glutathione S-transferase T1 genotype was present (p = 0.006). The risk of wheezing was increased when maternal glutathione S-transferase M1 was present (p = 0.04). The increased risk of asthma and wheezing associated with late gestation paracetamol exposure in the presence of maternal glutathione S-transferase M1 was further enhanced when this enzyme was also present in the child.

The rates of sulphated and glucuronidated paracetamol clearance were assessed in vivo by measuring the excretion of these compounds in the urine.[89] The rate constant for paracetamol glucuronide formation in neonates was considerably smaller than in adults but the average rate constant for sulphated paracetamol formation was somewhat larger than in adults. The glucuronide to sulphated ratios of paracetamol in the urine was 0.12 ± 0.09 in infants 28 to 32 week old and 0.28 ± 0.35 in infants 32 to 36 weeks old.[4]

The pharmacokinetics of paracetamol were studied by different authors and the pharmacokinetic parameters of the more significant studies are summarised in Table 3. The clearance (ml/kg/min) of paracetamol increased from 0.18, at 28 postconceptional weeks, to 2.6 by 60 weeks.[90]

The doses and the kinetic parameters of this drug are summarised in Table 3. The presence of non-conjugated hyperbilirubinemia was associated with reduced clearance of paracetamol. Paracetamol plasma concentrations between 10 and 23 µg/ml are predicted to reach steady-state after 15 mg/kg paracetamol every 6 hours for a neonate of 40 weeks of postmenstrual age.[91]

Midazolam

Midazolam is a short-acting benzodiazepine with rapid onset of action and is the most frequently used hypnosedative to suppress behavioural responses to pain.[92] It has anxiolytic, muscle relaxant and anticonvulsant activity, now mostly used to generate anterograde amnesia and to stop prolonged seizure in children.[16] Hypnosedatives (midazolam and propofol) can be used as an adjunct to analgesia, but opioids are preferred when sedation is required in ventilated neonates.[93] The sedative and anticonvulsant properties of midazolam are related to GABA accumulation and occupation of benzodiazepine receptors.[15] GABA receptors are responsible for most inhibitory neurotransmission. A recent review on the clinical pharmacology of midazolam in neonates and children has been published.[94]

Ng et al.[95] reviewed the literature on the intravenous midazolam infusion for sedation of infants in the "neonatal intensive care unit." These authors conclude that there are insufficient data to promote the use of midazolam infusion as a sedative for neonates undergoing intensive care.[8]

For sedation, the dose of midazolam in neonates ranges from 50 to 150 µg/kg either by intravenous or intramuscular route.[15] For continuous intravenous infusion, the recommended dose is 10 to 60 µg/kg/h.[15] The dosage needs to be increased after several days of continuous therapy because of development of tolerance and/or increased clearance. When minimal sedation is required, midazolam may be administered intranasally (200 to 300 µg/kg[15]). The bioavailability of intranasal midazolam ranges from 50 to 83%.[96–98]

Midazolam manages the neonatal seizures refractory to conventional treatment.[99,100] The recommended dose for anticonvulsant activity is a loading dose of 150 µg/kg administered intravenously and a maintenance infusion of 60 to 400 µg/kg/h.[15]

In adults, the recovery of unchanged midazolam in urine is 1%.[34] Midazolam is hydroxylated to form 1-hydroxymidazolam by hepatic CYP3A4[15,131–134] and by CYP3A5[101, 102–105]. The glucuronidation of 1-hydroxy-midazolam is immature in preterm infants.[106] The pharmacokinetic parameters of midazolam in neonates, children and adults are reported in Table 4. Midazolam is not free from adverse effects when administered to neonates. The first intravenous loading dose of midazolam administered to preterms not infrequently causes respiratory depression, hypotension, a fall in cerebral blood flow, and paradoxical agitation.[16]

Propofol

Propofol is a rapid-acting intravenous anaesthetic.[16] An intravenous dose of 2.5 mg/kg is used during neonatal intubation. Propofol is a high-extraction drug, its clearance mainly depends upon the hepatic blood flow. In adults, propofol is conjugated in the liver with glucuronic acid and with sulphate. However, multiple cytochrome P450 forms (CYP2B6, CYP2C9 and CYP2A6) contribute to the metabolism of propofol in adults[143]. The urinary excretion of unchanged propofol is <1% in adults.[110]

In neonates, the contribution of propofol glucuronidation is 34% versus 77% in adults.[111] There is a large interindividual variability in the clearance of propofol; in 9 neonates with a postmenstrual age ranging from 27 to 43 weeks, the clearance of propofol ranged from 3.7 to 78.2 ml/kg/min. The volume of distribution ranged from 1.33 to 7.96 l/kg. The kinetic parameters of propofol are summarized in Table 5. In neonates, the clearance is reduced compared with older children.

This drug should never be given to any young child at a rate exceeding 4 mg/kg/h.[16] Prolonged sedation is now widely used to provide sustained sedation for patients requiring intensive care, but should not be used in this way, especially in children less than 3 years old because there is small, but currently unpredictable, risk of sudden "propofol infusion syndrome" collapse.[16]

Ketamine

The plasma levels of oral ketamine (10 mg/kg) peak 30 min after the administration, and the bioavailability of ketamine is about 16%.[16]

The half-life, the clearance and the volume of distribution of ketamine (1 mg/kg/hour) are 2.8 ± 0.6 hours, 16.0 ± 3.7 ml/kg/ml and 3.2 ± 1.8 l/kg, respectively, in children 1 week to 30 months old.[113] Two mg/kg of ketamine administered intravenously or 4 mg/kg administered intramuscularly provide about 10 to 15 min of surgical anaesthesia.[16] For sustained intravenous administration, a loading dose of 1 mg/kg followed by 500 µg/kg/h[16] is given. Ketamine relieved pain caused by tracheal suction in 16 infants who received 0.5 or 1.0 or 2.0 mg/kg ketamine intravenously.[114] A ketamine infusion regimen is usually supplemented with intravenous midazolam (0.2 mg/kg).

Midazolam reduces ketamine's cardiovascular stimulation and emergence phenomena, and does not activate metabolites.

■ DISCUSSION

The analgesic reviewed have a longer half-life in neonates than in adults. They also have a clearance smaller in neonates than in adults. There is an exception with fentanyl, which has a clearance higher in neonates[59] than in adults.[34] The kinetics of fentanyl obtained by Santeiro et al.[59] were obtained in infants maintained on a continuous infusion of fentanyl (rate 0.53 to 1.9 µg/kg/h), and a postnatal age of $16 + 9$ days. There was a significant correlation (r = 0.80; p = 0.03) between postnatal age and clearance. The data obtained by Santeiro et al.[59] were obtained under different conditions than those obtained with the other neonates and cannot be compared with the data obtained in adults.[34] In the cases reported in,[58] in[79] and in,[115] the clearance was obtained in infants with a postnatal age up to two months. Thus, the comparison of the kinetic parameters between neonates and adults is difficult in these cases. Remifentanil is rapidly degraded in blood and other tissues by esterases[77] and the degradation rate is similar in the preterm and term serum.[78]

In preterms, paracetamol has a clearance of 1.2 ml/kg/min, with a variability of 30.5%.[91] In a study of population pharmacokinetics, conducted with 283 infants, whose age ranged from 28 and 64 weeks (median 40 weeks),[90] the clearance of paracetamol was 3.0 ml/kg/min (variability was 44%). In adults, the clearance of paracetamol is 5.0 ml/kg/min.[34]

The clearance of midazolam is 1.8 ml/min/mg in healthy prematures and 6.6 ml/min/mg in adults. The clearance of propofol is 13.6 ml/kg/min in neonates[110] and 27.0 ml/kg/min in adults.[34] In children 1 to 3 years old and in adults, the clearance of propofol is $53.0 + 13.0$ and $27.0 + 5.0$ ml/kg/min,[120] respectively, suggesting that the clearance of this drug is higher in infancy than in adults. In two other articles[109,112] the clearance of propofol was 28.0 and 29.0 ml/min, respectively. These values are difficult to compare with the clearance in adults, because they are not corrected for body weight. However, assuming a body weight between 2 and 3 kg, the clearance reported in[109,112] should be lower than the adult value.

The variation of volume of distribution between neonates and adults varies with the drugs. Morphine has a volume of distribution which is similar in adults and neonates. According to [authors], the volume of distribution of fentanyl is larger in adults than in neonates[56,57]. An exception was reported by Santeiro et al.[59] who found a volume of distribution higher in infants than in adults.

In the cases described by Dewhurst et al [58], Penido et al[79] and by de Wildt et al[115] the volume of distribution is higher in infants than in adults, but the postnatal age is up to 2 months. These findings suggest that the volume of distribution of fentanyl,[59] sufentanil[115] and remifentanil[116] increases with postnatal development.

In infants, the volume of distribution of paracetamol (acetaminophen) ranges in a narrow interval and the mean values are 0.9 l/kg[90] and 1.1 l/kg.[91] In adults, the volume of distribution is $0.9 + 0.1$ l/kg.[34] For midazolam, propofol, and ketamine, little variation of the volume of distribution is observed between neonates and adults.

Effective pain management remains an important indicator of the quality of care provided to neonates, but observations on neuro-apoptosis and integration of newer techniques and compounds prompt caregivers to reconsider the clinical and research aspects of effective pain management.

Pharmacologic pain management for painful events and some medical conditions have improved considerably for infants in the last years. The use of continuous infusion of opioids, epidural analgesia, and peripheral nerve blockage has enhanced the ability of neonatologists to treat postoperative and medical pain safely and effectively. Local anaesthetics and non-opioids analgesics have been instituted for the treatment of pain from some procedures.

The metabolism of newborns must be taken into account when considering pharmacologic treatment for pain. An understanding of newborn pharmacokinetics and pharmacodynamics provides the basis for safe and effective dosing of anaesthesia and analgesia. Pharmacokinetics are affected by the quality of absorption, distribution and elimination of drugs by infants. Consideration also must be given to the differences in preterm and fullterm metabolic functions. Preterm neonates require lower doses or longer dose intervals than fullterm neonates to maintain similar therapeutic concentrations. A reasonable starting dose of opioids for preterm infants who are not mechanically ventilated is between one fourth and one third the recommended starting dose for term neonates.

■ CONCLUSIONS

All neonates should be closely monitored, and they may develop opioid tolerance rapidly, so large doses of opioids may be required to achieve adequate pain control for infants with continued severe pain. Better evaluation of pain, especially chronic pain and pain in the smallest infants, remains a challenge. The risk/benefit balance should be carefully addressed when considering analgesic and sedative treatment in a neonate, using currently available data and keeping in mind the major knowledge gaps remaining in this field. Analgesia in newborns differs in many ways from that of adults. Both pharmacokinetics and pharmacodynamics vary with the postnatal development. This makes pediatric analgesia more complicated than analgesia in adults. We feel further research is required to ensure that the doses recommended for treatment of analgesia in neonates are evidence-based. Such research may result in an improvement in the efficacy of analgesics in the neonatal period.

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■ CONFLICT OF INTERESTS

The author declares that there is no conflict of interests regarding the publication of this paper.

■ RESUMO

OBJETIVOS: Os objetivos deste estudo são (1) descrever a farmacologia clínica de analgésicos em crianças e (2) o tratamento farmacológico da dor em recém-nascidos.

MÉTODOS: A pesquisa bibliográfica foi realizada utilizando as bases de dados PubMed e EMBASE como ferramentas de busca.

RESULTADOS: Os analgésicos opióides são os analgésicos mais utilizados para a dor aguda e incluem morfina por via intravenosa (50 a 200 ug/kg), metadona por via oral (50 a 200 ug/kg), fentanil (0,5 a 4 mg/kg), alfentanil (10 a 20 ug/kg), sufentanil (10 a 15 ug/kg), e remifentanil (5 ug/kg). Fentanil, alfentanil, sufentanil e remifentanil são opióides de curta ação analgésica. Os analgésicos não opióides podem ser utilizados para a dor moderada e incluem paracetamol oral (acetaminofeno, de 12 a 15 mg/kg), o midazolam benzodiazepina intravenosa (50 a 150 ug/kg) que porém não é recomendado em recém-nascidos, o propofol (2,5 mg/kg), que é utilizado para a indução da anestesia geral, e Ketamina (2 mg/kg por via intravenosa ou 4 mg/kg por via intramuscular), que produz transe de curta duração, com profunda analgesia e amnésia.

CONCLUSÃO: O uso de analgésicos não-opióides aumentou nos últimos anos para o tratamento da dor não aguda. Se a prevenção ou eliminação da dor não é possível, uma meta mais realista podem ser intervir agressivamente para minimizar a dor e os seus efeitos.

■ REFERENCES

1. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. N Engl J Med. 1987;317(21):1321-9.
2. Anand KJ. Systematic analgesic therapy. In: Anand KJ, Stevens B, McGrath P, editors. Pain in neonates. Amsterdam: Elsevier; 2000; p. 159-88.
3. Berde CB, Sethna NF. Analgesics for the treatment of pain in children. N Engl J Med. 2002;347(14):1094-103.
4. van Lingen RA, Deinum JT, Quak JM, Kuizenga AJ, van Dam JG, Anand KJ, Tibboel D, Okken A. Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates. Arch Dis Child Fetal Neonatal Ed. 1999;80(1):F59-63.
5. Lago P, Benini F, Agosto C, Zacchello F. Randomised controlled trial of low dose fentanyl infusion in preterm infants with hyaline membrane disease. Arch Dis Child Fetal Neonatal Ed. 1998;79(3):F194-7.
6. Scott CS, Riggs KW, Ling EW, Fitzgerald CE, Hill ML, Grunau RV, Solimano A, Craig KD. Morphine pharmacokinetics and pain assessment in premature newborns. J Pediatr. 1999;135(4):423-9.
7. van Lingen RA, Simons SH, Anderson BJ, Tibboel D. The effects of analgesia in the vulnerable infant during the perinatal period. Clin Perinatol. 2002;29(3):511-34.
8. Aranda JV, Carlo W, Hummel P, Thomas R, Lehr VT, Anand KJ. Analgesia and sedation during mechanical ventilation in neonates. Clin Ther. 2005;27(6):877-99.
9. Walter-Nicolet E, Annequin D, Biran V, Mitanchez D, Tourniaire B. Pain management in newborns: from prevention to treatment. Paediatr Drugs. 2010;12(6):353-65.
10. Carbajal R, Gall O, Annequin D. Pain management in neonates. Expert Rev Neurother. 2004;4(3):491-505.
11. Carbajal R, Nguyen-Bourgain C, Armengaud JB. How can we improve pain relief in neonates? Expert Rev Neurother. 2008;8(11):1617-20.
12. Ranger M, Johnston CC, Anand KJ. Current controversies regarding pain assessment in neonates. Semin Perinatol. 2007;31(5):283-8.
13. Bergqvist LL, Katz-Salamon M, Hertegård S, Anand KJ, Lagercrantz H. Mode of delivery modulates physiological and behavioural responses to neonatal pain. J Perinatol. 2009;29(1):44-50.
14. Debillon T, Zupan V, Ravault N, Magny JF, Dehan M. Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2001;85(1):F36-F41, Jul.
15. Young TE, Mangum B, Neofax A. A Manual of Drugs used in neonatal care. 23rd. Montvale 07645, New Jersey, USA: Thomson Reuters; 2010.
16. Neonatal Formulary. 6th. West Sussex, PO22 9NQ, UK: John Wiley & Sons, Limited European Distribution Centre New Era Estate, Oldlands Way Bognor Regis; 2011.
17. Kahn DJ, Richardson DK, Gray JE, Bednarek F, Rubin LP, Shah B, Frantz ID 3rd, Pursley DM. Variation among neonatal intensive care units in narcotic administration. Arch Pediatr Adolesc Med. 1998;152(9):844-51.
18. Tibboel D, Anand KJ, van den Anker JN. The pharmacological treatment of neonatal pain. Semin Fetal Neonatal Med. 2005;10(2):195-205.
19. Beasley SW, Tibballs J. Efficacy and safety of continuous morphine infusion for postoperative analgesia in the paediatric surgical ward. Aust N Z J Surg. 1987;57(4):233-7.
20. Millar AJ, Rode H, Cywes S. Continuous morphine infusion for postoperative pain in children. S Afr Med J. 1987;72(6):396-8.
21. Farrington EA, McGuinness GA, Johnson GF, Erenberg A, Leff RD. Continuous intravenous morphine infusion in postoperative newborn infants. Am J Perinatol. 1993;10(1):84-7.
22. van Dijk M, Bouwmeester NJ, Duivenvoorden HJ, Koot HM, Tibboel D, Passchier J, de Boer JB. Efficacy of continuous versus intermittent morphine administration after major surgery in 0-3-year-old infants; a double-blind randomized controlled trial. Pain. 2002;98(3):305-13.
23. Esmail Z, Montgomery C, Courtrn C, Hamilton D, Kestle J. Efficacy and complications of morphine infusions in postoperative paediatric patients. Paediatr Anaesth. 1999;9(4):321-7.
24. Anand KJ, Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. Arch Pediatr Adolesc Med. 1999;153(4):331-8.
25. Anand KJ. Systematic analgesic therapy. In: Anand KJ, Steven B, McGrath P, editors. Pain in neonates. Amsterdam: Elsevier; 2000; p. 159-88.
26. Anand KJS. Pharmacological approaches to the management of pain in the neonatal intesnsive care unit. J Periatol. 2007;27:S4-11.
27. Chay PC, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationships of morphine in neonates. Clin Pharmacol Ther. 1992; 51(3):334-42.
28. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. Anesthesiology. 1987;66(2):136-9.
29. Pokela ML, Olkkola KT, Seppälä T, Koivisto M. Age-related morphine kinetics in infants. Dev Pharmacol Ther. 1993;20(1-2):26-34.
30. Bhat R, Chari G, Gulati A, Aldana O, Velamati R, Bhargava H. Pharmacokinetics of a single dose of morphine in preterm infants during the first week of life. J Pediatr. 1990;117(3):477-81.
31. Barrett DA, Elias-Jones AC, Rutter N, Shaw PN, Davis SS. Morphine kinetics after diamorphine infusion in premature neonates. Br J Clin Pharmacol. 1991;32(1):31-7.
32. Thummel KE, Shen DD, Isoherranen N. Design and optimization of dosage regimens: Pharmacokinetic data. In: Brunton L, Chabner B, Knollman B, editors. Goodman & Gilman's, the Pharmacological basis of Therapeutics. 12th. New York: Mc Grow Hill; 2011; p. 1899-90.
33. Choonara IA, McKay P, Hain R, Rane A. Morphine metabolism in children. Br J Clin Pharmacol. 1989;28(5):599-604.
34. Gourlay GK, Wilson PR, Glynn CJ. Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology. 1982;57(6):458-67.
35. Porter Fl, Anand KJS. Epidemiology of pain in neonates. Res Clin Forums. 1998;20:9-16.
36. Suresh S, Anand KJ. Opioid tolerance in neonates: a state-of-the-art review. Paediatr Anaesth. 2001;11(5):511-21.
37. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. Crit Care Med. 2000;28(6):2122-32.
38. Berde CB, Beyer JE, Bournaki MC, Levin CR, Sethna NF. Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. J Pediatr. 1991;119(1 Pt 1):136-41.
39. Shir Y, Shenkman Z, Shavelson V, Davidson EM, Rosen G. Oral methadone for the treatment of severe pain in hospitalized children: a report of five cases. Clin J Pain. 1998;14(4):350-3.
40. Chana SK, Anand KJ. Can we use methadone for analgesia in neonates? Arch Dis Child Fetal Neonatal Ed. 2001;85(2):F79-81.
41. Rosen TS, Pippenger CE. Disposition of methadone and its relationship to severity of withdrawal in the newborn. Addict Dis. 1975;2(1-2):169-78.
42. Kreek MJ. Methadone disposition during the perinatal period in humans. Pharmacol Biochem Behav. 1979;11(Suppl):7-13.
43. Hamon I, Hascoët JM, Debbiche A, Vert P. Effects of fentanyl administration on general and cerebral haemodynamics in sick newborn infants. Acta Paediatr. 1996;85(3):361-5.
44. Barrington KJ, Byrne PJ. Premedication for neonatal intubation. Am J Perinatol. 1998;15(4):213-6.
45. Stevenson B, Gibbins S, Frank LS. Treatment of pain in neonatal intensive cure. Pediatr Clin North Am. 2000;47:633-50.
46. Wilson AS, Stiller RL, Davis PJ, Fedel G, Chakravorti S, Israel BA, McGowan FX Jr. Fentanyl and alfentanil plasma protein binding in preterm and term neonates. Anesth Analg. 1997;84(2):315-8.
47. Koehntop DE, Rodman JH, Brundage DM, Hegland MG, Buckley JJ. Pharmacokinetics of fentanyl in neonates. Anesth Analg. 1986;65(3):227-32.
48. Feierman DE, Lasker JM. Metabolism of fentanyl, a synthetic opioid analgesic, by human liver microsomes. Role of CYP3A4. Drug Metab Dispos. 1996;24(9):932-939.
49. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology–drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157-67.
50. Lacroix D, Sonnier M, Moncion A, Cheron G, Cresteil T. Expression of CYP3A in the human liver–evidence that the shift between CYP3A7 and CYP3A4 occurs immediately after birth. Eur J Biochem. 1997;247(2):625-34.

51. Allegaert K, Van den Anker JN, Debeer A, Cossey V, Verbesselt R, Tibboel D, Devlieger H, de Hoon J. Maturational changes in the in vivo activity of CYP3A4 in the first months of life. Int J Clin Pharmacol Ther. 2006;44(7):303-8.

52. Saarenmaa E, Neuvonen PJ, Fellman V. Gestational age and birth weight effects on plasma clearance of fentanyl in newborn infants. J Pediatr. 2000;136(6):767-70.

53. Collins C, Koren G, Crean P, Klein J, Roy WL, MacLeod SM. Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. Anesth Analg. 1985;64(11):1078-80.

54. Davis PJ, Killian A, Stiller RL, Cook DR, Guthrie RD, Scierka AM. Pharmacokinetics of alfentanil in newborn premature infants and older children. Dev Pharmacol Ther. 1989;13(1):21-7.

55. Killian A, Davis PJ, Stiller RL, Cicco R, Cook DR, Guthrie RD. Influence of gestational age on pharmacokinetics of alfentanil in neonates. Dev Pharmacol Ther. 1990;15(2):82-5.

56. Katz R, Kelly HW. Pharmacokinetics of continuous infusions of fentanyl in critically ill children. Crit Care Med. 1993;21(7):995-1000.

57. Santeiro ML, Christie J, Stromquist C, Torres BA, Markowsky SJ. Pharmacokinetics of continuous infusion fentanyl in newborns. J Perinatol. 1997;17(2):135-9.

58. Bailey PL, Stanley TH. Intravenous Opioid anestetics. In: Miller RD, editor. Anesthesia. 4th. New York: Churchill Livingstone; 1994; p. 291-387.

59. Dewhirst E, Naguib A, Tobias JD. Chest wall rigidity in two infants after low-dose fentanyl administration. Pediatr Emerg Care. 2012;28(5):465-8.

60. Fahnenstich H, Steffan J, Kau N, Bartmann P. Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. Crit Care Med. 2000;28(3):836-9.

61. Foster D, Upton R, Christrup L, Popper L. Pharmacokinetics and pharmacodynamics of intranasal versus intravenous fentanyl in patients with pain after oral surgery. Ann Pharmacother. 2008;42(10):1380-7.

62. Olkkola KT, Hamunen K. Pharmacokinetics and pharmacodynamics of analgesic drugs. In: McGrath P, editor. Pain in neonates. 2nd Revised and Enlarged Edition. Amsterdam: Elsevier; 2000; p. 135-58.

63. Pokela ML. Effect of opioid-induced analgesia on beta-endorphin, cortisol and glucose responses in neonates with cardiorespiratory problems. Biol Neonate. 1993;64(6):360-7.

64. Pokela ML, Koivisto M. Physiological changes, plasma beta-endorphin and cortisol responses to tracheal intubation in neonates. Acta Paediatr. 1994;83(2):151-6.

65. Saarenmaa E, Huttunen P, Leppäluoto J, Fellman V. Alfentanil as procedural pain relief in newborn infants. Arch Dis Child Fetal Neonatal Ed. 1996;75(2):F103-7.

66. Meuldermans W, Woestenborghs R, Noorduin H, Camu F, van Steenberge A, Heykants J. Protein binding of the analgesics alfentanil and sufentanil in maternal and neonatal plasma. Eur J Clin Pharmacol. 1986;30(2):217-9.

67. Wiest DB, Ohning BL, Garner SS. The disposition of alfentanil in neonates with respiratory distress. Pharmacotherapy. 1991;11:308-11.

68. Marlow N, Weindling AM, Van Peer A, Heykants J. Alfentanil pharmacokinetics in preterm infants. Arch Dis Child. 1990;65(4 Spec No):349-51.

69. Klees TM, Sheffels P, Dale O, Kharasch ED. Metabolism of alfentanil by cytochrome p4503a (cyp3a) enzymes. Drug Metab Dispos. 2005; 33(3):303-11.

70. Lundeberg S, Roelofse JA. Aspects of pharmacokinetics and pharmacodynamics of sufentanil in pediatric practice. Paediatr Anaesth. 2011; 21(3):274-9.

71. Meistelman C, Benhamou D, Barre J, Levron JC, Mahe V, Mazoit X, Ecoffey C. Effects of age on plasma protein binding of sufentanil. Anesthesiology. 1990;72(3):470-3.

72. Greeley WJ, de Bruijn NP, Davis DP. Sufentanil pharmacokinetics in pediatric cardiovascular patients. Anesth Analg. 1987;66(11):1067-72.

73. Schmidt B, Adelmann C, Stützer H, Welzing L, Hünseler C, Kribs A, Roth B. Comparison of sufentanil versus fentanyl in ventilated term neonates. Klin Padiatr. 2010;222(2):62-6.

74. Anand KJ, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anaesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med. 1992;326(1):1-9.

75. Cascone S, Lamberti G, Titomanlio G, Piazza O. Pharmacokinetics of Remifentanil: a three-compartmental modeling approach. Transl Med UniSa. 2013;7:18-22.

76. Welzing L, Ebenfeld S, Dlugay V, Wiesen MH, Roth B, Mueller C. Remifentanil degradation in umbilical cord blood of preterm infants. Anesthesiology. 2011;114(3):570-7.

77. Ross AK, Davis PJ, Dear Gd GL, Ginsberg B, McGowan FX, Stiller RD, Henson LG, Huffman C, Muir KT. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. Anesth Analg. 2001;93(6):1393-401.

78. Welzing L, Oberthuer A, Junghaenel S, Harnischmacher U, Stützer H, Roth B. Remifentanil/midazolam versus fentanyl/midazolam for analgesia and sedation of mechanically ventilated neonates and young

79. Penido MG, Garra R, Sammartino M, Pereira e Silva Y. Remifentanil in neonatal intensive care and anaesthesia practice. Acta Paediatr. 2010;99(10):1454-63.

80. Saarenmaa E, Neuvonen PJ, Huttunen P, Fellman V. Ketamine for procedural pain relief in newborn infants. Arch Dis Child Fetal Neonatal Ed. 2001;85(1):F53-6.

81. Peeters MY, Allegaert K, Blussé van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, Knibbe CA. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010;49(4):269-75.

82. Shah V, Taddio A, Ohlsson A. Randomised controlled trial of paracetamol for heel prick pain in neonates. Arch Dis Child Fetal Neonatal Ed. 1998;79(3):F209-11.

83. Cuzzolin L, Antonucci R, Fanos V. Paracetamol (acetaminophen) efficacy and safety in the newborn. Curr Drug Metab. 2013;14(2):178-85.

84. Allegaert K, Naulaers G, Vanhaesebrouck S, Anderson BJ. The paracetamol concentration-effect relation in neonates. Paediatr Anaesth. 2013;23(1):45-50.

85. Allegaert K, Anderson BJ, Naulaers G, de Hoon J, Verbesselt R, Debeer A, Devlieger H, Tibboel D. Intravenous paracetamol (propacetamol) pharmacokinetics in term and preterm neonates. Eur J Clin Pharmacol. 2004;60(3):191-7.

86. Shaheen SO, Newson RB, Ring SM, Rose-Zerilli MJ, Holloway JW, Henderson AJ. Prenatal and infant acetaminophen exposure, antioxidant gene polymorphisms, and childhood asthma. J Allergy Clin Immunol. 2010;126(6):1141-8.e7.

87. Levy G, Khanna NN, Soda DM, Tsuzuki O, Stern L. Pharmacokinetics of acetaminophen in the human neonate: formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and D-glucaric acid excretion. Pediatrics. 1975;55(6):818-25.

88. Anderson BJ, van Lingen RA, Hansen TG, Lin YC, Holford NH. Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. Anesthesiology. 2002; 96(6):1336-45.

89. Palmer GM, Atkins M, Anderson BJ, Smith KR, Culnane TJ, McNally CM, Perkins EJ, Chalkiadis GA, Hunt RW. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. Br J Anaesth. 2008;101(4):523-30.

90. de Wildt SN, de Hoog M, Vinks AA, van der Giesen E, van den Anker JN. Population pharmacokinetics and metabolism of midazolam in pediatric intensive care patients. Crit Care Med. 2003;31(7):1952-8.

91. Bellù R, de Waal KA, Zanini R. Opioids for neonates receiving mechanical ventilation. Cochrane Database Syst Rev. 2008; (1):CD004212.

92. Pacifici GM. Clinical pharmacology of midazolam in neonates and children: effect of disease. A review. Intern J Pediatr. 2014.

93. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Cochrane Database Syst Rev. 2003; (1):CD002052.

94. Knoester PD, Jonker DM, Van Der Hoeven RT, Vermeij TA, Edelbroek PM, Brekelmans GJ, de Haan GJ. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. Br J Clin Pharmacol. 2002;53(5): 501-7.

95. Burstein AH, Modica R, Hatton M, Forrest A, Gengo FM. Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration. J Clin Pharmacol. 1997;37(8):711-8.

96. Rey E, Delaunay L, Pons G, Murat I, Richard MO, Saint-Maurice C, Olive G. Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. Eur J Clin Pharmacol. 1991;41(4):355-7.

97. Hu KC, Chiu NC, Ho CS, Lee ST, Shen EY. Continuous midazolam infusion in the treatment of uncontrollable neonatal seizures. Acta Paediatr Taiwan. 2003;44(5):279-81.

98. Castro Conde JR, Hernández Borges AA, Doménech Martínez E, González Campo C, Perera Soler R. Midazolam in neonatal seizures with no response to phenobarbital. Neurology. 2005;64(5):876-9.

99. Gonzalez FJ, Coughtrie M, Tukey RH. Drug Metabolism. In: Brunton L, Chabner B, Knollman B, editors. Goodman and Gilman's. The Pharmacological Basis of Therapeutics. 12th. New York, USA: Mc Graw Hill; 2011; p.259.

100. Gorski JC, Hall SD, Jones DR, VandenBranden M, Wrighton SA. Regioselective biotransformation of midazolam by members of the human cytochrome P450 3A (CYP3A) subfamily. Biochem Pharmacol. 1994;47(9):1643-53.

101. Wang RW, Newton DJ, Liu NY, Shou M, Rushmore T, Lu AY. Inhibitory anti-CYP3A4 peptide antibody: mapping of inhibitory epitope and specificity toward other CYP3A isoforms. Drug Metab Dispos. 1999; 27(2):167-72.

102. Keubler A, Weiss J, Haefeli WE, Mikus G, Burhenne J. Drug interaction of efavirenz and midazolam: efavirenz activates the CYP3A-mediated midazolam 1'-hydroxylation in vitro. Drug Metab Dispos. 2012; 40(6):1178-82.

infants: a randomized controlled trial. Intensive Care Med. 2012; 38(6):1017-24.

103. Ince I, de Wildt SN, Peeters MY, Murry DJ, Tibboel D, Danhof M, Knibbe CA. Critical illness is a major determinant of midazolam clearance in children aged 1 month to 17 years. Ther Drug Monit. 2012;34(4):381-9.

104. de Wildt SN, Kearns GL, Murry DJ, Koren G, van den Anker JN. Ontogeny of midazolam glucuronidation in preterm infants. Eur J Clin Pharmacol. 2010;66(2):165-70.

105. Rigby-Jones AE, Nolan JA, Priston MJ, Wright PM, Sneyd JR, Wolf AR. Pharmacokinetics of propofol infusions in critically ill neonates, infants, and children in an intensive care unit. Anesthesiology. 2002;97(6): 1393-400.

106. Jones RD, Chan K, Andrew LJ. Pharmacokinetics of propofol in children. Br J Anaesth. 1990;65(5):661-7.

107. Allegaert K, Peeters MY, Verbesselt R, Tibboel D, Naulaers G, de Hoon JN, Knibbe CA. Inter-individual variability in propofol pharmaco-kinetics in preterm and term neonates. Br J Anaesth. 2007;99(6):864-70.

108. Allegaert K, de Hoon J, Verbesselt R, Naulaers G, Murat I. Maturational pharmacokinetics of single intravenous bolus of propofol. Paediatr Anaesth. 2007;17(11):1028-34.

109. Allegaert K, Vancraeynest J, Rayyan M, de Hoon J, Cossey V, Naulaers G, Verbesselt R. Urinary propofol metabolites in early life after single intravenous bolus. Br J Anaesth. 2008;101(6):827-31.

110. Smits A, De Cock RF, Cossey V, Knibbe CA, Allegaert K. Is indirect hyperbilirubinemia a useful biomarker of reduced propofol clearance in neonates? Biomark Med. 2012;6(3):283-9.

111. Hartvig P, Larsson E, Joachimsson PO. Postoperative analgesia and sedation following pediatric cardiac surgery using a constant infusion of ketamine. J Cardiothorac Vasc Anesth. 1993;7(2):148-53.

112. Greeley WJ, de Bruijn NP. Changes in sufentanil pharmacokinetics within the neonatal period. Anesth Analg. 1988;67(1):86-90.

113. Bovill JG, Sebel PS, Blackburn CL, Oei-Lim V, Heykants JJ. The pharmacokinetics of sufentanil in surgical patients. Anesthesiology. 1984;61(5):502-6.

114. de Wildt SN, Kearns GL, Hop WC, Murry DJ, Abdel-Rahman SM, van den Anker JN. Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. Clin Pharmacol Ther. 2001;70(6):525-31.

115. Burtin P, Jacqz-Aigrain E, Girard P, Lenclen R, Magny JF, Betremieux P, Tehiry C, Desplanques L, Mussat P. Population pharmacokinetics of midazolam in neonates. Clin Pharmacol Ther. 1994;56(6 Pt 1):615-25.

116. Lee TC, Charles BG, Harte GJ, Gray PH, Steer PA, Flenady VJ. Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics. Anesthesiology. 1999;90(2):451-7.

117. Murat I, Billard V, Vernois J, Zaouter M, Marsol P, Souron R, Farinotti R. Pharmacokinetics of propofol after a single dose in children aged 1-3 years with minor burns. Comparison of three data analysis approaches. Anesthesiology. 1996;84(3):526-32.

118. Saint-Maurice C, Cockshott ID, Douglas EJ, Richard MO, Harmey JL. Pharmacokinetics of propofol in young children after a single dose. Br J Anaesth. 1989;63(6):667-70.

119. Davis PJ, Galinkin J, McGowan FX, Lynn AM, Yaster M, Rabb MF, Krane EJ, Kurth CD, Blum RH, Maxwell L, Orr R, Szmuk P, Hechtman D, Edwards S, Henson LG. A randomized multicenter study of remifentanil compared with halothane in neonates and infants undergoing pyloromyotomy. I. Emergence and recovery profiles. Anesth Analg. 2001;93(6):1380-6.

120. Chiaretti A, Pietrini D, Piastra M, Polidori G, Savioli A, Velardi F, Ciano F, Di Rocco C. Safety and efficacy of remifentanil in craniosynostosis repair in children less than 1 year old. Pediatr Neurosurg. 2000;33(2): 83-8.

121. Allegaert K, Tibboel D, van den Anker. Pharmacological treatment of neonatal pain: in search of a new equipoise. Seminars in Fetal & Neonatal Medicine. 2013;18:42-7.

122. Allegaert K, Veyckemans F, Tibboel D. Clinical practice: analgesia in neonates. Eur J Pediatr. 2009;168(7):765-70.

123. van Dijk M, Ceelie I, Tibboel D. Endpoints in pediatric pain studies. Eur J Clin Pharmacol. 2011;67(Suppl 1):61-6.

124. Meek J. Options for procedural pain in newborn infants. Arch Dis Child Educ Pract Ed. 2012;97(1):23-8.