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Clinical Pharmacokinetics of Sedatives in Neonates

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Summary

Sedation is currently administered to neonates experiencing pain and stress during intensive care for medical diseases, as well as postoperatively. Drugs commonly used for sedation in neonates include benzodiazepines (midazolam and lorazepam), chloral hydrate and opioids (fentanyl and morphine). Sedation protocols and dosage schedules are, in most cases, adapted from those which have been developed in children and even adults. The effectiveness and safety of the sedative agents remain underevaluated, however, due to the difficulties of quantifying pain and stress in neonates, and because of the limited use of validated scoring methods by practitioners.

Among the benzodiazepines, midazolam is probably the drug of choice for continuous sedation. However, its elimination is delayed in the neonatal period and hypotension may occur when given as a bolus injection or when taken with opioids. Lorazepam requires further evaluation to exclude severe neurotoxicity. Chloral hydrate is administered orally, but because of its delayed elimination and risk of accumulation, a single administration for short term sedation is recommended.

Among opioids, fentanyl (which was initially administered for postoperative analgesia) is now prescribed for sedation during mechanical ventilation. Toler-

ance and dependence may develop rapidly, limiting its usefulness for prolonged sedation. Although extensively studied in neonates, the efficacy and safety of morphine are not clearly determined, because of the limited number of patients included in individual studies. In addition, important interindividual differences in metabolism render dosage recommendations difficult. Alfentanil and sufentanil need further investigations to define their pharmacokinetic-pharmacodynamic properties in neonates.

Although the choice of drug is important, the way the drug is used and monitored is equally important. All the drugs used for the sedation of neonates have large inter- and intraindividual differences in disposition, justifying specific pharmacological knowledge and individual dosage adjustments based on clinical evaluation of the patient and the monitoring of drug concentrations.

In neonates sedation is required in clinical situations of pain and anxiety during intensive care for medical diseases and postoperative care. The capacity of the newborn to feel pain and stress has long been overlooked, probably because of the difficulties in evaluating these patients; and because the iatrogenic effects of neonatal intensive care have only recently been considered. A growing body of research suggests that neonates not only experience pain and stress,[1,2] but that their responses to painful stimulation may compromise their clinical conditions.[3]

The preventive efficacy of opioid anaesthesia on stress responses to surgery has been demonstrated in controlled clinical trials.[3,4] The use of major analgesia and sedation has been extended to the medical care of neonates undergoing mechanical ventilation for respiratory distress syndrome.[5] In this setting, the objectives of sedation and analgesia are to improve the patient's comfort on the one hand and to improve their compliance with mechanical ventilation on the other. Active expiratory efforts against the ventilator inflation may increase the risk of pneumothoraces[6] and intraventricular haemorrhages.[7] However, it is not clear whether sedation is able to prevent these complications, and what is an adequate level of sedation for a neonate undergoing intensive care.

Evaluating pain and stress is difficult in neonates and there is some confusion between the two; this explains why the use of analgesics and sedative agents for medical intensive care remains empirical and varies extensively between neonatal intensive care units (NICU). In the past agents with a long half-life ($t_{1/2}$), such as diazepam and phenobarbital, have been used for the sedation of neonates, generally with intermittent administration on an 'as required' basis. Agents with a short $t_{1/2}$ administered via continuous infusion are now preferred because they may provide a more regular effect and allow a more rapid recovery after cessation. Opioid analgesics, and particularly fentanyl, are being used widely in this indication, probably because of the experience gathered with these compounds in the field of neonatal anaesthesia.

In recent years, technical advances in the management of critically ill neonates have contributed to reducing the stress of intensive care. This includes advances in ventilation techniques, the use of long term arterial and venous lines, the reduction of environmental noise and individualised behavioural care. It now remains to be evaluated whether sedation, analgesia or a combination of both is required for neonates undergoing medical intensive care, and whether major analgesics offer a benefit over pure sedatives, and, in some situations, minor analgesics.

Sometimes referred to as tranquillisers or anxiolytics, sedatives constitute a pharmacological class difficult to define precisely, and this is further complicated by the different definitions used in different countries. Some authors also include barbiturates and antipsychotics in this therapeutic class because they have sedative properties at low doses.

We will limit this review to non-analgesic sedatives/hypnotics (benzodiazepines and chloral hydrate) and to opioids with are currently used for the sedation of neonates in the NICU, although opioids should be reserved for situations where some degree of analgesia is desired. General anaesthetics are occasionally prescribed for the sedation of neonates. Among them, only propofol will be presented briefly in this article. Wherever data are available, the pharmacodynamic properties of the compounds relevant to their use in the neonate are also presented.

1. Evaluation of Pain and Stress in the Neonate

Work by Anand and Hickey[8] showed that even the most premature human neonate possesses the pathways for pain at cortical and subcortical levels and that the physiopathological responses to pain and stress, including metabolic hormonal and cardiorespiratory changes, are similar if not greater in neonates than in paediatric patients and adults.

Different scales have been validated in paediatric patients to quantify pain and stress. Most of them have been adapted from adult scoring systems and are based on physiological measurements (heart rate, respiration, oxygenation, endorphins, etc.) and subjective items (facial expression, sociability, consolability, etc.) using verbal scales, numerical rating scales, colours and drawings and usually require verbal expression and contact.[9-13]

Data evaluating sedation and pain in neonates are very limited. Scores used during the neonatal period are similarly based on objective and subjective criteria. However, sleep is usually difficult to evaluate, crying cannot be scored in intubated babies, neither can verbal expression or contact be evaluated. Therefore, pain and stress remain very difficult to distinguish in acute clinical settings during the neonatal period.

A numerical agitation/sedation score was used to evaluate the effects of chloral hydrate,[14] while the efficacy of lorazepam has been tested by a visual analogue scale.[15] A behaviour score, which is simple to use and based on the assessment of 5 items (facial expression, sucking, spontaneous motor activity, excitability and responsiveness to stimulation, each scored 0 or 1) allowed the quantifying of the sedation obtained with midazolam during a placebo-controlled study.[16] The use of such scores to titrate sedation regularly is difficult and requires trained medical and nursing staff. This explains at least partly why the evaluation of the different sedative agents remains insufficient in neonates. However, their use on a routine basis is required for individual dosage adjustment, particularly during the neonatal period when major inter- and intraindividual differences in pharmacokinetics are observed.

2. Specific Issues for Pharmacokinetic Studies in Neonates

Neonates fall into the category of one of the most difficult patient groups to study and also have the most specific characteristics, which means the group requires particular attention. The developmental aspects of the kinetics of drugs in neonates have been largely reviewed,[17,18] and the issues raised by these studies were presented and discussed in Gilman and Gal.[19] Pharmacokinetic studies in neonates raise technical and ethical issues, mainly linked to the amount of blood that can be reasonably taken from infants.

As a rule, pharmacokinetic data are obtained from neonates who require the medication for their therapeutic care. Nevertheless, since pharmacokinetic studies on their own are generally without therapeutic benefit to the patients studied, sampling of more than a few millilitres of blood over a short period of time should be regarded as ethically unacceptable in neonates, and more so as these, often critically ill, patients encounter other blood losses and may be very sensitive to anaemia (notably neonates with respiratory distress syndrome). These difficulties result in severe limitation in individual pharmacokinetic studies. However, this obstacle can now be partly overcome by the use of highly sensitive analytical methods for the assay of small volumes of biological fluids, and by the use

of optimal sparse designs and population approaches for data evaluation.

For sparse samples to provide adequate information, sampling times should be optimised based on prior knowledge. But the pharmacokinetics of a drug in neonates may differ considerably from that in children and adults, and often more decidedly from the pharmacokinetics in children than that of adults. Extrapolation of the data should therefore be done very careful. In addition, many drugs show extremely large pharmacokinetic interindividual variability in critically ill neonates, so one single design may not be appropriate for all patients in a study. As an example, the clearance computed at steady-state as the ratio of infusion rate to concentration may be overestimated if the drug elimination is slower than expected and steady-state is in fact not reached at the time when samples are taken.

Another pharmacokinetic parameter which is often estimated with bias is terminal $t_{1/2}$. Because of limitations on the period of sampling and, for some drugs, unexpectedly slow elimination, the data obtained in neonates may not allow an accurate determination of the terminal elimination half-life ($t_{1/2\beta}$) in case of multiphasic kinetics. In particular, differences in $t_{1/2}$ reported across several studies may be artifactual and explained by differences in the interval of time over which samples were obtained, but also the assay sensitivity and the dose level.

The neonatal age is the period of life when the most profound and rapid physiological changes occur. The neonatal population included in pharmacological studies is highly heterogeneous in terms of age, bodyweight, disease and indications of therapy. The neonatal disease itself may influence the pharmacokinetics of the drug, modifying protein binding and tissue distribution, liver blood flow, liver function and renal function.

Generally, the characteristics of a drug in neonates will not be adequately described by a single set of parameter values. Examining the relationships between the individual pharmacokinetic parameters and covariates (e.g. gestational age, birthweight, or postnatal age) may require the study of a large number of patients and the use of multivariate approaches. Studies of small numbers of patients will often lack the power to detect covariates' effects and univariate analyses may be misleading because of confounding by other covariates. In these cases, the population approach offers the possibility to better address the effects of the covariates and estimate the interindividual variability, and to better account for unbalanced data across individuals. However, for some drugs with narrow therapeutic intervals, the interindividual variability may be so large that the average *a priori* dosage regimen will be inadequate for many individual patients.

Another issue that has been largely underevaluated for most drugs in neonates is the pharmacokinetic-pharmacodynamic interface. The therapeutic window is not necessarily the same in neonates and adults, and there is evidence that this is the case for sedative and analgesic agents. An integrated approach to pharmacokinetics-pharmacodynamics should be used in the future to allow the definition of adequate dosage regimens or guidelines for individial dose adjustment.

3. Sedative Agents

3.1 Benzodiazepines

At present, more than 20 benzodiazepines have been registered. They all exert qualitatively similar effects, including sedation-hypnosis, decreased anxiety, anticonvulsant activity, anterograde amnesia, and muscle relaxation. However, important differences in their pharmacodynamic and pharmacokinetic properties have led to varying patterns of therapeutic application. It is important to remember that benzodiazepines are not analgesics. However, unlike the barbiturates, they do not cause hyperalgesia.[20] The actions of benzodiazepines are believed to be a result of potentiation of the neural inhibition that is mediated by γ-aminobutyric acid (GABA).

Benzodiazepines bind to specific sites of the GABA receptor, where 2 types of benzodiazepine receptors, I and II, have been identified.[21] The receptors appear early in human ontogeny and are

already found at 7 weeks of gestation.[22,23] After birth, there is a steep increase in receptor density in the frontal cortex and cerebellum. In a neonate of 45 weeks post-conceptional age, the binding capacity of benzodiazepines was similar to that of adults in the cerebellum but lower in the frontal cortex.[22] The relative distribution of type I and II benzodiazepine receptors seems to vary in the course of development: in the visual cortex, type II receptors predominated in a 27-week fetus, type I subtype was increased in a newborn compared to the fetus, and type I and II were evenly distributed in adults.[23]

The various benzodiazepines show important differences in their pharmacokinetic behaviour in humans. Metabolism is probably the major determinant of their pharmacokinetic properties. Most benzodiazepines have multiple metabolites that are generally more or less active. Benzodiazepines are used in neonates either for their anticonvulsant or sedative properties. Only a few compounds have been pharmacokinetically evaluated in neonates.

3.1.1 Diazepam

Diazepam was one of the first sedative agents administered to neonates. It is now used in the NICU mainly as an anticonvulsant. Diazepam is mostly administered in neonates intravenously (despite its significant local irritation potential), oral and intrarectal administrations are also possible.[24]

The clinical pharmacokinetics of diazepam in neonates has been studied early, in some cases in neonates exposed transplacentally to the drug.[25,26] One important feature of diazepam is its extensive metabolism by the cytochrome P450 (CYP) linked mono-oxygenase system into a main active metabolite, desmethyldiazepam (nordazepam), that is eliminated more slowly than diazepam itself ($t_{1/2}$ of about 150 hours for desmethyldiazepam versus 20 to 35 hours for diazepam in adults).[27] This metabolism is present in the human fetal liver early during pregnancy.[28] The increased exposure to the metabolite is partly responsible for the prolonged clinical effects of diazepam in neonates, especially premature neonates, in association with a prolonged elimination of diazepam itself, with a $t_{1/2}$ (mean ± SD) of 75 ± 37 hours in premature neonates, and 31 ± 2 hours in fullterm neonates aged 5 to 8 days, compared with 18 ± 3 hours in children.[25,26]

In adults, diazepam is 99% bound to plasma proteins. The free fraction in cord blood after maternal treatment was found to be similar to that of adults (2%) and lower than that of the mother, thus resulting in drug accumulation in the fetus.[29]

During the first day of life, the diazepam free fraction doubles in the newborn, and then progressively decreases to reach adult values by the end of the first week.[30] In 100 neonates, changes in the diazepam and desmethyldiazepam free fraction paralleled changes in the free fatty acid concentrations, strongly suggesting a displacement from the binding sites by the latter.[30]

3.1.2 Lorazepam

Lorazepam is a lipophilic benzodiazepine with potent anxiolytic and anticonvulsant activity. In adults, it is well absorbed by the oral route, 75% protein-bound in plasma, and metabolised by glucuronidation before being eliminated in urine. The glucuronide metabolite is inactive.[31] Clinical experience with this agent in the neonate is largely restricted to its use as an anticonvulsant[32,33] but it may also be administered for its sedative properties.[15]

Pharmacokinetics

Pharmacokinetic data were obtained in 10 fullterm neonates with seizures who received an intravenous bolus administration of lorazepam 0.05 to 0.1 mg/kg,[33] and this was compared with data obtained in adults[34] and children.[35] The volume of distribution (Vd) at steady-state (Vd_{ss}) was slightly smaller in the neonates than in adults (0.76 versus 1.3 $L \cdot kg^{-1}$) and clearance (CL) was decreased (0.23 $ml \cdot min^{-1} \cdot kg^{-1}$) compared to that of adults (1.21 $ml \cdot min^{-1} \cdot kg^{-1}$) and children (1.3 $ml \cdot min^{-1} \cdot kg^{-1}$), resulting in a prolonged $t_{1/2\beta}$ of 40.2 hours compared with 12.9 hours in adults and 10.5 hours in children. A large interpatient variability was observed in this study, the $t_{1/2}$ ranging from 18 to 73 hours. The pharmacokinetics of lorazepam were not influenced by pretreatment with phenobarbitone or

phenytoin. The authors hypothesised that the reduced CL and the large interindividual variability were mainly explained by the immaturity of glucuronidation in the newborn.

Pharmacodynamics

Maloley et al.[15] report the successful use of lorazepam for the sedation of 15 neonates under mechanical ventilation. They used intermittent administrations of 0.1 to 0.4 mg/kg and a mean dosage of 2.9 mg/kg for 15 days. The number of doses and the daily dose (0.2 to 5.1 mg/kg/day) necessary to achieve deep sedation varied greatly across patients, independent of gestational age. Lorazepam was well tolerated in all neonates and no signs of withdrawal were noted after progressive discontinuation of treatment.

The clinical tolerability of lorazepam was also described as good in neonates treated for refractory seizures.[32] However, others report isolated cases of premature neonates presenting with abnormal movements of the limbs described as myoclonia or convulsions, starting within a few minutes following a bolus injection of lorazepam, and repeating in the subsequent hours.[36,37] The responsibility of the adjuvants contained in the drug preparation (benzyl alcohol and glycols) could not be excluded, although the doses administered were rather low compared with doses previously reported as toxic.[32,38]

The rapid occurrence of the symptoms after drug administration may suggest a relation with the peak concentration of either lorazepam or the solvents. In addition, 1 newborn of 33 weeks gestational age who received a total dose of lorazepam 1.5 mg/kg over 27 hours presented with major hypotonia necessitating prolonged assisted ventilation. This was probably explained by accumulation due to immature metabolism, since the plasma lorazepam concentration was 4453 nmol/L, while the toxic concentrations in adults has been reported to be 933 nmol/L.[37]

Lorazepam appears to be a potential candidate for neonatal sedation, even over prolonged periods.[15] However, further evaluation is needed, particularly to exclude serious neurotoxicity in relation to the abnormal movements reported. Bolus intravenous injections should probably be prescribed. In addition, accumulation may occur in some neonates and may require the monitoring of plasma concentrations in cases of prolonged administration.

3.1.3 Midazolam

Midazolam is an imidazobenzodiazepine available for parenteral administration as a water soluble salt at acidic pH. At physiological pH, the molecule is extremely lipophilic, allowing rapid tissue uptake and onset of action. Unlike the other benzodiazepines, midazolam has a short $t_{1/2\beta}$ and a short duration of action in adults.

Pharmacokinetics

In adults, the Vd is 1 to 2.5 $L \cdot kg^{-1}$, the distribution $t_{1/2}$ is less than 30 minutes and the $t_{1/2\beta}$ 1.5 to 3 hours. The total CL is about 50% of the hepatic blood flow (6.4 to 11 $ml \cdot min^{-1} \cdot kg^{-1}$). Protein binding is high (96%). Midazolam is 99% metabolised by CYP, and its main metabolite, 1-hydroxymidazolam, has a shorter $t_{1/2}$ and less activity than midazolam.[39]

Midazolam has been used for several years in NICUs; however, pharmacokinetic data in neonates were obtained only recently. In contrast, this drug has been associated with adverse effects, particularly hypotension, demonstrating the need for pharmacological evaluation of drugs used in neonates. A 2-step study was designed to study the disposition of midazolam in neonates. Preliminary pharmacokinetic data were collected in 25 neonates after either a single intravenous bolus dose of 0.2 mg/kg midazolam[40] or a continuous infusion of 0.06 mg/kg/h.[41] The pharmacokinetics were described by a 2-compartment model. In these neonates, the midazolam CL was reduced (1.8 $ml \cdot min^{-1} \cdot kg^{-1}$), the Vd lower (1.1 $L \cdot kg^{-1}$), and the terminal $t_{1/2}$ prolonged (9.8 hours) compared with those values in adults. Initial dosage regimens were derived from these results.

A multicentric population pharmacokinetic study was undertaken in a second step,[42] with the aim of studying the effects of gestational age, postnatal age, and other covariables on midazolam dis-

position. This study included a total of 187 neonates sedated for mechanical ventilation, having a gestational age between 26 and 42 weeks and a postnatal age between 0 and 10 days. The mean population CL was 1.2 ml • min^{-1} • kg^{-1}; the CL was directly proportional to bodyweight, 1.6-fold higher in neonates over 39 weeks gestation, and 0.7-fold lower in those receiving sympathomimetic amines. There was no relation between the pharmacokinetic parameters and postnatal age. The unexplained interpatient variability was very large, with a coefficient of variation of 65% for the CL, 85% for the central Vd, and 96% for the peripheral Vd.

Pharmacodynamics

The large pharmacokinetic interindividual variability renders the definition of an *a priori* dosage regimen for midazolam difficult. Moreover, the therapeutic interval of midazolam concentrations for sedation in neonates remains to be determined. Nevertheless, in the population study, 20% of the midazolam plasma concentrations were above 1000 μg/L, while concentrations between 100 and 500 μg/L have been described to provide adequate sedation in children.[43] Care must be taken in reducing the initial dosages administered to neonates, since the mean CL is 8-fold lower in the neonates than that in children, and then to titrate the dose according to the clinical effect.

In a double-blind, randomised, placebo-controlled study of 46 neonates sedated for artificial ventilation, infants of 33 weeks' gestation or more received a continuous infusion of midazolam 0.06 mg/kg/h and infants under 33 weeks' gestation received a loading infusion of midazolam 0.06 mg/kg/h for 24 hours followed by a maintenance infusion of 0.03 mg/kg/h.[16] Midazolam had a significantly better sedative effect than placebo, as assessed by a behaviour score. Heart rate and blood pressure were reduced by treatment but remained within the normal range for gestational age and there was no effect on ventilatory indices. The incidence of complications was similar in the 2 groups. No midazolam-related adverse effect was noted.

The main adverse effect reported after administration of midazolam to neonates was hypotension, and this was often associated with a bolus injection.[44,45] The co-administration of fentanyl may have potentiated hypotension in some cases.[45] In a prospective study, 15 neonates were randomised to receive an intravenous bolus dose of either midazolam 0.1 mg/kg or vecuronium 0.05 mg/kg.[46] A transient 8 to 23% decrease in blood pressure (mean 9mm Hg) was noted in all patients within 15 minutes following administration of midazolam, but not after administration of vecuronium. In 2 infants, a plasma expander was required.

As with lorazepam, several authors reported myoclonus following midazolam administration.[46,47] In 102 newborns of various gestational ages, the incidence of myoclonus was 6% and started 2 to 48 hours after the beginning of midazolam infusion and ceased a few hours after discontinuing the infusion, thereby ruling out withdrawal symptoms.[47] Reversible neurological abnormalities compatible with a withdrawal syndrome have been reported in children after midazolam infusions for 4 to 11 days,[48] but not in neonates.

Midazolam has been proven to provide relatively safe and effective sedation in neonates under mechanical ventilation. However, it cannot be considered an agent with a short $t_{½β}$ in neonates and its disposition is highly variable across patients, which may require individual dosage adjustments. Bolus intravenous doses should be precluded in neonates due to the occurrence of hypotension.

3.1.4 Flunitrazepam

Flunitrazepam has predominant sedative and hypnotic effects at therapeutic doses but also anticonvulsant properties. It is extensively metabolised and the major metabolites may participate in the clinical effects of the drug. Although included in sedation protocols of some NICUs, to our knowledge there are no data published on the pharmacokinetics, dosage recommendations or potential adverse effects of flunitrazepam in neonates.

3.1.5 Flumazenil

Flumazenil is a potent antagonist of benzodiazepines, extensively used in adult patients. Published data in paediatric patients is limited. At the dose of 5 to 10 μ/kg, flumazenil reversed coma induced by benzodiazepine overdose in 3 patients, aged 4, 7 and 14 years.[49] Flumazenil was administered as a bolus (10 μg/kg) followed by an infusion (5 μg/kg/min) in 12 children, aged 5 to 9 years, who had received midazolam during anaesthesia. All patients opened their eyes within 5 minutes of flumazenil administration. The flumazenil CL was 20.6 ml • min^{-1} • kg^{-1}, the apparent Vd_{ss} was 1.0 ml • kg^{-1} and the $t_{1/2\beta}$ was 35 minutes.[50] Two case reports are available on its use in neonates.[51,52]

3.2 Chloral Hydrate

Chloral hydrate is widely used as an oral sedative agent for short diagnostic and therapeutic procedures in children and adults. It was one of the first sedative agents used in neonates. It is well known as a prodrug, and is extensively and rapidly transformed in an active metabolite after absorption.[53]

3.2.1 Metabolism

Chloral hydrate is rapidly converted in the liver and erythrocytes into an active metabolite, trichloroethanol (TCE), by an aldehyde dehydrogenase. TCE is further inactivated by glucuronidation and eliminated in the urine. In case of saturation of the glucuronidation pathway, TCE is oxidised to trichloroacetic acid (TCA), and excreted by the kidneys.

In neonates with hepatic or renal insufficiency or with hyperbilirubinaemia, TCE may accumulate and achieve toxic concentrations.[54] Competition between bilirubin and TCE for glucuronidation may result both in hyperbilirubinaemia and TCE accumulation, particularly during the first week of life.[55]

3.2.2 Pharmacokinetics

Chloral hydrate is well absorbed after oral administration. In adults, the parent drug is not detectable after 10 minutes of intake because of its rapid metabolism.[56] In contrast, chloral hydrate was measured in plasma for several hours after administration of 50 mg/kg in neonates.[14] The $t_{1/2}$ of TCE is prolonged in neonates: 39.8 hours in premature infants in 1 study[57] and up to 66 hours in another study;[58] this may result in accumulation after repeated administrations.

Gorecki et al.[57] reported TCE concentrations remaining in plateau for 6 days in a 27-week premature infant after a single dose of chloral hydrate 80mg. After repeated administrations of 30 to 50 mg/kg in 12 neonates, TCE and TCA were detected in the plasma of 5 patients more than 4 days after the last administration.[59]

3.2.3 Pharmacodynamics

In adults, sedative concentrations of TCE range between 4 and 7 mg/L and the toxic concentration is 20 mg/L.[56] In 19 neonates given chloral hydrate 50 mg/kg every 4 to 6 hours, sedation scores paralleled the chloral hydrate plasma concentrations but showed no correlation with the TCE concentrations.[14] The authors concluded that, in the neonate, chloral hydrate and not TCE is responsible for the sedative effect of the drug. There are several reports of the toxic effects of chloral hydrate in neonates, most explained by the accumulation of the metabolites after repeated administrations. Signs of toxicity included central nervous system depression, cardiac dysrhythmias, hypotension, paradoxical agitation, hyperbilirubinaemia, renal failure, emesis and apnoea.[60] Toxic reactions may occur even after the drug has been discontinued since the metabolites may accumulate for several days. The administration of chloral hydrate 80mg every 6 hours in a 35-week neonate resulted after 4 days in a TCE concentration of 164 mg/L, with clinical signs of renal insufficiency, hypotension and hypotonia.[54]

Chloral hydrate is probably relatively safe for short term sedation in the neonate at single oral doses of 25 to 50 mg/kg. However, repeated administrations carry the risk of accumulation of the metabolites which may be associated with serious toxicity.

4. Opioid Agents

The use of potent narcotic/analgesic agents for neonatal anaesthesia has become widespread.[61] In this indication, opioid analgesics were shown to lower plasma β-endorphin concentrations[4] and, when used at high doses, to improve the postoperative clinical outcome.[3] Opioids are the most commonly administered drugs for sedation in adult intensive care units (ICU).[62] By extrapolation of the experience in adults and children, opioid agents, particularly fentanyl, have been increasingly used in NICUs for the analgesia and sedation of neonates under mechanical ventilation.[5]

In a randomised, placebo-controlled study, Pokela[63] showed that meperidine (pethidine) can reduce hypoxaemia and distress measured by a behavioural score during tracheal suction or routine nursing care. Morphine has been reported to lower cathecholamine concentrations in ventilated neonates[64] and to stabilise the fluctuations in arterial blood pressure in newborn infants with respiratory distress syndrome.[65] But it is not clear whether opioid agents offer a clinical therapeutic advantage over purely sedative agents or other analgesics in neonates undergoing intensive care. Questions have been raised relating to the widespread use of opioid analgesics in the newborn infant, in view of the absence of proper clinical evaluation and of some reports of adverse effects.[66-69] Nevertheless, in view of the *de facto* use of opiates for their sedative properties in the critically ill neonate, this therapeutic class will be addressed in this review.

4.1 Morphine

Substantial data on the clinical pharmacology of morphine in newborns have been gathered in the last decade, revealing detailed particularities of its metabolism, pharmacokinetics, and pharmacodynamics in this class of age.

4.1.1 Metabolism

In adults, morphine is largely eliminated in urine as glucuronide conjugates. The major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), are present in the plasma at significantly higher concentrations than morphine itself[70] and are believed to significantly contribute to the pharmacological activity of morphine. Studies in adults have confirmed the analgesic activity of M6G.[71]

In the rat, M6G elicited more potent analgesic effects than morphine, while M3G induced hyperventilation, hyperaesthesia, hyperactive motor behaviour, and, at high doses, convulsions.[72]

Morphine handling patterns exhibit a high variability among newborn infants, especially if premature[73] and maturational changes take place within a few weeks and even probably within a few days after birth. Choonara et al.[74,75] showed that glucuronidation of morphine is present in neonates, and even in very preterm infants of 24 to 25 weeks gestation, but at lower levels than in adults and children. As for adults, M3G was the predominant metabolite. The M3G/morphine ratios (mean ± SD) were 5.0 ± 4.6 in 9 preterm neonates aged 2 to 12 days, 8.0 ± 8.3 in 6 fullterm neonates aged 3 to 15 days, compared with 23.9 ± 6.4 in 9 children aged 1 to 16 years. In the preterm neonates, M6G was generally detected but at much lower concentrations and morphine concentrations were approximately 8-fold higher than in children exposed to the same range of doses. In the full term neonates, M6G plasma concentrations were generally greater than the morphine concentrations, which were similar to those in infants and children.

Bhat et al.[73] studied 16 preterm infants, less than 32 weeks gestational age and 1 to 66 days of postnatal age, following a single bolus intravenous injection of morphine: one-third of the patients had no metabolite detected in plasma nor urine and several infants excreted large amounts of unchanged morphine. Besides immaturity of hepatic glucuronidation, variability in these acutely ill neonates may also be explained by altered hepatic blood flow and the shunting of blood away from the liver by the ductus venosus. Unlike paracetamol (acetaminophen), sulphation remains a minor metabolic pathway of morphine in neonates.[76,77]

Table I. Pharmacokinetic parameters of morphine in neonates

n	Gestational age (week)	Postnatal age (day)	Dose (μg/kg)	Mean $t_{1/2}$ (range) [h]	Mean clearance [range] (ml/min/kg)	Mean distribution volume [range] (L/kg)	Reference
7	35-41	1-49	50-100 (bolus) then 6.2-40 μg/kg/h	7.9 [5.2-12]	7.8 [1.7-39]		69
7	36-41	1-4	20-100 μg/kg/h	6.8 [4.6-8.9]	6.3 [3.6-9.9]	3.4 [2.22-4.55]	78
3		29-65		3.9 [2.9-4.2]	23.8 [13.3-39]	5.2 [3.3-7.0]	78
9	24-37	2-12	10-42 μg/kg/h		4.7 [0.8-9.6]		76
10	30		100 (bolus)	10.0 [4.2-14.0]	3.4 [1.2-8.9]	1.8 (SD: 0.8)	79
7	31-37	≤5		7.4 (SD 1.7)	9.6 (SD 4)	5.2 (SD: 1.6)	79
3	38-40			6.7 [2.5-11]	15.5 [3.1-37.7]	2.9 (SD: 2.1)	79
26	26-38	15 (one 37)	50 (bolus) then 15 μg/kg/h	8.9 [4.2-18.3]	3.6 [2.0-9.7]	2.7 [1.2-4.4]	80
12	28-36	0-3	10-100 (bolus) then 7.5-30 μg/kg/h	10.6 [5.5-13.4]	2.2 [0.6-4.0]	2.0 [0.6-3.7]	81
7	37-40	1-3		7.6 [4.5-11.0]	2.0 [0.6-4.4]	2.1 [0.2-3.3]	81
7	37-40	3-15	12-51 μg/kg/h		20 [3-39]		75
12	>36	0-6	20 μg/kg/h	7.2[a] [5.1-15.8]	5.5[a] [3.2-8.4]	3.3[a] [1.7-4.5]	77
6		8-19		4.1[a] [1.8-5.6]	7.4[a] [3.4-13.8]	2.6[a] [2.2-3.1]	77
9	26-34	<1	100 then 12.5 μg/kg/h or 200 then 50 μg/kg/h	8.7	2.4 [2.0-3.2]	1.8	82
10	28-42 (median 40)	0-3	100 (bolus)	8.1 [1.2-20.5]	6.6 [1.1-15.9]	1.3 [0.9-2.4]	83
10		8-57		5.4 [2.1-12.0]	9.0 [3.2-15.2]	1.8 [1.0-3.5]	83
8	25-32	1-18 (median 2)	150 (bolus)	9.3[a] [4.1-13.9]	2.8[a] [1.9-6.6]	2.4[a] [1.7-2.9]	84
5	37-40	1-18 (median 2)	150 (bolus)	3.7[a] [1.8-6.6]	4.7[a] [1.8-6.6]	1.8[a] [0.6-2.7]	84

a Median minus SD.

Abbreviations and symbols: h = hours; n = number of patients; SD = standard deviation; $t_{1/2}$ = half-life.

4.1.2 Pharmacokinetics

In healthy young adults[71] and in children older than 1 year,[76-78] the pharmacokinetics of morphine are essentially similar, with a CL of about 20 $ml \cdot min^{-1} \cdot kg^{-1}$, an $t_{1/2\beta}$ of about 2 hours, and a Vd_{ss} of 2 to 4 $L \cdot kg^{-1}$. In the neonatal period, the CL of morphine is clearly lower and the $t_{1/2}$ longer than in children, while the Vd is similar; the pharmacokinetics of morphine are characterised by a very large interindividual variability, particularly in premature infants and during the first week of life, most likely explained by the metabolic changes occurring in these patients.

Across 11 studies in newborn infants, the mean CL ranged from 2 to 20 $ml \cdot min^{-1} \cdot kg^{-1}$, the mean $t_{1/2}$ from 3.4 to 10.6 hours, and the mean Vd from 1.3 to 5.2 $L \cdot kg^{-1}$.[69,74,75,77-84] The results of these studies are summarised in table I. Part of the differences across the studies is probably accounted for by the various gestational ages, postnatal ages, and clinical conditions studied, as well as the various designs and dose levels applied. However, a large variability was also noted within homogeneous groups of patients in the individual studies, even though they included rather small numbers (7 to 26) of infants. Particularly, the range for morphine CL within homogeneous groups of neonates was 2- to 13-fold. No data is available on the absorption and disposition of morphine after oral administration in the neonate.

The effects of gestational age and post-natal age on the pharmacokinetics of morphine have not

been clearly established, mainly because of the small size of the studies and the large interindividual variability. Nevertheless, some conclusions can be drawn from the compilation of these studies. Morphine CL is the lowest (about 2 to 4 ml • min^{-1} • kg^{-1}) in the very first days of life, irrespective of gestational age.[81,82,84] It increases with postnatal age[77,78,83] to reach the adult value between the first and sixth months of life.[77,78,85]

Beyond the very first days of life and for similar postnatal ages, morphine CL is lower in preterm than in term neonates.[74,75,79,83] It is also reduced in critically ill neonates compared with those who are not.[83] The $t_{1/2\beta}$ decreases with increasing gestational age.[80,83] The Vd does not differ between premature and term infants.[83] Morphine is 18 to 22% unbound to plasma protein in preterm and full term neonates, compared to 32% in adults.[77,79]

4.1.3 Pharmacodynamics

The pharmacological effects of opioids are the result of opioid receptor stimulation. The reported minimum concentrations required for analgesia are between 4 and 65 μg/L in children.[85,86] There has been an early report that newborns are more susceptible to the respiratory depressant effect of morphine compared with adults when similar doses are administered on a mg/kg basis,[87] a response believed to be primarily attributable to a greater permeability of the infant blood-brain barrier to morphine. However, the data available nowadays rather suggest that the apparently increased sensitivity is explained by the pharmacokinetics of morphine and that, at similar concentrations, neonates may even be less sensitive to the morphine analgesic effects than adults.

A study in children 11 days to 7 years of age reported a 7-fold higher morphine plasma concentration at return of pain in infants compared with older children.[85] In a study of morphine in 19 ventilated neonates aged 0 to 3 days (both preterm and term), Chay et al.[81] found a clear concentration-effect relationship for both the therapeutic effect and the occurrence of adverse effects. To produce adequate sedation in 50% of patients i.e. the patients remain quiet when undisturbed but respond to stimulation, a morphine concentration of 125 μg/L was required, while concentrations above 300 μg/L were associated with more frequent adverse effects. The authors suggested that the lower formation of the active metabolite, M6G, and the immaturity of the brain opiate receptors may explain the high morphine concentrations needed to achieve the target clinical effect in the newborn patients.

Lynn et al.[88] studied the respiratory effects of intravenous morphine infusions after cardiac surgery in 30 patients, 2 to 570 days old, 8 of them being 2 to 11 days old. Steady-state morphine concentrations over 20 μg/L resulted in hypercarbia and depressed CO_2 response curve slopes in about 70% of patients, irrespective of age.

Several investigators have reported adverse effects associated with the administration of morphine in neonates, including seizures,[69] bradycardia,[69,81] severe hypotension related to overdose,[79] urinary retention,[73] transient hypertonia[82] and CO_2 retention.[81,87] The adverse effects of morphine in infants have been associated with high plasma concentrations[69,81] and reduced CL.[81] Several authors reported a moderate decrease in the mean blood pressure following loading infusions or bolus doses;[64,79,80,82] it is possible that this related primarily to the reduction of stress due to the effect of the drug, rather than to unwanted adverse effects.

The major variation in drug disposition makes the administration of morphine in the neonatal age group difficult. Based on the results of their pharmacokinetic-pharmacodynamic study in neonates under mechanical ventilation, Chay et al.[81] recommended a dosage regimen consisting of a loading infusion rate of 150 μg/kg/h for 100 minutes and a maintenance infusion of 22.5 μg/kg/h. However, further pharmacokinetic-pharmacodynamic evaluation in larger numbers of patients is required; if a narrow therapeutic interval is confirmed, individual titration may be necessary based on clinical observation and potentially concentration measurements of morphine and its metabolites.

4.2 Fentanyl

Fentanyl is a synthetic opiate with a clinical potency of 50 to 100 times that of morphine, mainly because of its extreme lipid solubility and greater access to the central opiate receptors. It is known for its fast onset and short duration of action, but multiple doses may result in accumulation and delayed recovery due to redistribution from peripheral compartments.[89]

Fentanyl has become a drug of choice for general anaesthesia, especially for cardiac surgery, and postoperative analgesia in neonates, because it preserves cardiovascular stability.[61] Its use for prolonged sedation of neonates[5] during ventilatory support has become increasingly widespread, although prospective studies of sufficient numbers of patients to evaluate its safety and efficacy in this indication are lacking.

4.2.1 Metabolism

Fentanyl is a highly lipid-soluble compound that is cleared in adults by *N*-dealkylation and hydroxylation in the liver, with approximately 6% excreted unchanged by the kidneys.[89,90] It is a high hepatic extraction drug. Little is known about the factors affecting its metabolism in critically ill neonates. The ability of the liver to extract fentanyl is presumably a function of the maturity of the CYP system and of hepatic blood flow. Several authors have reported observations of nil CL in neonates undergoing abdominal surgery, which may be explained by the abdominal pressure causing a bypass of the liver.[91,92]

4.2.2 Pharmacokinetics

Only scarce data are available on the pharmacokinetics of fentanyl in the neonate and most were obtained after administration of high single doses for surgical anaesthesia. In adults, the pharmacokinetics of fentanyl are characterised by a CL of 10 to 18 ml · min^{-1} · kg^{-1}, a Vd_{ss} of 1.5 to 2.5 L/kg, and a terminal $t_{1/2}$ of about 2 hours. In neonates, the CL is similar, the Vd_{ss} larger, and the $t_{1/2\beta}$ prolonged; like for morphine, there is a large interindividual variability.[93,94]

In 2 studies, fentanyl was administered as a single intravenous dose of 10 to 55 μg/kg for surgical anaesthesia in 14 and 11 neonates. The pharmacokinetics were described by a 2– or 3-compartment model; the mean clearances were 17.9 ml · min^{-1} · kg^{-1} (range 3.4 to 58.7) and 19.2 ml · min^{-1} · kg^{-1} (range 0 to 32.8); the mean Vd_{ss} were 5.1 L · kg^{-1} (range: 1.3 to 13.5) and 8.5 L · kg^{-1} (range: 4.8 to 11.9), respectively.[91,92] Seven of 14 patients displayed a transient rebound in plasma fentanyl levels of 0.5 to 7.0 μg/L within 15 hours after injection, and 2 of also required markedly prolonged ventilatory support.[91] Gauntlett et al.[92] found that CL increased with postnatal age, most of the increase occurring by 2 weeks of age. Koehntop et al.[91] found no difference between preterm and fullterm neonates but they did not specify the gestational ages of their patients. In these 2 single-dose studies, the terminal $t_{1/2}$ ranged from 1.25 to 15.9 hours.

Roth et al.[5] studied 20 neonates under mechanical ventilation for severe respiratory distress syndrome. After a loading dose of 5.0 to 12.5 μg/kg, fentanyl was given by continuous infusion of 0.5 to 2 μg/kg/h. Despite the small number of patients studied, the CL showed an extremely large interindividual variability, ranging from 2 to 85 ml · min^{-1} · kg^{-1}. The CL was similar in the neonates of more and less than 34 weeks of gestational age, with means of 12 and 13 ml · min^{-1} · kg^{-1}, respectively.

4.2.3 Pharmacodynamics

In adults, a fentanyl concentration of 1 to 3 μg/L is needed for adequate analgesia during anaesthesia, although there is considerable interindividual variability.[89] Collins et al.[95] reported that when used as the sole anaesthetic agent in neonates undergoing ligation of the ductus arteriosus, fentanyl produced adequate anaesthesia at plasma concentrations between 7.7 and 13.6 μg/L. In a study of neonates undergoing mechanical ventilation for severe respiratory distress syndrome, Roth et al.[5] reported that fentanyl was well tolerated and provided adequate sedation at mean plasma concentrations of about 2 μg/L.

However, the usefulness of fentanyl for intensive care may be limited by the development of tolerance and dependence. Arnold et al.[96,97] described the rapid installation of tolerance to sedation after continuous intravenous infusions of fentanyl in neonates undergoing extracorporeal membrane oxygenation (ECMO). The clinical endpoint being the neonates sedated but arousable, the mean fentanyl infusion rate increased from 9 to 22 μg/kg/h and the mean plasma fentanyl concentration from 3 to 14 μg/L over a period of 6 days of infusion, while most infants manifested spontaneous movement of the extremities and eye opening and some were described as agitated. There is evidence in animals that continuous opioid administration produces tolerance much more rapidly than intermittent administration.[98] The tolerance leads to an increasing dose requirement and possibly a withdrawal syndrome on discontinuation of the drug.

In Arnold's series,[96] 57% of neonates had an abstinence syndrome after discontinuation of the fentanyl infusion. Neonates who had received a total dose greater than 1.6 mg/kg or ECMO duration greater than 5 days appeared to have a significantly greater likelihood of developing an abstinence syndrome. Katz et al.[99] also observed a high incidence of narcotic withdrawal, dose- and duration-dependent, in a prospective series of 23 children aged 1 week to 22 months who required sedation for mechanical ventilation. A total fentanyl dose over 2.5 mg/kg or a duration of infusion of more than 9 days was 100% predictive of withdrawal.

Even at high bolus doses (>10 μg/kg), fentanyl was shown to cause no significant haemodynamic changes in infants.[100,101] It may blunt stress responses in the pulmonary circulation after suctioning, which may be advantageous for infants with pulmonary hypertension.[102] However, fentanyl produced significant depression of both pressor and depressor baroresponses in neonates, as tested by injection of phenylephrine and nitroglycerin respectively, which may impair the ability of neonates to compensate for rapid changes in systolic blood pressure.[103] Fentanyl may have potentiated the hypotensive effect of midazolam in some observations.[45]

A potentially deleterious effect of fentanyl in patients requiring ventilatory support is chest wall rigidity. Chest wall rigidity following a single dose of 3 μg/kg has been reported in premature neonates,[104] and at birth following administration of fentanyl to the mother,[105] this was reversed after administration of naloxone. Other adverse effects reported were delayed elimination of meconium and increased peak concentrations of bilirubin (12.1 *vs* 9.7 mg/dl in a control group), which may be due to the depressant action of opioids on the smooth muscle.[5]

As with morphine, the highly variable disposition of fentanyl in neonates makes individual dose administration difficult and necessitates individual titration according to clinical response. The occurrence of tolerability after a few days of continuous infusion limits the usefulness of the drug when prolonged sedation is required. In view of the good haemodynamic tolerability of fentanyl, bolus administrations for short term analgesia or sedation should be further evaluated.

4.3 Alfentanil

Alfentanil is a synthetic fentanyl analogue with one-third the clinical potency of fentanyl, a more rapid onset and offset of action, intermediate total body CL, and smaller Vd. The mean distributional $t_{1/2}$ results in rapid equilibration between blood and brain tissues and accounts for the rapid onset of action (1 to 2 minutes). Its propensity for weaker binding to tissues and stronger binding to plasma proteins (87 to 92% in adults) tends to prevent alfentanil from attaining the widespread distribution in tissues of fentanyl.[89] Of the fentanyls, alfentanil would appear to be best suited to infusion because of its small Vd and short terminal $t_{1/2}$, which would allow maximal control of effects.

4.3.1 Pharmacokinetics

The pharmacokinetics of alfentanil are generally best described by a 2-compartment model.[106,107] In adults, the Vd_{ss} is about 0.5 L/kg, the CL about 4 ml · min^{-1} · kg^{-1}, and the $t_{1/2\beta}$ about 1.7 hours.

Children demonstrate a smaller Vd and shorter $t_{1/2}$ than adults.[107] The results of pharmacokinetic studies of alfentanil in neonates are summarised in table II.

The disposition of alfentanil in neonates has almost exclusively been studied after a single dose. Compared with both older children and adults, newborns tend in average to have a smaller CL (0.9 to 3.2 ml • min^{-1} • kg^{-1}), a greater Vd (0.5 to 1 L • kg^{-1}) and a prolonged $t_{1/2\beta}$ (4.1 to 8.7 hours).[106,107,108-111] The lower CL may be related to immature enzyme systems or decreased hepatic blood flow. The large Vd may be due to the increase in total body water and decrease in protein binding in the neonate compared with older infants and children. Both the decreased CL and increased volume explain the prolonged $t_{1/2}$. However, individual neonates may possess pharmacokinetic characteristics close to the adult values.

The interindividual variability in the pharmacokinetic parameters was large in all studies, especially for CL: for instance, the CL range across 22 neonates was >20-fold in the study by Marlow et al.[68] There was no association between gestational age, or age and CL, in any of the studies. However, all the studies lacked power due to the small sample sizes and the neonates studied were all <5 days old. The pharmacokinetics of alfentanil in neonates beyond 1 week of postnatal age cannot be extrapolated from the available data and may be markedly different.

4.3.2 Pharmacodynamics

In adults, concentrations of alfentanil between 35 and 50 μg/L are recommended for sedation during mechanical ventilation, although for analgesia during surgery concentrations over 200 μg/L are recommended. No pharmacodynamic data regarding the analgesic and sedative effects of alfentanil in neonates are available. It is not guaranteed that adult equivalent sedative doses are effective in reducing the stress of mechanical ventilation in neonates.

A loading dose of alfentanil 20 μg/kg administered over 2 minutes in 20 neonates also receiving muscle relaxants (median gestational age 30 weeks) produced a rapid and significant fall in heart rate, blood pressure (mean 18%), and arterial oxygenation.[68] Yet, Davis et al.[106] and Killian et al.[110] found that the administration of alfentanil 25 μg/kg over 30 minutes produced no significant haemodynamic alteration in 6 preterm neonates receiving intensive care.

In the study by Wiest et al.,[109] 1 patient experienced mean arterial pressure fluctuation, but the loading dose of 8 μg/kg was haemodynamically well tolerated in all individuals. Pokela et al.[111] reported the occurrence of muscle rigidity in 13 of 20 mechanically ventilated newborns who were administered a bolus dose of alfentanil 9 to 15 μg/kg over 1 minute. Four infants had severe rigidity and jerking comparable to convulsive activity, transiently impairing ventilation and oxygenation. Electroencephalographic recordings for 3 infants, of whom 2 showed rigidity and 1 also had jerking,

Table II. Pharmacokinetic parameters of alfentanil in neonates

n	Gestational age (week)	Postnatal age (day)	Dose (μg/kg)	$t_{1/2\beta}$ SD [range] (h)	Clearance ± SD [range] (ml/min/kg)	Distribution volume ± SD [range] (L/kg)	Reference
6	27-36	1-3	25 (bolus)	8.7 ± 5.1	2.2 ± 2.4	1.0 ± 0.4	106
22	25-36	0-4	20 (bolus)	5.3[a] [1-21]	0.87[a] [0.4-9.6]	0.5[a] [0.1-1.0]	108
13	35-41	0-4	8 (bolus) then 2.5-10 μg/kg/h	4.1 ± 2.6 [1.4-8.9]	3.2 ± 2.2 [1.1-8.4]	0.5 ± 0.2 [0.4-1.1]	109
5	26-35	0-3	25 (bolus)	7.6 ± 1.8	1.3±0.7	0.8 ± 0.5	110
5	≥36	0-3	25 (bolus)	5.5 ± 0.8	1.7±0.5	0.8 ± 0.3	
15	30-40	0-3	9-15 (bolus)	[0.5-10.8]	[0.9-25.3]	[0.1-2.9]	111

a Median.

Abbreviations and symbols: n = number of patients; SD = standard deviation.

showed no evidence of seizure activity. The authors recommended that alfentanil should not be used without simultaneous muscle relaxation.

The theoretical advantages of alfentanil over fentanyl for continuous sedation may be blunted in the neonates by the large interindividual variability in its disposition characteristics. Clearly, more pharmacokinetic-pharmacodynamic evaluation is warranted in neonates, the more so as serious adverse events have been reported.

4.4 Sufentanil

Sufentanil has about 5 to 10 times the clinical potency of fentanyl, and pharmacokinetic properties intermediate to those of alfentanil and fentanyl. The unbound fraction in plasma in adults is 8%; sufentanil has a higher affinity for plasma proteins than fentanyl, offset by high tissue affinity, so that it achieves a less extensive extravascular distribution than fentanyl but one which is greater than for alfentanil.[89]

The free fraction of sufentanil is significantly higher in the newborn (19.5%) than in children and adults, and strongly correlates with the α_1-acid glycoprotein concentration.[112] The pharmacokinetics of sufentanil in neonates have only been studied in a few patients and after a single administration for surgical anaesthesia. The concentration-time course of sufentanil was best described by a 3-compartment model. Neonates were found to have a significantly smaller CL, larger Vd_{ss}, and longer $t_{1/2\beta}$ than infants and children.

In 9 neonates administered an intravenous bolus dose of sufentanil 10 to 15 μg/kg before elective cardiac surgery, the CL (mean SD) was 6.7 ± 6.1 ml · min^{-1} · kg^{-1}, the volume at steady-state Vd_{ss} 4.2 ± 1.0 L · kg^{-1}, and $t_{1/2\beta}$ 12.3 ± 5.7 hours.[113] In this study children were also included, and the neonatal group had the greatest variation in the pharmacokinetic parameters. Greeley and DeBruijn[114] further studied 3 infants at 1 to 8 days of age and again 3 to 4 weeks of age, who were administered a single bolus dose of sufentanil 10 μg/kg for major surgery. The CL and the Vd_{ss} of sufentanil increased and its $t_{1/2\beta}$ decreased with increasing age, despite the fact that the clinical condition had worsened in most patients. This suggested that these developmental changes were related to a maturation of the hepatic microsomal enzyme maturation. The increase of CL was quite dramatic, since values ranged from 1.7 to 6.7 ml/kg/min in the first week, and from 12.9 to 19.3 ml/kg/min by age 20 to 28 days. Vd_{ss} was 2.6 to 2.9 L · kg initially, and 3.2 to 3.6 at 1 month. As the neonates studied all had cardiac disease, the pharmacokinetic parameters may not apply to other populations of neonates.

Greeley et al.[113] suggested that neonates may be less sensitive to the anaesthetic effects of sufentanil because, in their study of cardiac surgery, anaesthetic supplementation occurred at a significantly higher plasma sufentanil concentration in the neonatal group (2.5 μg/L) compared with the childrens' group (about 1.6 μg/L). One neonate in this study had severe bradycardia and hypotension after sufentanil administration. As with alfentanil, further pharmacokinetic and pharmacodynamic evaluations of sufentanil are needed in neonates to determine whether this drug might be useful in the intensive care setting.

4.5 Meperidine (Pethidine)

Meperidine has a pharmacological profile close to that of morphine, with 7 to 10 times less clinical potency.[20] It is eliminated in adults mainly by hepatic metabolism, but in newborn infants significant amounts of unchanged meperidine can be found in urine together with metabolites. The main metabolite, normeperidine, has a longer $t_{1/2}$ than the parent compound, and may produce tremor and convulsions in case of accumulation.

Meperidine disposition has been studied in neonates whose mothers had been given meperidine during labour. Its $t_{1/2\beta}$ after birth was found to be 2 to 7 times longer than in adults.[115,116] Pokela et al.[117] studied the pharmacokinetics of meperidine in 13 neonates and 8 infants after a 1 mg/kg intravenous bolus dose. The CL ranged from 5.3 to 13.8 ml · min^{-1} · kg^{-1} in the term neonates less than 1 week old, was 1.8 and 3.2 ml · min^{-1} · kg^{-1} in 2 preterm neonates less than 1 week old, and ranged

from 3.5 to 34.9 ml • min^{-1} • kg^{-1} in infants older than 3 weeks. Over the entire population, the $t_{1/2}$ ranged from 3.3 to 59.4 hours and the Vd_{ss} from 3.3 to 11.0 L • kg^{-1}. The CL, but not the other parameters, was significantly correlated with age, gestational age and bodyweight. Several infants showed rebound increases in meperidine concentrations, presumably attributable to enterohepatic circulation or sequestering. In this study, meperidine administered as a single dose was well tolerated and there were no clinically significant changes in arterial blood pressure or heart rate during or after meperidine injection.

Ventilatory depression in neonates following meperidine 0.5 mg/kg intramuscularly was similar to that expected in adults.[87] However, meperidine should be used carefully in neonates, particularly in regard to multiple doses, because of the risk of neurotoxicity in cases of the accumulation of the metabolite.

4.6 Naloxone

Naloxone is a competitive inhibitor of opiate receptor sites. It is mainly indicated for treatment of opioid overdose. The average $t_{1/2}$ of naloxone in premature newborns is 70 minutes.[118] The currently recommended dose of naloxone is 0.1 mg/kg for infants and children from birth to 5 years of age.[119] This dose may be repeated as needed to maintain opiate reversal.

A report suggests that a continuous infusion may be appropriate.[120] In a 3.9kg full term neonate aged 25 days given fentanyl 26 μg/kg in error for anaesthesia, a bolus dose of naloxone 200μg followed by an intravenous infusion of 200 μg/h for 24 hours allowed rapid extubation and maintenance of spontaneous breathing.[120]

5. General Anaesthetics

General anaesthetics, such as ketamine, thiopental and γ-sodium hydroxybutyrate, occasionally prescribed for sedation, will not be discussed. Propofol is the only general anaesthetic that will be discussed briefly, because it has become currently used as a sedative agent in ICUs.

5.1 Propofol

Propofol is a intravenous anaesthetic agent with unique pharmacokinetic properties. Propofol is characterised by a large Vd with extensive redistribution and a rapid metabolic CL. Recovery from its clinical effects is rapid, despite a long $t_{1/2\beta}$ related to a slow release from lipophilic tissues. The Vd of propofol is larger and its CL rate is higher in children than in adults. In children over 4 years, CL following a single bolus injection of 2.5 mk/kg was 30 to 40 ml • min^{-1} • kg^{-1}.[121-123]

Propofol is extensively prescribed for induction and maintenance of anaesthesia in adults and children. Its clinical use has been expanded to sedation in ICUs or for ambulatory anaesthesia in adults.[124] There is a large variability in the response of patients to propofol. Infusion rates of 75 to 300 μg/min/kg are usually required for anaesthesia, while sedation can be obtained with infusion rates of 25 to 100 μg/min/kg.

Its use for sedation in paediatric intensive care remains controversial, as serious adverse effects have been reported. Five children, aged 4 weeks to 6 years and intubated for respiratory tract infection, developed metabolic acidosis and fatal cardiac failure 5 to 6 days after the initiation of propofol at high doses (4 to 10 mg/kg/h) for sedation.[125] Additional cases have been published.[126,127] Temporary neurological adverse effects are also reported in children receiving high doses of propofol.[128-130]

Experience with propofol for sedation in paediatric patients, including neonates, is very limited and its potential advantages for short term sedation remain to be evaluated rigorously. High doses and long term infusions should be avoided.

6. Discussion and Conclusions

Numerous drugs are currently used for sedation in critically ill newborn babies. Among them, benzodiazepines (midazolam and lorazepam), chloral hydrate and opioids (fentanyl and morphine) are the most prescribed. Although the choice of drug is

important, the way the drug is used and monitored is crucial.[131]

For all sedative agents that have been studied in neonates, the 2 major conclusions were invariably the delayed elimination compared with that of adults and children and the large pharmacokinetic interindividual variability. Most sedative agents, if not all, are lipophilic compounds degraded by extensive hepatic metabolism. Many of the enzymatic reactions responsible for the metabolism of these agents are immature at birth, explaining their low CL in neonates, especially premature neonates.

The rapid maturational changes in the enzymatic systems occurring in the neonatal period may account for the large interindividual variability, and probably also for intraindividual variability in the case of prolonged or repeated administrations. Maturation may have taken place *in utero* if the mother was exposed to metabolic inducers.

Because the pharmacokinetics of drugs were generally studied in critically ill neonates with multisystem illness, a myriad of other factors may have additionally influenced the CL or the distribution of these agents, such as hepatic blood flow, dehydration, plasma protein levels, and nutritional state. For some agents, such as morphine or midazolam, a relationship between the CL and postnatal age or gestational age could be evidenced. However, the interindividual variability was large even within homogeneous cohorts of neonates, making *a priori* dosage adjustments of limited clinical relevance. The dose will, in many cases, need to be titrated individually according to the clinical response. Provided therapeutic intervals have been defined, therapeutic drug monitoring of concentrations might be useful in adjusting the dosage in cases of prolonged administration; it may also serve to detect accumulation of the parent drug or a metabolite of potential toxicity.

Another difficulty for the proper use of sedative agents in neonates is the lack of pharmacokinetic-pharmacodynamic evaluation. For opioids, it was long believed that neonates were more sensitive than adults to their respiratory depressant effects. This conclusion was derived from comparisons of the dose-effect relationship.[87] However, the apparent higher sensitivity to the drug effects may indeed be the consequence of higher systemic exposure due to delayed elimination. Reports suggest that higher concentrations of morphine,[81] fentanyl[95] and sufentanil[113] may be required for adequate sedation or analgesia in neonates compared with historical data in adults. The pharmacological effects of opioids and benzodiazepines are the result of receptor stimulation and it is likely that these receptors are not completely mature at birth.[22] Therefore, there is a need to specifically study the concentration-effect relationship of sedative agents in neonates.

None of the available pharmacological agents demonstrates an ideal pharmacokinetic profile for the sedation of neonates. The agents with rapid elimination in adults, such as midazolam and fentanyl, have a considerably prolonged mean terminal $t_{1/2}$ in neonates, thereby allowing less therapeutic control. Whereas delayed elimination results in slower achievement of steady-state, loading bolus doses to attain effective concentrations more rapidly are, for some agents, limited by the occurrence of adverse effects, particularly hypotension. In the case of repeated or prolonged continuous administration, the accumulation of the parent compound or its metabolites may expose the neonates to potentially serious toxicity, as is the case for meperidine, chloral hydrate, and possibly morphine.

Most importantly, all agents exhibit a wide interindividual variability in their disposition, with, in many cases, >10-fold ranges for CL. Therefore, initial dosage regimens derived from mean pharmacokinetic parameters may reveal inappropriate for many, individual patients. For all these reasons, the use of sedative agents in neonates should be reserved to environments where rescussitation facilities are available.

Among the agents reviewed, lorazepam, chloral hydrate, fentanyl and meperidine appear to be relatively safe in the neonate when administered as single doses for short term sedation or analgesia. However, bolus intravenous administration should

be approached with care, especially in patients with unstable haemodynamics.

For prolonged sedation in neonates requiring mechanical ventilation, midazolam and fentanyl are the 2 agents for which most experience has been acquired in NICUs. However, the usefulness of fentanyl appears limited by the development of rapid tolerance to its effects. Lorazepam, alfentanil and sufentanil might be good candidates for sedation or analgesia in the NICU, but further evaluation is required and the relevance of their respective adverse effects needs to be clarified. Finally, the respective place of purely sedative agents and major analgesics remains to be determined. Minor analgesics should not be forgotten. Combinations of sedative agents and analgesics may be explored, such as continuous sedation with a benzodiazepine associated with intermittent administration of analgesics for invasive procedures. However, care must be taken with therapeutic associations as the agents may potentiate the other's effects, particularly haemodynamic adverse effects.

Although sedation has been widely used in the NICU, specific pharmacological knowledge of the individual sedatives is lacking, including therapeutic concentrations, optimal dosages and potential adverse effects. In addition, pain and stress remain difficult to evaluate in the neonate. Complex scoring methods are necessary to compare the different sedative agents. However, since major inter- and intraindividual differences in pharmacokinetics are observed in neonates, simple behaviour scores are mandatory and their use on a routine basis is recommended to control the effectiveness of sedation and adjust individual dosage requirements.

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