REVIEW ARTICLE

From Benchmark to Bedside, Use of Opioids in Neonates and Infants Undergoing Major Surgical Interventions: Essence for a Sufficient Nociceptive Blockade

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While for a long time it has been perceived that neonates and young children do not perceive pain as the adult, this notion had to be corrected on the basis of neurophysiological data and the ontogenisis of the nociceptive system. Also, it has been demonstrated conclusively that neonates and the young infant perceive pain at a much lower nociceptive input which is largely due to a still immature inhibitory descending neuronal pathway. Minor inflictions are threfore perceived as a strong painful input, resulting in a greater size of the receptive field, long lasting pain sensations at high intensity, all which may have an impact on a lowering of the pain threshold, a change of behavioral patterns and a lesser performance at school at later life.

Pain as being induced during surgery makes administration of potent opioids mandatory. One, however, has to take into consideration that because of the immature development of the opioid subreceptor system, before reaching a max. analgsic level, respiratory depression and muscular rigidity become apparent. In addition, because of the immaturity of liver enzymes, the age-related rapid change in the volume of distribution and the elimination half-life, the duration action of an opioid cannot be predicted. It is therefore is advisable to titrate the dose to effect and not on a mg/kg-basis.

keywords: Neonate; descending inhibitory noceptive system; ontogenisis opioid-subreceptors; tolerance development; type of opioid

Due to several misconceptions and misinformation, the neonate as well as the young infant in comparison to the adult for a long time have been exposed to unnecessary nociceptive input during any kind of surgical intervention [1]. Some of the major misconceptions are as follows:

1. The neonate has lesser nociceptors in his skin.

This claim however could not be confirmed by neurophysiological studies.

2. The fibers for nociception in the neonate have no myelin sheath, and thus are of no significance for the transmission of pain.

This claim by means of neurofunctional data is not correct, in as much as the A_{β}-fibers in comparison to the A_{δ}-fibers even in the adult, are characterized by a thin myelin sheath while the important pain conducting C-fibers do have not myelin sheath at all.

3. The whole CNS and especially the cortex is not fully developed in the neonate; therefore any kind of perception of pain cannot take place.

By neurofunctional means all painful afferents are being switched at subcortical centers, where hormonal and neurovegetative defense mechanism are being initiated. Cortical areas are not necessary for such a reaction.

4. Any pain-propagated endogenous release of endorphin is sufficiently high enough for pain control.

For one, the endorphinergic system in the neonate is not sufficiently developed and second the endorphinergic system is only being activated by painful stimuli. This release however, is not sufficiently high enough to block all incoming intense painful afferents.

5. The neonate will not remember the incidence of painful afferents at all.

This claim can also be applied to the adult, as the reaction to a painful stimulus will not need to be programmed.

6. It is adequate to administer a volatile agent to the neonate to render the patient unresponsive to surgery, as such anesthetics are sufficiently potent to block any kind of incoming pain stimulus.

Numerous studies, however, have demonstrated that in spite of an unconscious mind, nociceptive afferents still reach subcortical areas resulting in the release of stress hormones and an unnecessary stimulation of the cardiovascular system.

In addition, volatile anesthetics have been shown to result in a marked downside effect on the later development of brain function as studies have clearly demonstrated a reduced ability in concentration and a 60% higher risk of behavioral disorder being suggestive for ADHS in later life of kids having undergone repetitive exposures to a volatile anesthetic below 3-4 years of age [2-4]. Among the negative effects of general anesthesia being used for a surgical procedure in early childhood, also there was an associated long-term diminution of language abilities and cognition, as well as a regional volumetric alterations in brain structure [5]. All this data leads us to the necessity to use a combined type of anesthesia with potent opioids, and avoid any kind of a volatile agent in the neonate when planning a major surgical intervention.

In addition to these recently acquired experimental data, it is superstitious to think that neonates and infants feel no or

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only minor pain. While neonates and infants cannot express their individual pain sensations only vaguely, the objective nociceptive component still can be quantified as a nervous impulse and a humoral reaction. This is can be seen quite clearly in the neonate who withdraws the affected limb or screams to a nociceptive input [5]. This is underlined by the fully functional development of afferent nervous fibers and organs at the 22th week of gestation, necessary to perceive pain [6]. And although myelination of nervous fibers and maturation of the cerebral cortex in the neonate is yet not fully completed, much of the incomplete myelination will only result in a delayed speed of the afferent nociceptive input. This however, is fully compensated by the shorter distances the afferent pain stimulus has to travel to the cortex (Figure 1) (Table 1).

The nociceptive component in the neonate can be visualized by looking at the humeral changes. An insufficient or no nociceptive blockade can readily be envisaged by well defined cardio-respiratory changes, specifically in an increase in the pulmonary artery pressure and resistance, as well as an increase in specific hormonal and metabolic changes [8]. What neonates do perceive at first sight is pain, resulting in an increased release of stress hormones such as ACTH, epinephrine, norepinephrine corticosteroids aldosterone, and glucagon. ACTH stimulates synthesis and release of glucocorticosteroids such as cortisol and cortisone from the adrenals. In addition, catecholamines, glucocorticosteroids induce a diminished release of insulin, with a reduced glycogenesis and glycolysis during and after operation resulting in a reduced uptake of glucose by the cell [9]. Therefore insufficient intraoperative blockade and shielding from stressful afferents in the neonate and especially the preterm infant induce a state of hyperglycemia and hyperlactemia going in hand with an increase in the metabolism of proteins.

Due to this increase in substrate mobilization of glucose from glycogen (glyogenolysis), proteins and an increase in lipolysis with an ensuing hyperglycemia, hyperlactemia, and a rise in nitrogen release as well as an increase in free fatty acids in the blood, the body ends up in a high hyperglcemic, hypermetabolic state. This will result a loss of tissue, a weakening of the immune system and a state of hypercoabilty. Insufficiently anesthetized neonates will demonstrate this catabolic state up to 3 days following an operation [8]. Such hormonal and metabolic reactions in conjunction with the increase in the pulmonary artery pressure to a surge of incoming unblocked nociceptive afferents [10-11] become especially apparent in the early years of life, having long term effects on later neuronal development (Figure 1). This can be seen in the clinical course of neonates who have been anesthetized with either fentanyl or sufentanil, demonstrating a highly significant reduction in postoperative complications and a reduced need for assisted ventilation [10-11].

Table 1- Increase in neuronal parameters at postnatal development of human neurons from the middle frontal sulcus. Adapted from [7].

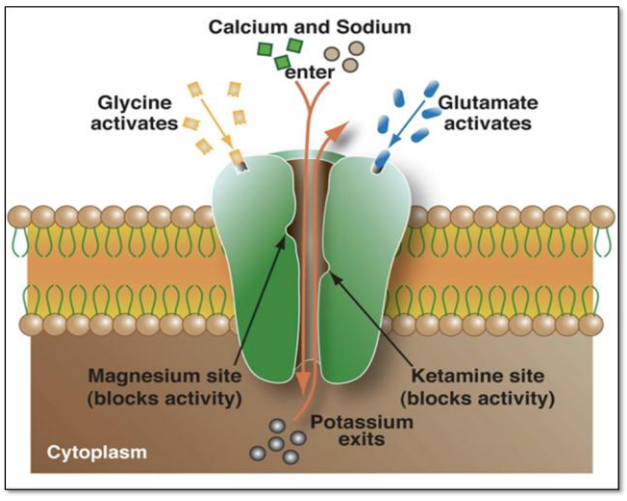
Dendrites	Neonate	6 month of age	24 month of age	Adult
Number of branches (n)	3,1	15,6	16,7	40,8
Total length (µm)	203	2367	3259	6836

Figure 1- Ontogenesis of fusiform neuronal cells of the CNS of man. The first cell at the very left represents the junctions of a two-year-old infant; the last neuronal cell to the very right represents the die syncytial branching of neuronal cells in an adult. Adapted from [7].

Increased formation of excitatory NMDA-receptors in the neonate responsible for later hyperactive nociceptive state

Although the notion that any increased barrage of nociceptive afferents would result in a change of CNS development in the neonate was already suggested approximately 50 years ago, it has only recently been demonstrated in preclinical studies in newborn animals, that an increased or a reduced input of stimuli to the brain results in permanent changes of hormonal and immunological reactions to later stress in life [12]. Hand in hand with such changes there is a reduction in the expression of neurotransmitters, their associated receptors, combined with cellular changes [13]. Because of such findings it was postulated, that the connection between perinatal sensory sensations, trauma, and later behavioral patterns in adult life is being mediated via the N-methyl-D-aspartate- (NMDA) receptor. Such assumption is corroborated by data demonstrating that any kind of excessive stimulation of pain fibers is accompanied by the release of excitatory neurotransmitters such as glutamate or glycine, which bind to the metabotropic and NMDA-receptor sites (Figure 2). This is followed by an increased inflow of Ca^{++}-ions, which eventually induce a change in the secondary messenger system with an induced expression of genes within the cell, followed by a „wind-up“ and a central sensitization to any kind of later nociceptive input [14-16].

Figure 2- The N-methyl-D-aspartate (NMDA) receptor with its binding sites for glycine and glutamate resulting in an over activation of the neuron. Note, that aside from Mg^{++}ions, ketamine, being an unspecific NMDA-antagonist, are able to reduce over activity and „wind-up“ of nociceptive afferents.

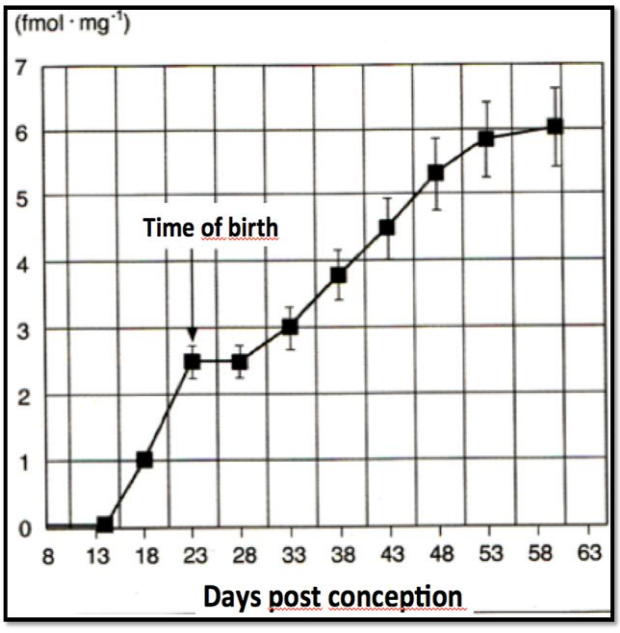


Effects of central sensitization and "wind-up", are specifically up regulated and detectable over a prolonged period of time in a neuronal system undergoing development, such as in the neonate or the infant [17,20-23]. Characterized by an up regulated activity of the NMDA-system, it results in an increased excitability of sensory neurons and a higher incidence of pain perception [24]. Any increase of NMDA-receptors however leads to intracellular changes [17-18,25-26], and a state of hyperalgesia to any kind of sensory input, which now becomes permanent. Such an increase in NMDA-receptors specifically is critical in the postnatal phase where most of the development in brain function takes place, and which is characterized by the rapid increase in neuronal cellular structures [27]. And while the increase in the formation of NMDA-binding sites takes place in the dorsal column as well as in the supraspinal cortex [25,28]. any increase in NMDA-activation is followed by an intracellular Ca^{++}-inflow [23], which eventually leads to an increase in sensitivity of neuronal structures involved in the mediation of painful afferents [18,29]. Specific neonatal cortical cells, after NMDA-activation even show to develop into a higher excitatory state (Figure 2), they demonstrate a shift in their molecular reaction following a Ca^{++}-induced signal, initiating a survival or even a preprogrammed death signal for neuronal cells [30].

Ontogenesis of opioid receptor systems in the neonate

In order to avoid manifestation of such intracellular changes, any kind of sufficient analgesia and a blockade of all incoming nociceptive afferents are mandatory in the neonate or the infant undergoing any kind of surgical intervention. And while sufficient intraoperative analgesia is only possible by means of opioids the question immediately arises if the newborn already has sufficient set of specific opioid receptor sites in order to take full advantage of powerful analgesics? At birth not all opioid receptor sites have fully developed and differentiated. Their number increases exponentially and animal studies have shown that there is a 16-fold increase when compared to birth (Figure 3).

Figure 3- Stereospecific binding of radioactive ^{3}H-naloxone in rat cerebral tissue homogenates (fmol/mg wet weight) at different times after conception (mean ±SD). Adapted from [31].



However, there is a marked difference in regional distribution of receptor density, which has an implication for the use of opioids in the neonate. This is clearly outlined in table 2 where the pons-medullary region, in contrast to the more rostral parts of the cerebral cortex, shows the highest receptor density. This signals that pons and medulla region at birth are already sufficiently equipped with opioid receptors, being close to the adult age (Table 2).

As a consequence, opioids when being applied to the newborn, first and utmost of all will bind to those receptor sites existent in the medullary region, with the consequence of inducing opioid related effect originating from the pons/medulla area.

Table 2- Regional increase of receptor density of opioid binding sites in the CNS of newborn and adult rats (fmol/mg wet weight). Adapted from [31].

Region of CNS	Neonate	Adult	Increase (%)
Parietal cortex	1,0	7.12	612
Hippocampus	1,3	10.73	725
Striatum	7,4	22.40	202
Thalamus	3,7	23.30	530
Hypothalamus	5,4	20.70	283
Pons-Medulla region	3,9	10.50	169

In contrast, the hippocampus and the cortex during postnatal development demonstrate an increase of opioid receptor sites by 725% and 612% respectively, which is in total contrast to the pons/medullary region having only a 16fold increase was found. Such differences in the increase of opioid receptors suggests a close connection to neuroanatomical, neurophysiological and neurochemical data [32], which outline the early end differentiation within the caudal parts of the CNS in contrast to further rostral located neuronal structures. Such preclinical data however also clarifies why clinically opioids, when given to the newborn first and utmost induce respiratory depression and bradycardia, effects which have their site of origin in respiratory- and cardiovascular regulating centers within the pons/medulla region. On the other hand such results also outline the necessity of using potent opioids with a high affinity to the specific receptor especially in the neonate, who has a not fully developed receptor system. By using of fentanyl, alfentanil or even sufentanil, one is able to attain a sufficient deep level of analgesia. This is because the affinity of those opioids to their binding sites differs markedly in regard to other agents, as only opioids with a high affinity (i.e. fentanyl, alfentanil or even sufentanil) correlate with an analgesic potency. And since potency correlates closely with their affinity [33], lesser binding sites are necessary to block all incoming nociceptive stimuli as they are induced by the surgeon [34-35]. And since highly potent opioids need a much lesser amount of binding sites to induce analgesia, while opioids with lesser affinity (i.e. pethidine, morphine, hydromorphone) would need more receptors for a sufficient analgesic level, the anesthesiologist has to make the right choice for optimal care. This need for potent opioids in case of less receptor availability has been demonstrated conclusively for sufentanil being able to induce an analgesic ED50 at only 2% of available receptor occupancy [36].

Difference in the ontogenesis of opioid receptor subsides

The clinical observation that opioids when used in the newborn first and utmost all induce respiratory depression, which thereafter is followed by analgesia. This effect can be explained by animal research data which may give some plausible explanation of this particular effect [37]. Appling morphine as a prototype opioid to two days old rats induced a marked depression in respiratory rate by 75%, a dose which at the same time was not able to elicit a sufficient analgesic level as measured by the tail withdrawal reflex (Table 3). Adult rats on the contrary being subjected to the same dose of morphine, experienced total analgesia however, demonstrating only a 33% depression in respiratory rate. Such data underlined the phenomenon being observed repetitively in the OR that opioids in the neonate first induce respiratory depression, which is more pronounced and prolonged than in the adult [38].

A possible explanation for such a diverse reaction to an opioid in the neonate very likely is the difference in maturity of the opioid receptor subsites, namely mu, delta and kappa. And by looking on data derived from opioids binding- and displacement studies it could be demonstrated, that morphine in low concentrations is able to displace ^{3}H-naloxone (as a specific ligand for the mu-opioid receptor site) as well as ^{3}H-D-Ala-D-Leu-Enkephalin (DADL) being a specific ligand for the delta-opioid receptor, using similar concentration in rats at young age (Figure 3). Thus morphine in the first days of life displaces the specific ligand at the different receptor sites with similar affinity. This is a strong index that final differentiation into the receptor subtypes like mu and delta will take place later in life. With advanced age, however, a steady differentiation of opioid receptors is obvious; and since morphine has a very low affinity for the delta site higher concentrations of this agent is necessary in order to displace the specific radioactive enkephalin ligand ^{3}H-DADL. In contrast to the delta ligand, morphine from the start demonstrates superior binding qualities (a high affinity) to the opioid mu-receptor, which ultimately does not change its affinity during later times of development.

Therefore an increase in age results is a steady differentiation of opioid receptors into their subsites. Thus morphine being highly selective for the mu-receptor reflects similar displacement concentrations in the very young and in the adult rat, while the same agent will demonstrate inferior affinity to the delta-site, which with higher age, results in an increase in concentrations necessary to displace the endogenous ligand enkephalin, which selectively binds to the opioid delta-receptor. Why is such a differentiation of opioid subreceptor sites of clinical importance? It demonstrates conclusively that already at birth opioid mu-receptor are in existence with no further increase in the later stages of life. This is in contrast to the opioid delta-receptor, which only in a later period of development reaches its final stage of differentiation. This is clinically important, and as pointed out by Pasternak and coworker [40], only due to this intimate interaction of the mu- and the delta-site, opioids are able to induce a sufficient deep level of analgesia (Figure 5), an assumption which later was corroborated also by others [41-42].

Only after such final differentiation of the opioid delta-receptor and its interaction with the mu-binding site, coupling induces an allosteric change of the conformation of the mu-receptor site, which eventually results in a sufficient opioid-mediated analgesia [43]. At the same time such data clarifies why in contrast to the adult patient much higher concentration of an opioid are necessary in order to induce a sufficient level of analgesia in the neonate. In regard to body weight much higher dosages of the opioid would have to be given to achieve the desired analgesia, which is headed by a marked respiratory depression.

The relevance of delta-opioid receptors in mediating the analgesic effect of any mu-type opioids is further underlined by experimental data using different highly specific delta peptide ligands [44]. In this regard subanalgesic doses of the delta-peptide D-Ala^{2}-D-Leu-Enkephalin were able to increase morphine–induced analgesia while another peptide, D-Ala^{2}-Met-Enkephalinamide reduced the analgesic effect [44].

Table 3- Respiratory rate (breaths/min) and level of analgesia (tail withdrawal reflex) following 5 mg•kg^{-1} of morphine in 2 and 14 days old rats (mean ±SD). Modified from [37].

Age (days)	Respiratory rate before opioid	Respiratory rate after opioid	Decrease (%) in respiratory rate	Analgesic level (%)
2	140 ±9	37 ±4	74	0
14	135 ±8	91 ±7	33	100

Figure 4- Morphine concentrations (nmol•l^{-1}), necessary to displace 50% of a radioactive tracer from its specific binding site in cortical tissue of rats. Adapted from [39].

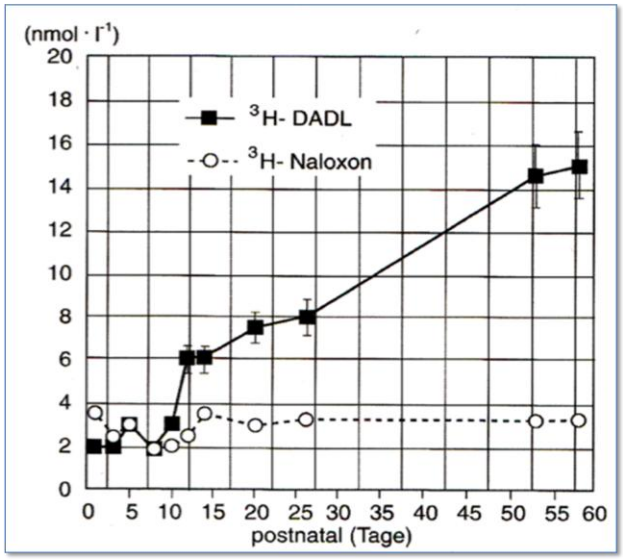
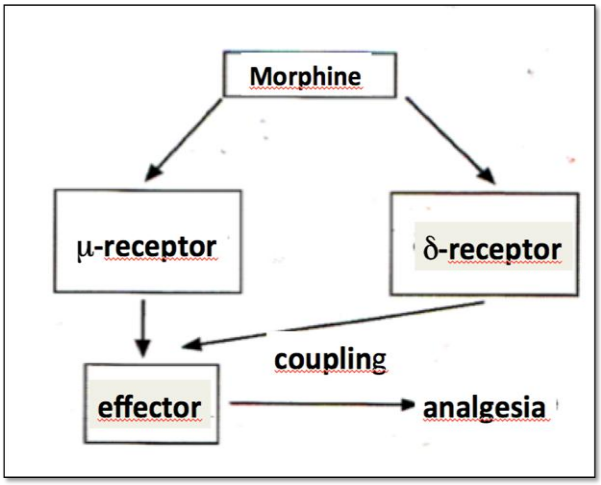


Figure 5- Significance of coupling between the opioid mu- and delta-receptor, necessary for a sufficient deep level of analgesia. Modified after [43].



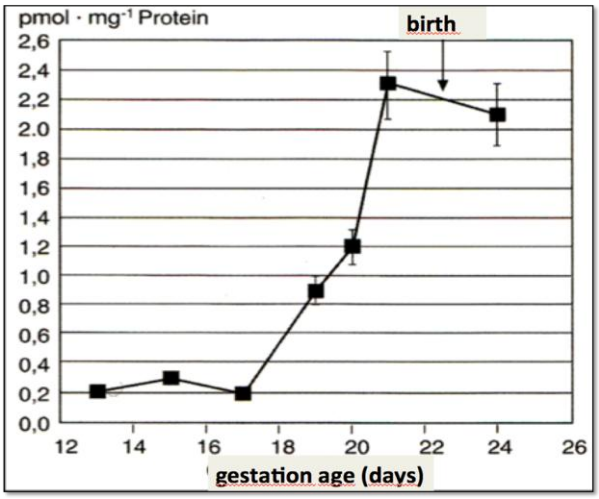
In summary, due to the immature metabolic rate of the liver, a higher penetration rate of opioids through the still undifferentiated blood-brain barrier [45] as well as a still undifferentiated opioid subreceptor population [46], pronounced respiratory depression and a relative resistance to induce analgesia has to be expected in the neonate or the preterm. In such patients, inducing a deep level of analgesia, however, is possible by using higher dosages than usually necessary.

Such not fully developed opioid receptor sites also result in some implications in obstetrics where the relative weak opioid agent pethidine (meperidine) is being used repetitively for obtunding pain during labor. In spite the relative low analgesic potency of pethidine this opioid, after having crossed the placental barrier does result in respiratory depression in the newborn at a time period immediately following birth. In contrast to the pure opioid agonist pethidine, other derivatives from the group of mixed agonist/antagonist such as nalbuphine are preferred as they induce a lesser degree of respiratory depression, because their analgesic potential is being mediated by the kappa-subgroup of opioid receptors [47]. Although this group of opioid analgesic in the adult is characterized by a respiratory ceiling effect [48-49], it still can markedly depress respiration in the neonate (Table 4). The causative factor for such a kappa-receptor induced respiratory depression is the typical kappa-mediated sedation, which stems from those 65% of kappa-receptors already being functionally existent at birth [50]. In order to circumvene such problems of respiratory depression in the newborn, an agent of the group of partial agonist such as meptazinol [51], presents a solution as it induces practically no respiratory depressive effects in the neonate [52-53].

Table 4- Endexspiratory CO_2- (%) und arterial pO_2- (mmHg) in the neonate of mothers whom for control of labor pain had received either intramuscular nalbuphine or pethidine. Adapted from [54].

Minutes post partum	Nalbuphine 10 mg i.m.	Pethidine 100 mg i.m.	Respiratory parameters
1	4,63	6,08	endexsp. CO2
5	4,59	5,56	endexsp. CO2
6	35,8	50,8	paO2

Figure 6- Increase in sigma-(^{3}H-phencyclidine) binding sites in rat cerebral homogenates depending on age (mean ±SEM). Adapted from [55].



Long-term effects of repetitive painful stimuli in the neonate

Nociception in the newborn

Although all the data being derived from animal studies

related to the procession of painful afferents in the newborn cannot be directly transferred to the human, they do however demonstrate certain parallels and give explanations for the majority of features as they are observed in the clinic. That being said, it has to be noticed that the 22th week after conception, the nociceptive system is already fully developed [56] and even the projecting nerve layers which ascend from the thalamus directly rise to the sensory cortex, are fully functional [57]. Contrary, the neuronal development within the spinal cord has not been fully completed [58]. First of all, motor neurons in the anterior horn of the spinal cord develop; this is followed by synaptic interneuron connections. Only thereafter, neurons of the lamina I and II of the spinal cord, as well as connections which direct nociceptive afferents are being shaped [59]. Within the first postnatal week finally, synapses between the afferent neurons and the interneuron network arise, being responsible for either a potentiation or a reduction in transmission to the next higher pain propagating pathways [56]. Therefore it is of no surprise that due to the immaturity of synaptic connections between the primary afferent pathways and dorsal root neurons, in newborn animals there is a vast fluctuation in latency of response to a given stimulus [58,60].

Similar to the animal, the mechanism of inhibition of painful afferent stimuli to the interneuron network has not fully matured in the preterm and neonate, as inhibitory interneurons will only mature after birth [61]. Thus, low-threshold stimuli from Aß- und Aδ-fibers are immediately directed to superficial nociceptive neurons in the dorsal horn [57], and when being administered repetitively, result in a sensibilization within the nociceptive system [60]. Since the descending, inhibitory pathways develop much later than the nociceptive system, protective or defense mechanism against nociceptive afferents is insufficient or actually do not exist at this stage of development. Therefore it can be concluded that the neonate perceives any kind of otherwise harmless touch as a painful stimulus, resulting in a reflex withdrawal of a limb, while at the same time painful stimuli in a small area of the skin, due to an overlapping as well as a greater size of the receptive fields, will be perceived as a large size painful infliction [62]. Thus, any kind of trauma or pain will last much longer as all nociceptive afferents will be transmitted without delay and with increased intensity to higher pain-perceiving centers within the central nervous system [63]. As a results of such a barrage of incoming painful afferents, expression of so called "immediate early genes" induce the formation and the synthesis of additional pain transmitting receptor sites as well as neurotransmitters within the cell, resulting in a sensibilization of all incoming nociceptive stimuli in future times [64]. This is followed by a reduction in pain threshold and an increase in sensitivity to all later sensory afferents. Such ontogenetic developments, which take part shortly after birth, have nothing to do with the supraspinal pain processing pathways. This is because studies in the neonate could conclusively demonstrate that facial grimacing and gestures after a painful stimulus will only be evident in the 21th-31st post partal week [1,65]. This is in contrast to vegetative reactions, which become obvious after the 22nd gestational week.

Supraspinal centers, necessary to evoke the affective component of pain such as thalamus, gyrus cingulate, somatosensory cortex, and their thalamocortical connections are already existent at birth. However, similar to the pain inhibiting neurons in the spinal cord, they are not fully developed at time of delivery resulting in a lack of the sensory impression „pain“. Because the sensory neurons occupy larger receptive fields than in the adult [66], all sensory input from non-nociceptive as well as nociceptive afferents will be perceived for a longer time period and with a higher intensity. As a result of this there is cueing of a nociceptive stimulus with a resulting decline of the threshold for pain in later life. Such a sensitization in the human preterm and the neonate eventually results in hyperalgesia and allodynia [56,58]. Contrary to the adult, low-threshold Aß-fibers are responsible for such a development and repetitive sensations of touch in the newborn will induce an increased pattern of defense and/or a manifestation with increased agitations [67].

Due to such findings it is conceivable, not only to demand a sufficient blockade of all pain, but at the same time inherit the concept of preemptive analgesia, where a sufficient blockade of all painful stimuli is achieved before their initiation. This concept especially holds true in the preterm and the neonate undergoing any kind of surgical intervention, where maturation of the antinociceptive system has not terminated, and because of the plasticity of neuronal structures, insufficient analgesia lays the cornerstone for a later increase in painful behavior. This is the major reason why especially in the field of neonatology, sufficient analgesia is mandatory, where repetitive painful manipulations such as heel prick, tracheal suction, change of dressing, etc. should be reduced to the mere minimum. Such data are underlined by studies in term neonates undergoing circumcision and who up to 7 days after the procedure demonstrated an increased irritability, an attention deficit, a reduced motor performance as well as a change in sleeping and sucking behavior. In addition after such painful experience, newborns demonstrated an increase in pain reaction up to the 6th months of the intervention [68].

While long-term effect of repetitive painful stimuli on behavioral pattern is largely unknown, comparison studies in preterm do demonstrate an increase in cardiovascular reactivity and a simultaneous reduction in their behavioral pattern. Following additional analysis of surgical interventions in the neonate it became obvious that that the number of invasive procedures closely correlated with a change in behavioral patterns [60].

Repetitive painful stimuli seem to modify the neurobiological mechanism at different levels of the nociceptive system. Thus, repetitive painful insults in the newborn induced a lowering the pain threshold as well as an increase in local neuronal innervation when compared to a term neonates [69]. Also, repetitive painful afferences in the neonate result in a sensibilization of peripheral neuronal structures [6], which later in the 4th year of life are manifested by a higher rate of somatization of ailments of unknown origin [70]. Similarly, other studies have demonstrated, that early experience of pain in early infancy shape later pain experience and behavior, which is reflected in different gastrointestinal disorders in later adult life. Also, children being repetitively exposed to pain demonstrate a significant trend in social isolation, a lesser grade of performance in school tasks [71] and marked emotional reaction to stressful situations [72]. Such data pinpoint the relevance of early exposure to nociceptive stimuli, which have an effect on the later development of behavioral patterns. These preprogrammed patterns as they are induced by the sum of nociceptors in their early life, do have a marked effect on their later childhood and adult age, effecting changes in their hormonal reactions and decreased learning capabilities [70]. Such data being derived from clinical studies at the same time can be underlined by controlled animal studies in the rat, which showed a reduction in exploration of its environment, an early onset of cognitive deficits going in hand with a loss of neuronal cells

within the hippocampus [73-74]. In addition, following painful stimuli a weakening of the immunological-endocrinological response to stress, a preference for alcohol, and a reduction in c-fos expression in the sensory cortex was demonstrated [75]. Such long-term changes, which effect the plasticity of the hypothalamus, the frontal cortex, and the hippocampus in the newborn, seem to go in hand with an increased expression of glucocorticoids, which by themselves result in a reduced binding at the receptor system affecting the regulation of the autonomic nervous system, the hypothalamic-pituitary-adrenal axis (HPA axis) and the later reaction to stress [29,67]. Although extrapolation of such changes in the development of changes within the nociceptive systems in rats cannot be extended to human as one by one, they however do point to the significance of such changes in the neonate under the prerequisite of an increased nociceptive input and its relevance for a behavior pattern in later adult life [30]. Such behavioral changes which only surface in later life become plausible if one takes into consideration the changes dendrites undergo in branching and their total length from the neonate to childhood and later the adult (Figure 1). Since the syncytial branching within the nervous system is largely completed by the neuronal input after birth, it ultimately is a predestined factor for later behavior in life (Table 1).

Practical considerations using opioids in the neonate

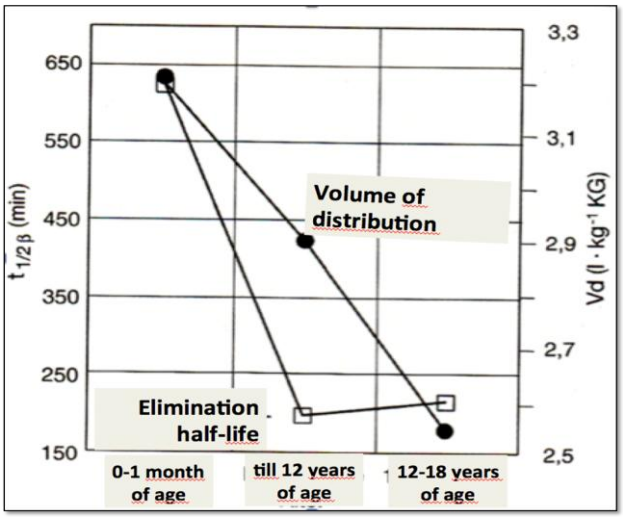
Although the class of opioids can be considered as agents which do suppress nociception most effectively, their pharmacokinetic profile in the neonate and the child in comparison to the adult are characterized by specific differences:

1. They present a higher volume of distribution and a longer elimination half-life in the newborn (Figure 7). Especially, when opioids are given repetitively, the prolonged elimination half-life results in an accumulation with a prolonged duration of action and a postoperative respiratory overhang [76]. This is because the relative increase in the volume of distribution results in a prolongation of the elimination half-life, because the amount of opioids accumulating in the larger volume of distribution needs a much longer period to be excreted and because of the continuous refill into the circulating blood volume, it results in prolonged receptor occupancy. As a net result there is a longer duration of action.

2. Opioids meet an immature enzyme activity in the liver. Since the liver is the organ, which guarantees the removal and the inactivation of the agent, any reduced metabolization rate corresponds with a prolongation in clearance (Figure 7). Within the first months after birth however, there is a marked increase in the metabolization rate, which is reflected in a reduced need for opioids, necessary for instance for sufficient sedation in the ICU.

3. Opioids readily pass the blood-brain barrier (BBB). This barrier is not fully developed in the first days of life, being easily permeable for any kind of opioid [18]. This point however, is of no significance, because the BBB although being a physiologic barrier for all centrally acting agents and especially those being used in anesthesia, the group of potent opioids like fentanyl or sufentanil due to their lipohilicity easily overcome this barrier. Therefore potent opioids, when being used in newborn at term who already have an intact and mature, fully functional barrier function, practically do not encounter any limitation [78]. This, however, gains some importance in the preterm, where the BBB demonstrates a significant immaturity. This has been demonstrated in animal data, which clearly document only a loose connection of cells and capillaries within the BBB, being readily permeable for all kinds of agents. Only in the later life span this previously loose cell association is consolidated [79]. Therefore the preterm with its higher barrier permeability demonstrates a larger amount of opioids molecules passing through the BBB, resulting in higher receptor occupancy and which elicit a more pronounced clinical effect.

Figure 7- Differences in elimination half-life ($t_{1/2\beta}$) and the volume of distribution (V_d) of sufentanil at different age groups.
Adapted from [77].



4. Opioids, on the other hand, encounter an undifferentiated opioid subreceptor system. At birth only 40% of all opioid receptor subsites have been developed [80]. This lesser number at birth results in the need of higher amounts of the agent in order to attain a sufficient level of analgesia (Table 5).

Table 5- Use of different opioids in the neonate for establishing a sufficient level of analgesia in the ICU. In comparison to the adult higher dosages of fentanyl are necessary which, however, are well tolerated. Modified from [81].

Type of opioid	Single dose application	Continuous infusion rate
Morphine	0,05-0,1 mg•kg-1 (every 4. to 8. hour)	0,005-0,015 mg•kg-1•h-1
Tramadol	0,5-2,0 mg•kg-1	Not recommended (nausea, vomiting)
Pethidine	0,25-0,5 mg•kg-1 (every 8- to 12-hour)	Not recommened-fomation of norpethidine!
Fentanyl	10 µg•kg-1 (every 4. to 6. hour)	2--3 µg•kg-1•h-1
Alfentanil	20 µg•kg-1	5 µg•kg-1•h-1

On the other hand, it is known that morphine and some its derivatives such as codeine and didydrocodeine are prodrugs and to the main part, elicit their analgesic potency after being converted metabolically into their active counterpart. However, due to the still not sufficiently developed enzyme activity within the liver of the neonate the transformation into the active metabolite is very much unpredictable. This has been clearly demonstrated in a study in neonates which

demonstrated a large interindividual variability in the formation of the active metabolite following the administration of either codeine or dihydrocodeine [82].

Morphine on the one hand is being converted mainly into their metabolites morphine-3- and morphine-6-glucoronide [83], by a family of isoenzymes, the uridine-diphosphate-gluroronosyltrans-ferase [65]. Morphine-6-glucoronide, however, can be considered a potent analgesic with a marked respiratory depressive effect [84,82], while morphine-3-glucoronide, the main metabolite of morphine, conveys an opioid antagonistic effect [85]. What is important in regard to the mediation of analgesic potency is the relation of morphine-3- to morphine-6-glucoronide [86], so it is becoming clear that depending on the maturity of the liver enzymes in the neonate, a large interindividual variation in analgesic efficacy was observed. And even in the newborn there is a close inverse correlation of birth weight and the ratio of morphine-6- to morphine-3-glucoronide which increases with the increase of the birth weight and developmental age [87].

The observed higher incidence of respiratory depression in newborn animal pups as described by Kupferbereg and Way in 1960 may be attributed to the insufficient function of the blood-brain-barrier (BBB) resulting in higher effective concentrations of the agent within the CNS [86]. Clinical studies by Purcell-Jones [38], however, did not corroborate this assumption, because in only 13% of the investigated newborns respiratory depression or apnea became obvious. In addition, following the administration of morphine after open heart surgery, in a wide variety of age groups similar CO2-response curves were derived [88]. From such data it can be concluded that the administration of equianalgesic dosages and not of doses which are calculated in reference to body weight, the risk of developing a respiratory depression in the neonate is not greater as in the toddler; therefore individual dose titration to affect can be considered a guideline for the use of opioids in the neonate.

Codeine, a methyl morphine is metabolized in the liver by 10% to morphine, which eventually mediates the analgesic effect [89]. The residual amount of codeine is methylated to the inactive norcodeine, which either is excreted through the urine in its conjugated or its unconverted form. Little is known about the kinetics and the dynamics of codeine in neurosurgical interventions and anesthesia of children [1,27]. However, unrelated to the dose, a number of cases of acute respiratory depression have been reported following intravenous or intramuscular administration [38,90]. This largely stems from the fact that due to the immaturity of metabolic pathways within the liver, a prolonged half-life of codeine as well as its metabolite morphine has to be anticipated (Table 6).This is one of the major reasons why the effects of analgesia as well as respiratory depression cannot be predicted.

In an increasing appearance, the synthetic opioids fentanyl, alfentanil and also the potent opioid sufentanil are being used for major surgery in the neonate. These opioids do have the advantage that they induce a highly potent analgesic effect, while at the same time their metabolites do not exert any activity. All three piperidine derivatives are metabolized by cytochrome P450 [22]. Due to their narrow margin of safety in regard to respiratory depression, they can only be used for the intraoperative period. An additional area of use is the intensive care unit (ICU), where especially fentanyl (2-3 µg/kg/h) but also sufentanil are being used as the sole agents for sedation and adaptation to the respirator. However due to the rapid development of tolerance, an adaptation of higher dosages often may become necessary [91]. The cause for such development of tolerance is a desensibilization of the opioid receptor to attached opioid [92], as well as an increase in the metabolic rate of the liver [76]. A major advantage of those highly potent opioids is the abandonment of any kind of muscle relaxant, although after fentanyl but more so after alfentanil a high incidence of muscle rigidity has been reported [93-94]. Therefore alfentanil, being a lesser potent opioid, is not considered a beneficial sedative of the neonate within an ICU setting, especially when in comparison to fentanyl, it does not present any advantages. The one agent that has been totally eliminated from the ICU is the mother compound of all piperideines, i.e. pethidine (Demerol™) because its metabolite nor-pethidine especially in the newborn induces excitatory effects which are prone to develop into epileptic seizures with agitation and dysphonia [19, 24]. The latter can be attributed to the physiologic immaturity of the kidneys, which especially is existent in the preterm but also in the neonate.

Postoperative Analgesia in the Newborn: Practical considerations

In general, if one does not expect intense pain such as following smaller size surgical interventions, and where there is no need for postoperative respiratory support, opioids other than fentanyl or sufentanil with a much lesser affinity to the specific receptor site are advocated. For one there is tramadol used in dosages ranging from 0.075 - 0.1 mg/kg i.v. or at 0.25 mg/kg/h when given by continuous infusion and given for up to 5 days following the surgical intervention. In small sized surgery such as herniotomy or circumcision paracetamol (acetaminophen) or metamizole in dosages from 20-30 mg/kg can be given rectally or orally. Codeine being a medium potent opioid is another option that can be taken into consideration especially following inguinal herniotomy and where dosages from 1-2 mg/kg orally are considered sufficient to block postoperative pain.

Also, a representative of the group of mixed agonists/antagonists such as nalbuphine (0.15-02 mg/kg) is an option, since this opioid is characterized by a ceiling effect in regard to respiratory depression [48]. Another opioid with a retarded formulation such as dihydrocodeine (DHC) may be a suitable alternative [95], since this compound inherits a very low respiratory depressive component. One opioid, however, should be eliminated by all means, and this is pethidine (meperidine); it is because this opioid results in the formation of the metabolite norpethidine, which especially in the neonates may induce epileptic seizures [96].

Once however, intense pain is being experienced, morphine in dosages of 0.01-0.02 mg/kg is advocated by some clinicians starting with a concentration of 0.02-0.05 mg/kg i.v. and adjusted to need at 5 minutes intervals. However, due to its high incidence of PONV, piritramide an agent with a longer duration of action of 5-6 hours, no formation of pharmacologically active metabolites, no cardiovascular depressive effects, no spasm of the smooth musculature and a lower incidence of PONV represents a better alternative. This opioid is being given in dosages of 0.05-0.1 mg/kg i.v. for medium to severe postoperative pain [97]. For practical reasons, a dose in reference to the body weight has been demonstrated to be a good thumb of rule (Table 7).

Table 6- Comparative pharmacokinetic data of opioids in the neonate and infants at different ages. Adapted from [81].

Age	Elimination half-time (1/2ß in min)	Clearance (Cl in ml•kg-1•min-1)	Distribution volume (Vd in L•kg-1)
Neonate 0 - 8 days	635	4,2	2,7
Neonate 20 - 28 days	217	17,3	3,4
0 -1 Month	737	6,7	4,15
1 Month - 2 Years	214	18,1	3,09
2 - 12 Years	140	16,9	2,73
12 - 16 Years	209	13,1	2,75

Table 7- Doses of piritramide for postoperative pain therapy in children using a continuous administration mode with a perfusion pump (preparation of a basic solution using 4 ampoules, 8ml, 60mg; thus 1 ml piritramide equals 1.2 mg).

Body weight (kg)	day of operation 0.038 mg/h	Pump level	1st postop day	Pump level	2.-3. postop day	Pump level
30	1.14	1	0.72	0.6	0.57	0.5
40	1.52	1.3	0.96	0.8	0.76	0.6
50	1.90	1.6	1.2	1.0	0.95	0.8
50	2.26	1.9	1.44	1.2	1.33	1.0
70	2.66	2.2	1.68	1.4	1.33	1.2
80	3.04	2.5	2.02	1.6	1.52	1.3
90	3.52	2.9	2.16	1.8	1.71	1.4

When opioids are used for postoperative pain relief the most simple and most effective way of administration is the intravenous route. The subcutaneous as well as the intramuscular route should be rejected, due to the individual differences in reabsorption and because of time-related and quantitatively non-predictable plasma concentrations. Therefore the intravenous administration offers a number of advantages:

1. The effect will kick in fast
2. A maximal effect is achieved in a short period of time
3. After administration the plasma concentration progressively declines

If however, after major operation intensive postoperative care or respiratory support is needed, opioid derivatives of the µ-type (fentanyl, sufentanil, piritramide) should be favored (Table 5). In such cases sufficient analgesia often presents the indication for respiratory support, where any kind of muscle relaxant is not necessary and where sedatives such as benzodiazepines are only given intermittently in few cases, since any kind of continuous administration will result in a prolonged elimination half-life with several days of overhang, which even makes it more difficult to wean the patient from the respirator.After morphine as well as after piritramide, surveillance by means of pulse oximetry is mandatory, because in neonates and young children with a reduced metabolic rate of the liver below the age of six months, a potential silent respiratory depression has to be anticipated [98].

In order to achieve a sufficient level of analgesia in the neonate, specific vital parameters and behavioral patterns can be used as guidance for the appropriate dose. According to a study of Büttner and coworker 13 of these clinically routinely used monitoring parameters reached a high level of specificity and sensitivity [99]. Aside from facial gestures, frowning, body posture (arms, legs, fingers, toes and body torso), motor unrest or crying, other vital parameters such as respiratory and heart rate, blood pressure and oxygen saturation, all mirror a general distress of the little patient. Because most of the vital parameters are also affected by cardiac, pulmonary, central nervous or hematological changes, they only serve as a clinical useful tool when used in combination with behavioral patterns. Combined in the "premature infant pain profile"[24] or the KUS-scale (Kindliche Unbehagens- und Schmerzskala) [100] they present useful tools to determine if the neonate is receiving sufficient amounts of an analgesic for postoperative pain relief. If only 4 of these 5 items is judged as positive than some kind of pain therapy should be initiated, especially when higher counts are shown.

Since it is difficult to identify pain in the preverbal age, different scores have been developed with which the intensity of postoperative pain and distress in the neonate can sufficiently be determined. For instance the objective pain scaling consists of four items, which are determined at regular intervals giving a good idea of the present level of pain [101]. Each item is judged as 1, 2 or 3 with a possible max. count of eleven:

Item 1. **The circulatory system:** The blood pressure is 10%, 20% or even 30% above the preoperative value.

Item 2. **Verbal articulation:** the newborn is quiet; it is crying but can be calmed; it is crying but cannot be calmed

Item 3. **State of mind:** the neonate is sleeping; it is restless; it is in panic.

Item 4. **Body language:** the neonate slumbers and seems to have no pain; it has some pain and points to the affected side; it has intense pain and pulls back the affected body part when being touched.

Conclusion for the use of opioids in the neonate: The bottom message

Use of opioids in order to induce a sufficient intraoperative analgesic level in extended operations is also possible in the neonate. However, due to the immature metabolization rate of the liver and in addition to the incomplete formation of opioid subreceptor sites in the neonate [46], early respiratory depression has to be anticipated. The intraoperative dose of

the opioid is adjusted to effect, and is not based on a mg/kg calculation. Depending on the maturation status of receptors such doses may exceed those usually given to children or the adult. In addition, one should also focus on the development of muscular rigidity after administration of a potent opioid. The rigidity develops prior to the maximum analgesic effect resulting in the inability to ventilate and resulting in an impaired gas exchange. This phenomenon however can be reversed rapidly by a low dose of a muscle relaxant. For larger size operations such as ductal ligature, diaphragmatic hernia, omphalozele, necrotizing enterocolitis, or craniotomy high potent opioids with a higher receptor specificity such as those from the piperidine family (fentanyl, sufentanil) should be used. The eventual postoperative respiratory depression is of irrelevance, since automatically postoperative surveillance or even respiratory support in the neonatal intensive care is planned.

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