Newborn anaesthesia: pharmacological considerations

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Inhalation anaesthetics

For the inhalation anaesthetics there are age-related differences in uptake and distribution, in anaesthetic requirements as reflected by differences in MAC, in the effects on the four determinants of cardiac output (preload, afterload, heart rate and contractility), and in the sensitivity of protective cardiovascular reflexes (e.g., baroreceptor reflex). These differences limit the margin of safety of the potent agents in infants.

Alveolar uptake of inhalation anaesthetics and hence whole-body uptake is more rapid in infants than in adults.[1] Lung washout is more rapid in infants than in adults because of the larger ratio between alveolar minute ventilation and lung volume (FRC) (3.5:1 in the infant vs. 1.3:1 in the adult). Increased brain size ($ml \cdot kg^{-1}$), limited muscle mass, limited fat content, and proportional differences in the distribution of cardiac output contribute to differences in uptake. Age-related differences in tissue partition coefficients also influence the equilibrium tissue concentration and the rate of change in the tissue concentration. Early in an anaesthetic induction (at equal inspired concentrations) the infant will have higher tissue concentrations in brain, heart, and muscle than will the adult.

MAC, an estimate of anaesthetic requirement, is, in part, age related.[2] Neonates require 25 per cent less anaesthetic than infants; infants have a greater anesthetic requirement than older patients. MAC is dramatically lower in newly born animals than in their 12-hour-old counterparts. The response of the newborn to painful stimuli is attenuated even in the awake state. Most likely this is related to the immaturity of the central nervous system; elevated concentrations of progesterone and β-endorphin and β-lipoproteins may also play a role in the decrease in MAC in neonates.

Several investigators have studied the age-related cardiovascular effects of the potent inhalation anaesthetics at known multiples of MAC. At end-tidal concentrations of halothane bracketing MAC, Lerman *et al.*[2] noted no difference in the incidence of hypotension or bradycardia in neonates and in infants one to six months of age. Likewise, we[3] have noted no age-related differences in the determinants of cardiac output in developing piglets 1–20 days during either halothane or isoflurane anaesthesia. Halothane produced hypotension by a reduction in contractility and heart rate; in much older animals halothane also decreases peripheral vascular resistance. In piglets although blood pressure was equally depressed with isoflurane and halothane, cardiac output was better preserved during isoflurane anaesthesia.

In awake man or animals decreases in blood pressure are compensated for by an increase in heart rate, myocardial contractility, and peripheral vascular resistance. Potent inhalation anaesthetics depress baroreceptor reactivity in a concentration dependent manner. In infants or newborn animals baroreceptor reflexes are more depressed (at equipotent anaesthetic concentrations) than in older animals.[4,5] This further limits the safety of potent anaesthetics in infants. Moreover, Cook *et al.*[6] have demonstrated that the cardiovascular index for halothane is smaller in younger animals than in older animals. The cardiovascular index is a reflection of the therapeutic index (i.e., the ratio between the anaesthetic concentration at cardiovascular collapse to that of anaesthesia).

Thus, potent inhalation anaesthetics must be used with caution in newborns and infants. Because of

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the reduced margin of safety paediatric anaesthetists frequently favour nitrous-oxide-relaxants anaesthesia (reinforced with small doses of narcotics). For that reason a discussion of the clinical use of narcotics and muscle relaxants is, likewise, appropriate.

Ketamine

On a $\mu g \cdot kg^{-1}$ basis the amount of ketamine, a nonbarbiturate cyclohexamine derivative, required to prevent gross movements is four times greater in infants under six months than in six-year-olds.[7] Acute studies show little metabolism of ketamine by the newborn. Recently, we determined the pharmacokinetics of ketamine in different-aged patients. In infants less than three months of age the volume of distribution was similar to that in older infants but the elimination half-life was prolonged. Hence, clearance was reduced in the younger infants. Reduced metabolism and renal excretion in the young infant are the likely causes. In the "anaesthetic" state associated with ketamine, respiration and blood pressure are usually well maintained. However, use of ketamine in infants, has been associated with respiratory depression and apnoea, generalized extensor spasm with opisthotonus, an increase in intracranial pressure, and acute increases in pulmonary artery pressure.

Fentanyls

The dose of fentanyl needed to guarantee satisfactory anaesthesia for infants is unknown. Age-related differences in the kinetics and sensitivity to fentanyl and changes in kinetics associated with profound pathophysiologic conditions make generalizations difficult.[8–11] However, in the neonate fentanyl clearance seems comparable to that of the older child or adult; fentanyl clearance is markedly reduced in the premature infant. The elimination half-life is prolonged in neonates and in premature infants. These marked variations in kinetics reflect age differences and perhaps differences in anaesthetic, dose, and duration of sampling. We noted that in infants having cardiac surgery fentanyl ($50\ \mu g \cdot kg^{-1}$) was not uniformly effective in blunting cardiovascular responses nor hormonal responses to surgery despite rather uniform fentanyl plasma concentrations. The cardiovascular effects of fentanyl at doses of 30–75 $\mu g \cdot kg^{-1}$ (with pancuronium) are minimal.[12] Modest decreases in mean arterial pressure and systemic vascular resistance index were noted by Hickey *et al.*[13] Other indexes of cardiac function were unchanged. Schieber *et al.*[14] documented that the cardiovascular effects of fentanyl (without relaxant) are concentration-dependent; a similar relationship between decreases in systolic blood pressure and concentration was noted by Koren *et al.*[15] Respiratory depression is likely concentration-related.

Several new analogs of fentanyl are undergoing clinical trials. Sufentanil is about seven times more potent than fentanyl and has minimal cardiovascular effects. Bradycardia is an uncommon feature. Hickey and Hansen[16] studied the cardiovascular effects of sufentanil (5–10 $\mu g \cdot kg^{-1}$)-pancuronium in infants with complex congenital heart disease. Mean arterial blood pressure and heart rate declined mildly. We (unpublished data) have seen more profound bradycardia and hypotension in such infants when sufentanil ($15\ \mu g \cdot kg^{-1}$) was given with metocurine. Blood pressure responses to incision/sternotomy were more attenuated at the higher dose of sufentanil; humoral responses to stimulation were minimal. The pharmacokinetic profile of sufentanil in infants is comparable to that of fentanyl.[17] Alfentanil is equally potent to fentanyl but has a shorter duration of action. Because of its relatively short duration of action alfentanil may be particularly useful in neonatal anaesthesia. Unfortunately, this has not been studied.

Muscle relaxants

Throughout childhood there is physical and biochemical maturation of neuromuscular junction, change in the contractile properties of skeletal muscle, and an increase in the relative amount of muscle as a proportion of body weight. There are also changes in the apparent volume of distribution of relaxants, possible changes in their metabolism, and changes in their redistribution and excretion. These factors influence dose–response relationships of muscle relaxants in infants and children.[18]

Depolarizing muscle relaxants

On a weight basis, infants require more succinylcholine than older children or adults to produce apnoea, depress respiration, or to depress neuromuscular transmission (EMG or twitch). The estimated ED_{95} for succinylcholine in infants is 2.0

$mg \cdot kg^{-1}$. Following an "intubating" dose of succinylcholine infants do not develop a phase II block (as defined by the criteria of Lee). Tachyphylaxis to succinylcholine occurs in infants with a cumulative dose of $4.0\ mg \cdot kg^{-1}$ and phase II block occurs at $6.0\ mg \cdot kg^{-1}$; tachyphylaxis and a phase II block occur at lower cumulative doses in older infants and children. Although the infant has about one-half the plasmacholinesterase concentration of the adult, at equipotent doses of succinylcholine the recovery time is not prolonged in infants.

When succinylcholine was given in equal doses on a surface area basis ($40\ mg \cdot m^{-2}$), there was no difference between infants and adults in the times to recover to 10, 50, 90 per cent neuromuscular transmission; this dose of succinylcholine produced complete neuromuscular blockade in all patients. A linear relationship exists between the log dose on a $mg \cdot m^{-2}$ basis and the maximum intensity of neuromuscular blockade for infants, children, and adults. In addition, there is a similar linear relationship between the logarithm of the dose on a $mg \cdot m^{-2}$ basis and to either 50 or 90 per cent recovery times for infants and children as a combined group. Because of its relatively small molecular size succinylcholine is rapidly distributed throughout the extracellular fluid. The blood volume and extracellular (ECF) volume of the infant are significantly greater than the child's or adult's on a weight basis. Therefore, on a weight basis ($mg \cdot kg^{-1}$) the infant requires about twice as much succinylcholine to produce 50 per cent neuromuscular blockade as do adults. Since ECF and surface area bear a nearly constant relationship throughout life ($6–8\ L \cdot m^{-2}$) it is not surprising that there is a good correlation between succinylcholine dose (in $mg \cdot m^{-2}$) and response throughout life. Redistribution and metabolism of succinylcholine obviously determine the recovery times. Redistribution of succinylcholine from a relatively small muscle mass into a relatively large ECF volume appears to rapidly terminate the neuromuscular blocking effects of succinylcholine.

In the infant and small child profound sustained sinus bradycardia (rates of 50 to 60/minute) is commonly observed; rarely, asystole occurs. Arrhythmias are more common following a second dose of succinylcholine. Nodal rhythm and ventricular ectopic beats are seen in about 80 per cent of children given a single intravenous injection of succinylcholine; such arrhythmias are rarely seen following intramuscular succinylcholine. Atropine (0.1 mg) appears to offer adequate protection against these bradyarrhythmias in all age groups. Recently, we[19] have seen several young infants who developed fulminant pulmonary oedema following intramuscular succinylcholine ($4\ mg \cdot kg^{-1}$). The pulmonary oedema occurred within minutes of the intramuscular injection; the pulmonary oedema responded to continuous positive pressure ventilation (CPAP). We speculate that this may represent a haemodynamic form of pulmonary oedema from an acute elevation of systemic vascular resistance and an acute decrease in pulmonary vascular resistance; in addition, "leaky" capillaries appear to be involved.

Non-depolarizing muscle relaxants

It has been suggested that the newborn is sensitive to d-tubocurarine (dTc), particularly in the first ten days of life. there is no increased sensitivity of hand muscles to dTc in infants as compared to adults. Likewise, there is no difference in the magnitude of neuromuscular blockade from $0.22\ mg \cdot kg^{-1}$ of dTc in infants under four months and those older than four months of age. However, in infants respiratory depression parallels the neuromuscular blockade noted in the hands; in adults neuromuscular blockade of the hand occurs prior to respiratory depression. This important observation suggests that the respiratory muscle of the infant may be more sensitive to dTc than those of the adult, or that the infant has less respiratory reserve than the adult. In actuality both may be true. Recent studies have re-examined this issue. During halothane anaesthesia the mean dose of dTc required to produce 95 per cent twitch depression and the time to recovery from 95 per cent block (5 per cent neurotransmission, T5) to 75 per cent block (25 per cent block (5 per cent neurotransmission, T5) to 75 per cent block (25 per cent neurotransmission, T25) or to 50 per cent block (50 per cent neurotransmission, T50) was the same in infants and children.[20] However, there was a wide range in the ED_{95} for dTc in the newborns ($0.15–0.62\ mg \cdot kg^{-1}$). Thus, some newborns are quite sensitive and some are relatively resistant to dTc.

The ED_{95} for dTc in adults during nitrous oxide-oxygen-narcotic anaesthesia is comparable to that noted in the infants and children during halothane anaesthesia. Since halothane potentiates

dTc neuromuscular blockade these data suggest that infants and children are resistant to dTc on a weight basis. I subsequently estimated the ED_{95} for dTc on a $\mu g \cdot m^{-2}$ basis in infants, children, and adults during halothane anaesthesia. The estimated ED_{95} for dTc in neonates was 4 $\mu g \cdot m^{-2}$; in children and adults it was 7–8 $\mu g \cdot m^{-2}$. Thus, the newborn is indeed sensitive to dTc when allowance is made for differences in the volume of distribution for relaxants and comparisons between age groups are made during comparable types and depth of anaesthesia.

Likewise, the ED_{95} ($mg \cdot kg^{-1}$) for metocurine,[21] pancuronium,[22] and gallamine and the time to recover from T5-T25 were comparable in infants and children. Most likely, infants are likewise sensitive to these relaxants on a $\mu g \cdot m^{-2}$ basis. We have determined the ED_{95} for atracurium, a non-depolarizing relaxant of intermediate duration, in adolescents, children, and infants during halothane anaesthesia using single dose curves. On a weight basis ($\mu g \cdot kg^{-1}$) the ED_{95} of atracurium in infants is comparable to that of adolescents; the ED_{95} of both are less than that of children.[23,24] Goudsouzian, using cumulative dose curves noted no difference in the ED_{95} for atracurium between adolescents and children.[25] On a $\mu g \cdot m^{-2}$ basis the ED_{95} for infants is about half that of adolescents or children. At equipotent doses the recovery times of neuromuscular transmission in infants are comparable to that noted in children; in both groups the recovery times are more rapid than those of adults. We have also noted that "light" isoflurane anaesthesia but not "light" halothane anaesthesia potentiates atracurium (i.e., decreases the ED_{95}) when compared to nitrous oxide-thiopentone-fentanyl. This has been confirmed by continuous infusion studies where the rate of atracurium infusion ($\mu g \cdot kg^{-1} \cdot min^{-1}$) is decreased by isoflurane anaesthesia when compared to the rate during balanced anaesthesia.

Goudsouzian *et al.* determined the ED_{95} for vecuronium, another non-depolarizing relaxant of intermediate duration, in adolescents and children during halothane anaesthesia.[26] Children had a higher ED_{95} than that measured in adolescents. Fisher and Miller noted no statistical difference in the ED_{50} for vecuronium between infants, children, and adults.[27] At equipotent doses of vecuronium the recovery time was prolonged in infants as compared to children or adults; the recovery in children was similar to that of adults. At equipotent doses gallamine, pancuronium, dTc, and metocurine have, obviously, significantly prolonged recovery times compared to atracurium and vecuronium. Renal clearance of these relaxants or their metabolites is probably limited in the first several months of life since GFR is limited. Atracurium which spontaneously decomposes has a shorter recovery time in infants than adults; vecuronium which is metabolized has a longer recovery time in infants than adults.

Keon and Downes (unpublished data) compared changes in heart rate, changes in blood pressure, and differences in intubating conditions in infants (average age 5.6 months) "anaesthetized" with nitrous oxide-oxygen followed either dTc (0.6 $mg \cdot kg^{-1}$) or pancuronium (0.1 $mg \cdot kg^{-1}$). None had received premedication. In both groups there were modest increases in pulse rate; transient episodes of bradycardia occurred in some infants in both groups during intubation. No infant given pancuronium developed significant hypotension or hypertension (greater than ten per cent change from control levels). In contrast, 25 per cent of the infants given dTc experienced decreases in blood pressure greater than ten per cent from control (range 11–26 per cent). We noted minimal effects of atracurium, gallamine, or pancuronium on the heart rate in infants. Unless the heart rate had slowed from halothane neither gallamine nor pancuronium exhibited any vagolytic effects. At equipotent doses ($1 \times ED_{95}$) in older children gallamine increases the heart rate twice that seen from pancuronium. These cardiovascular effects may be desirable in the younger child or infant during halothane. Neither metocurarine, atracurium, or vecuronium have significant cardiovascular effects at $2 \times ED_{95}$.

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