An evaluation of muscle relaxants in cesarean sections

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The author draws from the literature to review the various muscle relaxants used for cesarean sections, with special consideration given to the risk of placental transfer of these drugs.

The passage of drugs across the placenta has been the subject of a number of comprehensive reviews. The best and most prudent approach to the use of muscle relaxants often presents controversial views. The purpose of this article is to investigate and review the various muscle relaxants available to the anesthetist, and to determine which of these are best indicated for cesarean sections.

It has been my observation, that at the Hurley Medical Center in Flint, Michigan, succinylcholine is used and advocated more frequently than any other muscle relaxant. However, from various studies done and available literature on this topic, I intend to explore other relaxants, their possibilities, and their potential use for cesarean sections.

Of primary importance when considering which drugs are to be used in obstetric anesthesia is the risk of placental transfer of these drugs. The essential factors to be considered when administering drugs to the pregnant mother are:

1. The molecular weight of the drug.
2. The fat solubility of the drug.
3. The degree of ionization.
4. The concentration gradient.
5. The binding to maternal proteins.
6. The surface area and thickness of the membrane.

It is generally believed that all drugs used for the relief of apprehension and pain during labor and delivery are capable of passing through the placenta and affecting the infant. With some drugs, this has been proved; with others, it has been inferred. This is particularly important in light of recent work showing that, in animals, the fetus is four to five times as sensitive to depressant drugs as is the adult.

The newborn’s response to drugs is qualitatively and quantitatively different from that of the mother. The newborn shows marked susceptibility to the depressant effect of drugs. This heightened sensitivity is related, in part, to increased permeability of the blood brain barrier, inefficient renal function, absence of microsomal enzymes necessary for drug metabolism, and asphyxia and physical trauma associated with the delivery process.

The concept of the lipoid barrier appears to apply greatly to the factors affecting the diffusion of drugs across the placenta. The rate of transfer across the blood placental barrier is governed chiefly by the lipoid solubility of the nonionized or undissociated drug molecule. Other factors, such as concentration gradient, maternal and fetal flow, and molecular size, are usually of secondary importance.
Those drugs having a molecular weight of less than 350, traverse the placenta rapidly. A molecular weight of 600 to 1000 traverse slowly and greater-than 1000 are impermeable. Therefore, small molecules, such as nitrous oxide and ethylene (despite their lipid insolvibility) could pass through the submicroscopic holes. As a result, all drugs commonly used in obstetric anesthesia and analgesia traverse the placenta rather easily, since most are lipid-soluble, low-molecular weight compounds. Although the muscle relaxants appear to be notable exceptions to this rule, even with these compounds, there is a relative rather than an absolute barrier to their passage. With extremely large doses, they also appear in fetal blood.

Regardless of its physical nature, the rate of passage through the placental membrane of any substance is at least partially dependent upon the concentration gradient. For example, highly ionized drugs of low lipid solubility, such as succinylcholine and tubocurarine, may be found in fetal blood if high concentration gradients are produced by the use of large doses in the mother. The gradient achieved across the placenta is primarily a function of the quantity of the drug administered to the mother. However, other factors, such as distribution throughout the maternal and fetal extracellular space, binding to protein elements in plasma, excretion and metabolism by the mother, infant, and placenta, are also important.

Pathological changes in the placenta associated with systemic maternal diseases, such as preeclampsia and diabetes mellitus, may alter the permeability of the placenta. Furthermore, inborn errors of maternal metabolism (that is, atypical cholinesterase) may permit dangerous levels of drugs to accumulate. Contractions or cord compression may induce alterations in maternal and fetal blood flow through the placenta, thus affecting the transmission to an unknown degree.

This is especially important with the highly fat-soluble, poorly ionized compounds with no demonstrable barrier to their transfer. Their rates of penetration are limited primarily by the volumes of blood perfusing the placenta. Destruction by the placenta may also play an important role with some drugs. Finally, it is conceivable that conditions such as profound maternal asphyxia, hypotension, dehydration, or hemorrhage may weaken or eliminate the selectiveness of the placental lipid barrier.

Muscle relaxation for cesarean sections is seldom a problem, as the abdominal wall has been stretched by the increasing size of the pregnant uterus. Provided coughing and straining are avoided, the intestines are unlikely to obtrude. Myoneural blocking agents are not often required to achieve relaxation, but rather to ensure a tranquil operating field during the very light planes of anesthesia employed. At the same time, the anesthetist should be aware of the possibility of the patient awakening paralyzed during the operative procedure. An adequate amount of nitrous oxide should be given.

The single most important characteristic common to all muscle relaxants is the presence of a quaternary ammonium group in the molecule. As a result, at a normal pH range, these compounds are highly ionized and possess a low degree of lipid solubility. Because of these properties, the placenta forms a relative barrier to the passage of most relaxants. Usual clinical doses have no appreciative effects on the newborn; and with the exception of gallamine, significant quantities of the drugs cannot be detected biochemically in the infant’s blood.

If the concentration gradient across the placenta is extremely high, the relaxants may be found in cord blood and possibly produce clinical effects in the newborn. However, in rabbits, it has been tested that 1000-times the minimal maternal paralyzing dose is necessary to permit succinylcholine to pass the placenta and clinically affect the newborn rabbits.
The majority of muscle relaxants contain two quaternary nitrogen atoms. The exception to this is gallamine, which has three quaternary nitrogen atoms. Gallamine has no effect on the pregnant uterus; however, it readily crosses the placenta in significant amounts.4

There have been comparative clinical studies done and documented using pancuronium and tubocurarine in cesarean sections. Results indicate tubocurarine to be free of adverse effects.

The usual dose for pancuronium is 0.0875 mg/kg and 0.468 mg/kg for tubocurarine. The onset of relaxation with both relaxants is similar, but pancuronium appears to be five times as potent as tubocurarine when judged by response to nerve stimulation. Studies on pancuronium have reported it to produce conditions adequate for intubation in about two minutes and to have a duration of action similar to that of tubocurarine. Blood pressure is found to remain stable or to increase slightly in about one-half of the patients given tubocurarine.

The advantages of pancuronium over tubocurarine are said to be no histamine release and no ganglionic blockade and consequent fall in blood pressure.

Conclusion

In summary, the current concepts on the four most widely used muscle relaxants in anesthesia have been presented. Although much has been learned about the placental transfer of drugs, it is important for the anesthetist to recognize and understand the primary factors to be considered when administering drugs to the pregnant mother. Such factors as the drug’s molecular weight and solubility, the concentration gradient, and thickness of the membrane all play an important role in determining which drugs can safely be administered.

These comparative studies have concluded that there is no clinical evidence of significant placental transfer of pancuronium or tubocurarine. Furthermore, these are safe and efficient agents for incorporation into the standard thiopental, nitrous oxide, relaxant anesthetic technique for cesarean sections.5

Intermittent or continuously infused succinylcholine may be used for the reasonably quick surgeon, tubocurarine or pancuronium may be used for known slow surgeon, and gallamine should be avoided completely for use in cesarean sections.

REFERENCES

AUTHOR

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