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Fetal Neuromuscular Blockade with Vecuronium Bromide: Studies during Intravascular Intrauterine Transfusion in Isoimmunized Pregnancies

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Routine management of severe isoimmunized pregnancies has, since 1985 in our institution, included intrauterine intravascular transfusion.[1] This procedure requires complete immobilization of the fetus, because the umbilical vein has to be cannulated for about 35 min in order to allow sufficient time for blood replacement. Maternal sedation is not sufficient to perform the procedure,[2] and complete maternal general anesthesia increases risk to both mother and fetus. Furthermore, the procedure often has to be repeated two or more times during late pregnancy. For these reasons, fetal paralysis using neuromuscular blocking drugs has been used by several authors.[2–7]

Pancuronium bromide produces long-lasting fetal paralysis, and prolonged fetal monitoring is required until spontaneous fetal movements have resumed.[4–7] Vecuronium bromide seems to be more appropriate because it has a shorter duration of action and few hemodynamic effects even in preterm infants.** A preliminary study using vecuronium bromide in ten patients indicated that its duration of action was sufficient for the procedure, and no changes in fetal heart rate were observed.[8]

This study was carried out to assess the pharmacodynamic action of vecuronium bromide in human fetuses of various ages requiring intrauterine exchange transfusion for Rh isoimmunization.

CASE REPORTS

Seventeen intrauterine intravascular exchange transfusions were performed on 14 fetuses of 22–35 weeks gestational age. Intrauterine exchange transfusion was indicated by increased maternal antibody levels ($> 2\ \mu g \cdot ml^{-1}$) and critical titer level, associated with one or more of the following clinical or ultrasonographic criteria: maternal history of hydropic stillbirth, fetal transfusions, premature delivery with fetal disease, fetal intrauterine deaths, or increased fetal abdominal circumference, hydramnios, placental edema or hydrops at ultrasonographic examination.

Informed consent was obtained from all mothers, and the procedure was approved by the institution. The day before the procedure, mothers were admitted into the hospital, and clinical assessment of maternal and fetal conditions was performed.[9] Fetal heart rate recording for 20 min was obtained in each fetus, together with an ultrasonographic assessment of body measurements,[10] placental localization, and umbilical cord insertion. Hydropic fetuses and those exhibiting poor motor activity were excluded from the study.

All mothers received intramuscular atropine ($0.01\ mg \cdot kg^{-1}$) and midazolam ($0.1\ mg \cdot kg^{-1}$) 30 min before the procedure. All procedures were performed in the operating room under aseptic conditions. After infiltration of the maternal abdominal wall with 2% lidocaine, the umbilical vein was punctured at its placental insertion using the ultrasound-guided double-needle technique (Siemens Sonoline 5-MHz sector scanner).[11] Fetuses in whom the umbilical artery was inadvertently punctured were not considered further for the study, while exchange transfusion might be undertaken using the umbilical artery. Fetal blood group and initial hemoglobin concentration were first determined in each fetus; then, an initial dose of vecuronium bromide ($1\ mg \cdot ml^{-1}$), $0.1\ mg \cdot kg^{-1}$ estimated fetal weight, was injected into the umbilical vein just before blood exchange transfusion was started. The amount of each blood exchange represented 5% of estimated fetal blood volume.[1] The level of anemia (milligrams per deciliter) was calculated as the difference between normal hemoglobin concentration for the age and the initial measured hemoglobin value.[12] Cessation of fetal movements was evaluated by direct visualization on the ultrasonographic screen; the time until fetal movement ceases characterizes the onset of neuromuscular block. Duration of paralysis was evaluated by following its persistence, as well as by the time of reappearance of maternal perception of active fetal movements.

The estimated weight of each fetus was within the normal range for gestational age. All fetuses exhibited a low initial hemoglobin concentration, and intravascular exchange transfusion was deemed indicated

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** Hamza J, Macquin I, Wood C, Devictor D, Huault G: Cardiovascular effects of vecuronium versus pancuronium in premies with hyaline membrane disease (abstract). ANESTHESIOLOGY 67:A515, 1987.

TABLE 1. Characteristics of the Population and Pharmacodynamic Results (17 Procedures)

	Mean ± SD	Range
Gestational age (weeks)	29.2 ± 3.8	22–35
Estimated fetal weight (g)	1610 ± 700	500–2500
Initial hemoglobin concentration ($g \cdot dl^{-1}$)	6.8 ± 1.9	2.3–9.6
Final hemoglobin concentration ($g \cdot dl^{-1}$)	14.6 ± 1.6	10.3–16.6
Level of anemia ($g \cdot dl^{-1}$)	6.7 ± 1.9	4.2–11.1
Onset of paralysis (s)	97.6 ± 27.4	45–150
Reappearance of maternal perception of fetal movements (min)	122 ± 39	55–160

in all cases (table 1). Total duration of the procedure was 15–40 min; paralysis persisted during the entire procedure, and no supplemental dose was required. Using linear regression analysis, a positive significant correlation was found between onset of paralysis and gestational age ($P < 0.001$); the younger the fetus, the more rapid was the onset (fig. 1). No correlation was observed between onset of paralysis and initial hemoglobin concentration or level of anemia. Return of maternal perception of active fetal movements (n = 13) began after 55–160 min; no significant correlation with gestational age was found. No maternal or fetal adverse effects were observed, and all fetuses were delivered alive at 35.8 ± 1.7 weeks gestational age (mean ± SD).

DISCUSSION

This is the first report on pharmacodynamics and clinical use of vecuronium bromide in fetuses for intrauterine intravascular exchange transfusion.

Onset of paralysis is important to consider in these particular procedures, because a rapid onset will minimize the risk of needle dislodgement with fetal movements and the necessity of multiple venous punctures. This onset increases with fetal age. Few studies have precisely evaluated the possible changes in onset of paralysis according to the age. Fisher and Miller[13] found after a single dose of vecuronium 70 $\mu g \cdot kg^{-1}$ a shorter onset time in infants (7–45 weeks old) than in older children and adults. In a more extensive study, Schippers found a positive correlation between onset time and age from birth to 15 yr of age.†† These age-related changes in onset of paralysis could be related to variations in the volume of distribution of the drug[14,15] and/or to changes in neuromuscular junction sensitivity.[16,17] In addition, the onset time may be influenced by the particular disposition of fetal circulation and the increased cardiac output of alloimmunized fetuses.[18] However, the proportion of umbilical venous return bypassing the liver and directly entering the inferior vena cava across the ductus venous ranges from 8 to 92% in human fetuses and is not related to fetal weight,[19] whereas hepatic function itself is impaired in alloimmunized fetuses. The respective roles of possible first-pass effect and metabolism in age-related changes in onset time remain unknown.

Reappearance of maternal perception of fetal movements occurred in less than 3 h after injection. This time is similar to that reported by Daffos *et al.*[20] in a fetus of 33 weeks gestational age, who received 0.1 $mg \cdot kg^{-1}$ vecuronium for fetal magnetic resonance imaging for investigation of a posterior fossa abnormality. This time, however, is shorter than that reported with pancuronium bromide for intrauterine blood exchange in alloimmunized pregnancies; reappearance of fetal movements was reported to be as long as 210 min after 0.1 $mg \cdot kg^{-1}$ pancuronium bromide[6] and 5–8 h after 0.3 $mg \cdot kg^{-1}$,[7] thus suppressing clinical assessment of fetal well-being for a longer period of time. Indeed, after intravascular administration of pancuronium bromide, there are significant alterations in fetal heart rate (reduction in heart rate variability and abolishment of accelerations) that could otherwise be interpreted as indicative of fetal compromise.[6]

Reappearance of fetal movements was not correlated with gestational age. This contrasts with clinical studies showing age-related changes in duration of action of vecuronium bromide, and especially a prolonged duration of action in infants compared to older children and adults.[13,21] The lack of an age-related difference in the total duration of paralysis in our study may result from partial drug removal during blood exchange. In addition, no precise long-term assessment of paralysis was done because the ultrasonographic study was limited to the time necessary to perform the exchange transfusion. However, there is a close correlation between maternal perception

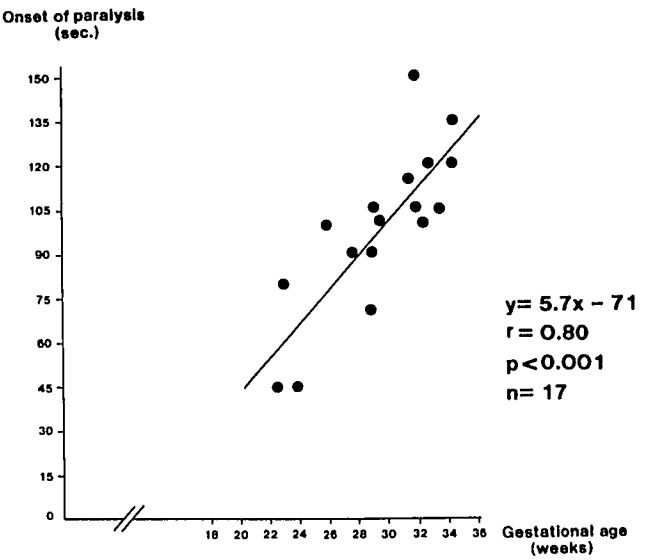

FIG. 1. Relationship between onset of paralysis and gestational age (weeks).

†† Schippers HC: Pharmacodynamics of vecuronium bromide in anaesthetized neonates, infants and children (medical thesis). Groningen, The Netherlands: Organon Technika, Inc., 1988, p 88.

of fetal movements and ultrasonographic assessment of these movements, and the number of maternally perceived fetal movements is constant from 24 weeks gestation to term.[22] The role of changes in fetal acid–base status during intravascular transfusion on vecuronium kinetics is also unknown.[23]

This study suggests that 0.1 $mg \cdot kg^{-1}$ single-dose vecuronium provides adequate conditions of fetal paralysis for intrauterine intravascular exchange transfusion, which requires only 30–40 min of fetal immobility in our clinical practice. Clinical assessment of fetal well-being by maternal perception and counting of active fetal movements[22] is feasible shortly after intravascular administration of vecuronium; this is of great value in these seriously ill fetuses undergoing invasive procedures.

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