Clinical Pharmacokinetics of Neuromuscular Relaxants in Pregnancy

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Contents

Summary ................................................. 483
1. Nondepolarising Neuromuscular Relaxants ................................................. 484
   1.1 Pharmacokinetics and Pharmacodynamics ................................................. 484
   1.2 Transplacental Passage ................................................................. 488
   1.3 Neonatal Effects ................................................................. 489
2. Succinylcholine ................................................. 491
   2.1 Pharmacokinetics and Pharmacodynamics ................................................. 491
   2.2 Transplacental Passage and Neonatal Effects ................................................. 492
3. Drug Interactions ................................................. 493
4. Conclusion ................................................. 493

Summary

Despite an increased in bodyweight, plasma volume by 45% and blood volume by 35% that might influence the volume of distribution of polar drugs, the apparent volume of distribution at steady state (Vss), volume of distribution (Vd) and the apparent volume of the central compartment (Vc) of atracurium, vecuronium and pancuronium are unchanged during pregnancy. With an elimination that is independent of renal, hepatic and enzymatic functions, the clearance of atracurium is also unchanged. This is corroborated by an unchanged clinical duration of atracurium during pregnancy. The clearance of pancuronium is increased by 27% during caesarean section. This may be explained by the increased glomerular filtration rate reported in pregnant women. The clinical duration of vecuronium in term and postpartum women is twice that reported in nonpregnant women. On the other hand, an increase in the clearance clearance of vecuronium during cesarean sections has been reported.

The umbilical/maternal vein concentration ratio (UV/MV) of nondepolarising neuromuscular relaxants varies from 7 to 26% and clinical doses of these drugs may induce partial residual curarisation in neonates. Fetal concentrations of nondepolarising neuromuscular relaxants are proportional to the maternal dose injected as demonstrated for pancuronium and vecuronium. Increasing UV/MV with longer drug injection to delivery intervals have been demonstrated for drugs with a high molecular weight, such as atracurium, but not for those with a low molecular weight, such as vecuronium, while conflicting results have been reported for pancuronium.
Despite decreased plasma pseudocholinesterases, the clinical duration of succinylcholine 1 mg/kg is unchanged in pregnant women, and only is slightly increased in postpartum women. On the other hand, larger doses of succinylcholine have induced prolonged apnoea and phase II block.

The use of a pretreatment dose of a nondepolarising neuromuscular relaxant to decrease fasciculations and subsequent postoperative muscle pain is not only unnecessary in pregnant women but may be hazardous, since it may produce unexpected significant curarisation with respiratory distress. At clinical doses, transplacental passage of succinylcholine is insufficient to produce curarisation of neonates except in those born to mothers with abnormal plasma pseudocholinesterases.

Magnesium sulfate, used in the treatment of pre-eclampsia, will enhance the blocking effects of nondepolarising neuromuscular relaxants but will have no effects on the characteristics of paralysis of succinylcholine. Histamine type 2 antagonists used to decrease the risk of aspiration during induction of anaesthesia do not influence the blocking properties of neuromuscular relaxants, while metoclopramide prolongs the block of succinylcholine.

Neuromuscular blocking agents are used to provide muscle relaxation for surgery during and after pregnancy as well as for cesarean section under general anaesthesia. Pregnancy is associated with marked physiological changes which may have an important influence on the pharmacokinetics and pharmacodynamics of these drugs. The influence of these modifications on the duration of neuromuscular relaxants varies depending on the agent used. Moreover, drugs administered to the mother have the potential to cross the placental barrier and reach the fetus. Consequently, extensive knowledge of the disposition pharmacokinetics, e.g. excretion and biotransformation, of neuromuscular blocking agents during pregnancy, as well as their effects on the neonate, are of prime importance for all physicians using neuromuscular blocking agents in pregnant women.

1. Nondepolarising Neuromuscular Relaxants

1.1 Pharmacokinetics and Pharmacodynamics

Physiological changes occurring during pregnancy which may modify drug pharmacokinetics and dynamics include:[1,2]

- increase in bodyweight and body fat
- expansion of body water, plasma volume by 45% and blood volume by 35%
- increase in cardiac output by 40%
- increase in glomerular filtration rate by 50 to 60% with no change in hepatic blood flow
- total protein levels and albumin-to-globulin ratio are decreased which may result in higher free blood concentrations of some substances.[3]

Increases in bodyweight, body water, plasma and blood volume should increase the volume of distribution (Vd) of hydrophilic or polar substances, and this has been demonstrated for some antibiotics, along with digoxin and lithium.[4] Although neuromuscular blocking agents are mostly distributed in the extracellular fluid, the apparent Vd at steady state (Vss), Vd and apparent volume of the central compartment (Vc) of atracurium[5] and pancuronium[6] are unchanged during pregnancy (table I). Vss values for vecuronium[7] reported during pregnancy are also similar to those reported in studies in healthy adults.[8]

While reviewing pharmacokinetic data in pregnancy, Reynolds and Knott[2] suggested that substances with a high rate of lipid solubility have a prolonged half-life during pregnancy. This is the case for caffeine, diazepam and thiopental.[2] On the other hand, polar drugs, particularly with direct renal elimination, will have a reduced half-life dur-