
Neostigmine, Atropine, and Glycopyrrolate: Does Neostigmine Cross the Placenta?

Richard B. Clark, M.D.,* Mark A. Brown, M.D.,† Danny L. Lattin, Ph.D.‡

DRUGS administered to the mother can cross the placenta and affect the fetus. Following is a description of such an event.

Case Report

The patient was a 22-yr-old pregnant woman (gravida 1, para 0). The gestational age of the fetus was estimated to be 31 weeks. The patient was diagnosed as suffering from paranoid schizophrenia and was receiving haloperidol and lorazepam. She required open reduc-

tion of a fractured elbow. General endotracheal anesthesia was used (the patient would not cooperate for regional anesthesia); the primary anesthetics were isoflurane and nitrous oxide. Thiopental was used for induction of anesthesia, succinylcholine to facilitate intubation, and vecuronium to prevent patient movement during the operation. The fetal heart rate and uterine contractions were monitored externally during the procedure. Left uterine displacement was performed. The patient was not in labor. Surgery proceeded satisfactorily, and the muscle relaxant effect was reversed at the termination of the anesthetic with neostigmine (5 mg) and glycopyrrolate (1 mg) intravenously. Preoperatively, the fetal heart rate was 153 beats/min but varied between 115 and 150 beats/min intraoperatively. Fetal heart rate immediately decreased to the range of 90-110 beats/min after administration of neostigmine and glycopyrrolate. Left uterine displacement was increased, and the fetal heart rate gradually returned to 120 beats/min. No atropine was given. The rate eventually reached 130 beats/min after 1 h. Four days postoperatively, however, the surgical repair was deemed unsatisfactory, and the patient underwent surgery. As before, general anesthesia was used along with vecuronium. Fetal heart rate and uterine contractions were monitored, and left uterine displacement was performed. At the end of the anesthetic, the muscle relaxant was antagonized with neostigmine (5 mg) and atropine (0.4 mg intravenously. There was no change in fetal heart rate. The patient awoke satisfactorily from the anesthetic without complication and delivered a healthy infant at term.

Discussion

It is well known that atropine will cross the placenta and that maternal administration results in an increase in fetal heart rate.¹ They have been interested in finding that a maximal contraction ratio of equilibria maternal administration of a quaternary ammonium indicating partial tran-

Most of the studies on anticholinesterases interfering from myasthenia, presented five case reports of labor and the postpartum myasthenia.² One other report, and another recent report, presented two case reports, diagnosis, course, patients with a diagnosis of either neostigmine or presented three case reports; two of them.³ Eden and Galen present eight patients undergoing in their clinical case studies were not done.⁴ None of the reports relate to in the neonates.⁵ Myasthenia infant was not reported.⁶ With regard to related, “The onset of the infant may be delayed by atropine acquisition by the mother given to the mother. Atropine is a lipophilic drug and may be expected to cross the barrier. It dissociates to form an equilibration, the free base atropine (loss of about 98.6% charged) and 1. The lipophilic-soluble fraction coefficient of 1. The of biologic membranes and glycopyrrolate are pounds that are ionized; they would be expected to transfer across the biologic membrane and then move across the placenta to a limit.¹

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References


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in fetal heart rate. The placental transfer of quaternary ammonium anticholinesterases, such as neostigmine, has been incompletely described. Proakis and Harris found that a maximal fetal/maternal serum concentration ratio at equilibrium for atropine of 1.0 occurs after maternal administration. They studied glycopyrrolate, a quaternary ammonium salt, and found a ratio of 0.4 indicating partial transfer. They did not study neostigmine.

Most of the studies involving quaternary ammonium anticholinesterases in pregnancy involve patients suffering from myasthenia gravis. McNall and Jafarina presented five case reports and discussed management of labor and the postpartum period in patients with myasthenia. One of the patients received edrophonium, and another received neostigmine. Chambers et al. presented two case reports and reviewed the etiology, diagnosis, course, and treatment of pregnant patients with myasthenia gravis and who were receiving either neostigmine or pyridostigmine. Plauché presented three case reports and described current developments; two of these patients received pyridostigmine. Eden and Gall presented eight case reports. All eight patients underwent thymectomy, with improvement in their clinical condition. Fetal anticholinesterase levels were not determined in any of these reports. None of the reports mentioned fetal or neonatal heart rates. Neonatal myasthenia developed in several of the infants. With regard to neonatal myasthenia, Plauché related, "The onset of characteristic weakness in the infant may be delayed as long as 48 hours by coincident acquisition by the baby of anticholinesterase drugs given to the mother."

Atropine is a lipid-soluble tertiary amine and would be expected to cross the placenta in the form of the free base. It dissociates in aqueous media and biologic fluids to form an equilibrium mixture of the salt and the free base atropine. At pH 7.4, this equilibrium consists of about 98.6% of the salt (protonated, positively charged) form and 1.4% of the free base (uncharged). The lipid-soluble free base has an octanol/water partition coefficient of 1.83, indicating it will readily cross biologic membranes by passive diffusion. Neostigmine and glycopyrrolate are quaternary ammonium compounds that are ionized completely at physiologic pH; they would be expected to undergo limited placental transfer. Both exhibit low lipid solubility but will cross biologic membranes to some extent, despite their positively charged nitrogen. Indeed, quaternary ammonium muscle relaxants and pyridostigmine pass the placenta to a limited extent.

We believe significant placental transfer of neostigmine occurred in our case. The fetal heart rate slowed when glycopyrrolate was used, inasmuch as neostigmine passed the placenta to a greater extent than glycopyrrolate and there was insufficient placental transfer of the anticholinergic drug to prevent the fetal muscarinic effect of neostigmine. During the second operation, atropine, rather than glycopyrrolate, was used to prevent the fetal muscarinic effects of neostigmine. Shinder and Levinson recommended, "Neostigmine, when used to reverse the effects of muscle relaxants, should be administered slowly and be preceded by adequate doses of atropine." They give no explanation as to why atropine would be preferable.

Glycopyrrolate and neostigmine, quaternary ammonium compounds, bearing a positively charged ionic nitrogen, pass the placenta with greater difficulty than nonionic compounds (e.g., atropine). We contend that the placental passage of neostigmine, which produces a pronounced pharmacologic effect, exceeds that of glycopyrrolate. To our knowledge, no one has determined the fetal/maternal serum concentration ratio of neostigmine; this discussion must remain speculative.

It appears that neostigmine has a higher partition coefficient than glycopyrrolate, although the octanol/water coefficient of neither drug has been determined. The clinical evidence, however, indicates clearly that the placental transfer of neostigmine is more extensive than that of glycopyrrolate.

In support of our finding, James reported in 1981 a case involving a woman of 7 months' gestation undergoing skin grafting for burns in which a glycopyrrolate-neostigmine mixture was used to reverse the effects of a nondepolarizing muscle relaxant. The fetal heart rate decreased abruptly from 140 to 60 beats/min, where it remained for 5 min until intravenous atropine was given.

We suggest that neostigmine and atropine, rather than neostigmine and glycopyrrolate, be used to reverse nondepolarizing muscle relaxants in pregnant patients to ameliorate the pronounced bradycardia induced by the neostigmine.

References


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### Renal Subcapsular Hematoma after Lumbar Plexus Block

**Sumihsa Aida, M.D.,* Hitoshi Takahashi, M.D.,† Koki Shimojo, M.D.‡**

THE lumbar plexus, which branches to the genito-ileal, lateral femoral cutaneous, obturator, femoral, and lumbosacral nerves, is located between the quadratus lumborum and psaos major muscles (a part of the plexus is contained within the psaos major muscle). Lumbar plexus block (LPB) has been described for use in patients with lumbosacral and lower extremity pain.1-3 Psoas compartment block is one form of LPB.1

Because the lumbar plexus is adjacent to the retroperitoneum and peritoneal cavity, introduction of a block needle into adjacent structures, such as the kidney, may result in complications. In the method described by Chayen et al.,1 an approach for LPB at the level of L4 vertebral body was presented. However, some practitioners introduce the block needle at the L3 level,4 at which there is a probability that the needle tip will be introduced into the kidney (fig. 1). We present two cases of renal subcapsular hematoma subsequent to LPB at the L3 level.

### Case Reports

#### Case 1

A 71-year-old, 47-kg, 155-cm woman received right LPB for treatment of low back pain associated with a herniated lumbar disc L3-L4 and L4-L5. The block was performed four times for 4 weeks at the level of L3 using a loss-of-resistance method,8 with a 15 cm 20-G needle and 10 ml 1% lidocaine. However, the low back pain became more intense 1 day after the last LPB, and she had difficulty walking for several days. Pain was localized to the right low back, but sciatica did not increase. The pain was treated with 750 mg oral mefenamic acid. Microscopic hematuria and slight elevation of the C-reactive protein concentration were noted, although other laboratory parameters were within normal limits (table 1). She was instructed to rest quietly at home. The pain did not decrease 10 days after the block, and ultrasoundography (fig. 2) and computed tomography (CT, fig. 3) examinations revealed an abnormal mass on the surface of the kidney. The renal capsule was intact for publication October 26, 1995.

Address correspondence to Dr. Aida: Department of Anesthesiology, Niigata University School of Medicine, 3-2-7, Chuo, Niigata, Japan.

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