REPORTS OF SCIENTIFIC MEETINGS

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The Anesthesiology Triad in Obstetrics

On September 11–12, 1981 a symposium, The Anesthesiology Triad in Obstetrics: Mother, Fetus, Physician, was held at Tarpon Springs, Florida under the sponsorship of the Pennwalt Corporation. The symposium had several purposes among which were to review the basic pharmacology and toxicology of local anesthetics as well as to present the most current data on possible neurotoxicity, cardiotoxicity, and systemic toxicity of local anesthetics. Nine faculty members presented data, ideas, and information to an audience of about 100 anesthesiologists with special interests in obstetrical and regional anesthesia. Among the speakers, Dr. Mieczyslaw Finster discussed placental transfer and fetal pharmacokinetics of local anesthetics. He cautioned that repeated doses of local anesthetic have a cumulative effect in both mother and fetus. Also, local anesthetic trapping occurs in the acidotic fetus since acidosis shifts more local anesthetic to the ionized state and charged molecules do not readily cross the placenta. Dr. Finster noted that high maternal protein binding might not fully explain low fetal/maternal blood ratios with bupivacaine and etidocaine since these agents have greater fat and tissue solubility than does lidocaine. He found higher brain/blood ratios in the guinea pig with bupivacaine than with lidocaine, suggesting that greater fetal tissue uptake with the former could produce lower blood levels. Dr. Finster noted that neonates metabolize lidocaine as efficiently as adults but that greater fetal volume of distribution led to a longer half-life since fetal tissues absorb proportionately more local anesthetic, making less drug available for metabolism and excretion. He also commented on the greater resistance of newborn compared with adult sheep to the toxic effects of local anesthetics on the cardiovascular and central nervous system; fetal sheep demonstrate even less vulnerability than the newborn.

Dr. Benjamin G. Covino stressed that all drugs are toxic if used improperly and that all local anesthetics are potentially toxic. Equivalent doses of different local anesthetics possess nearly the same degree of cardiovascular (CVS) and central nervous system (CNS) toxicity. Generally, the dose of local anesthetic causing cardiovascular depression exceeds that producing convulsions by four to five times. Hypoxia and acidosis greatly enhance brain and cardiac sensitivity to the toxic effects of local anesthetics. Dr. Philip R. Bromage pointed out that major neurologic sequelae may follow general anesthesia and that spinal cord and nerve root damage which follows regional procedures may be unrelated to spinal or epidural anesthesia. Spinal cord ischemia, disc herniation, and myelopathy subsequent to infection represent causes of CNS damage which may be unrelated to regional anesthesia. If major neurologic complications occur, Dr. Bromage's diagnostic plan incorporates a thorough physical examination, laboratory studies including a coagulation profile, X-ray examination of the spine, a myelogram, and electromyography.

Stephen Riggi, Ph.D., of Pennwalt Corporation presented criteria for the design of animal studies of local anesthetic agents. He stressed that animal studies can examine what might happen in humans but cannot mimic the clinical situation as the latter encompass many factors which are not fully understood. Dr. Riggi reported a dog study comparing injection of large subarachnoid doses of 1.5 per cent lidocaine with that of 3 per cent chloroprocaine which failed to reveal any differences between the drugs. Changes secondary to mechanical trauma, perhaps from increased subarachnoid pressure, were seen in both groups. A rat study revealed that neither 2-chloroprocaine, saline, nor an acidic vehicle caused gross pathologic changes in spinal cord or brain when introduced into the epidural space. An additional study examined the effects in African green monkeys of injection of large subarachnoid injections of either 0.75 per cent bupivacaine, 1.5 per cent lidocaine, 3 per cent 2-chloroprocaine, and Elliot's solution, a mixture with similar properties to spinal fluid. No neurologic or gross pathologic sequelae followed injection of any of the substances. Pennwalt investigators concluded that lidocaine, bupivacaine, and 2-chloroprocaine are not neurotoxic when used in recommended doses and that low *p*H solutions are not toxic to peripheral nerves or the spinal cord.

Dr. Sol M. Shnider reviewed several recent studies on the neurotoxicity of local anesthetics. Barsa *et al.* (ANESTHESIOLOGY 55:A161, 1981) compared the effect of 2-chloroprocaine with lidocaine, bupivacaine, and a combination of 2-chloroprocaine and bupivacaine on the rabbit vagus nerve preparation. Only solutions containing 2-chloroprocaine caused axonal degeneration and nerve conduction defects. A similar Pennwalt study failed to reveal any changes when either 2-chloroprocaine or lidocaine was injected near the rabbit vagus without exposing the nerve to air. However, when the vagus was exposed to air at the time of local anesthetic administration, 2-chloroprocaine and lidocaine caused nerve swelling and damage similar to that noted by Basra *et al.* Oxidative processes might account for the conflicting results of the two studies. Dr. Shnider also discussed a study by Ravindran *et al.* (ANESTHESIOLOGY 55:A163, 1981) which compared the effects of 3 per cent 2-chloroprocaine and 0.75 per cent bupivacaine introduced into the subarachnoid space of dogs. Seven of twenty dogs receiving 2-chloroprocaine developed hind limb paralysis and had subpial demyelinization of the cord associated with macropohage infiltration. All 15 bupivacaine-treated animals were normal. Dr. Shnider noted that the spinal cord changes resembled those found in cats following cerebrospinal fluid barbotage (Bunge RP, Settlage PH: J Neuropath Exp Neurol 16:471, 1957). Dr. Shnider also discussed his own study of *Macaca fasciculares* monkeys given either 3 per cent 2-chloroprocaine or 0.75 per cent bupivacaine in doses calculated to produce total spinal anesthesia. Hypotension was treated with ephedrine and respiratory arrest was countered with positive pressure ventilation. No animal demonstrated neurologic problems during seven days of post-spinal

observation. Autopsy seven days after spinal anesthesia revealed "barbotage lesions" of the spinal cord in one animal of each local anesthetic group. Finally, Dr. Shnider discussed the review and evaluation by Dr. David L. Scally of the Food and Drug Administration of clinical data summarizing adverse experiences with local anesthetics. A total of 14 cases of moderate to severe neurologic sequelae following epidural analgesia with 2-chloroprocaine were examined. Several of these involved or were compatible with inadvertent subarachnoid injections and resultant spinal anesthesia. Nine additional reports were cited of serious neurologic sequelae after the use of epidural lidocaine, mepivacaine, or bupivacaine. Dr. Scally's conclusion was that proof was lacking that 2-chloroprocaine is more offensive than these other drugs, when used for epidural anesthesia. Clinical experience with more than 1 million patients receiving many different local anesthetics placed the incidence of serious neurologic sequelae at 1:10,000 epidural anesthetics.

During the panel discussion, George A. Albright, M.D. voiced his concern about the safety of bupivacaine noting that at least five or six deaths have been associated with doses as small as 90–120 mg. He claimed that if inadvertent intravascular injection of bupivacaine occurred, it would lead to rapid cardiac uptake of the drug which subsequently would be hard to remove from cardiac tissue making resuscitation difficult. However, it was noted that an FDA investigation prompted by Dr. Albright's editorial on the subject (ANESTHESIOLOGY 51:285, 1979) concluded that bupivacaine possessed a margin of safety equal to that of other local anesthetics. Two large series of bupivacaine epidural anesthesia, one from Boston and one from Seattle, totalling approximately 40,000 cases reported 31 seizures and no cardiac arrests.

In summary, the symposium provided an excellent update of regional anesthesia in obstetrics and of the problems of local anesthetic toxicity. Not all questions could be answered. Missing was an explanation for the findings of Ravindran regarding neurologic sequelae following subarachnoid administration of 2-chloroprocaine in dogs and for the conflicting results of rabbit vagal nerve studies by Basra *et al.* and by Riggi. However, the material presented failed to incriminate either 2-chloroprocaine or bupivacaine as more toxic to the CNS or CVS than any other local anesthetic agent. The most appropriate conclusions that can be drawn from the symposium are that: 1) the overall record of regional anesthesia in obstetrics has been one of impressive safety with considerable benefit to both mother and child; and 2) all drugs are toxic if used improperly.

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