

of the cannula. Multiple alternatives to anesthetic induction have been discussed in both the elective and emergency situation. Endotracheal intubation is the preferred method of airway management during maintenance of anesthesia.

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Cerebrospinal Fluid Concentration of 5-Hydroxyindoleacetic Acid in Pregnancy

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Anesthetic requirement is reduced during pregnancy.¹ Perhaps increased tolerance to pain during pregnancy might modify the discomfort of labor and delivery, which could involve naturally occurring neuropeptides thought to influence pain perception. Plasma beta-endorphin levels during pregnancy increase progressively, reaching their highest concentration at delivery.² However, Steinbrook *et al.*³ observed that cerebrospinal fluid (CSF) levels of beta-endorphin did not change over the course of pregnancy or during labor.

Serotonin is a neurotransmitter that plays a significant role in nociception. Studies using pharmacologic, surgical electrophysiologic, and dietary manipulations demonstrate that increased activity of central nervous system serotonergic neurons are associated with analgesia, whereas decreased activity of the transmitter

correlate with hyperalgesia.^{4,5} The major metabolite of serotonin is 5-hydroxyindoleacetic acid (5-HIAA). Levels of 5-HIAA may provide direct information on the functional state of serotonergic neurons.⁶ Because CSF levels of serotonin or 5-HIAA in pregnancy have not been determined, we quantitated the release of 5-HIAA in maternal CSF during successive states of pregnancy and labor.

METHODS

Approval for this investigation was obtained from our Committee on the Protection of the Rights of Human Subjects. Subjects for the study were selected from patients who received spinal anesthesia. Four groups of 10 patients were studied: pain-free nonpregnant women, ages 18-40 years, undergoing elective surgery; women having cervical cerclage at 13-18 weeks' gestation; women having an elective repeat cesarean section at term; and women at term in painful active labor. No subject received narcotic, sedative, or oxytocic medications prior to the operation. All patients had not eaten for at least 4 h before the procedure. The sample of CSF consisted of the first 2 ml aspirated from a 25-gauge needle. All samples were kept in a freezer (-60°) until analysis was performed (no longer than 2 weeks). 5-HIAA levels were determined using high-pressure liquid chromatography described by Kilts *et al.*⁷ All values were corrected for loss during storage. Recovery

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TABLE 1. Concentration of 5-Hydroindoleacetic Acid (5-HIAA) in Cerebrospinal Fluid of Gynecologic and Obstetric Patients

| Group | Lumbar CSF 5-HIAA ng/mg ($\bar{x} \pm \text{SEM}$) | P vs. control |
|------------------------------------|---|---------------|
| Nonpregnant (n = 10) | 65.19 \pm 4.69 | P < 0.01 |
| Cesarean (n = 10) | 94.4 \pm 4.59* | P < 0.01 |
| Elective cesarean term (n = 10) | 116.58 \pm 7.63* | |
| Active labor term (n = 10) | 165.39 \pm 8.57* | P < 0.01 |

* Statistical difference between each of the other pregnant groups (P < 0.01).

of 5-HIAA from the CSF ranged from 82–91%. Statistical analysis was by analysis of variance.

RESULTS

CSF levels of 5-HIAA in all three groups of patients were significantly higher than in the nonpregnant control group (P < 0.01) (table 1). In addition, there was a significant difference in the mean levels of 5-HIAA between all three groups of pregnant women (P < 0.01), those in active labor having the highest concentrations.

DISCUSSION

These data indicate that CSF 5-HIAA levels increase throughout pregnancy, reaching the highest concentration at term in patients who are in active labor. The increase in serotonergic activity may in part explain the reduced anesthetic requirements seen in pregnancy. Palahniuk *et al.*¹ studied nonpregnant and pregnant sheep and were able to demonstrate 25–40% reduction in the minimum alveolar concentrations (MAC) for potent inhaled anesthetics. During pregnancy there is a gradual increase in serum progesterone concentration, which becomes maximal at term. Because of known anesthetic properties of progesterone, they postulated that hormonal changes that occur in pregnancy account for decreased MAC.

As a neurotransmitter, serotonin subserves a number of important physiologic and psychologic functions, including control of mood, sleep regulation, and pain perception. The result of numerous studies suggests that a decrease in serotonin activity results in hyperalgesia and increased activity produces analgesia.⁸ Animals given an electric shock or heat stressed produce more serotonin.^{9,10} Painful stimuli normally leads to increased activity of the serotonergic system, which at least partially inhibits or diminishes the intensity of the nociceptive reflex. Serotonin neurons also are involved in analgesic drug potency. Morphine has been shown to increase the turnover rate of serotonin. When pretreated with serotonin uptake blocking drugs, the effect of morphine is

enhanced, and when pretreated with serotonin-depleting drugs, a diminished effect of morphine is observed.⁴ Intrathecal administration of serotonin in rats, rabbits, and cats produced a significant dose-dependent elevation in response to aversive stimuli.¹¹ Finally, Ghia *et al.*⁵ measured CSF concentration of 5-HIAA in three groups of patients who received dural punctures for either anesthesia or diagnostic reasons. A pain-free control group consisted of patients undergoing elective surgery. The second group were those with acute pain due to appendicitis, thrombosed hemorrhoids, *etc.* The third group was patients with chronic pain who received differential spinal blocks as part of their pain clinic evaluation. Ghia *et al.*⁵ found the 5-HIAA levels were significantly higher in patients with acute and chronic pain compared with patients who were pain-free.

Central nervous system serotonin concentrations can be affected by diet, age, physical activity, amount of CSF withdrawn, and diurnal variation.⁵ We attempted to control for as many of these factors as feasible, although it was not possible or practical to strictly match diet and physical activity.

Plasma levels of serotonin were not measured, since it is doubtful that plasma concentrations influence or reflect levels in the CNS where the primary action is known to occur. The release of serotonin to the plasma and CSF seem to occur as a result of different mechanisms, and attempts to assign actions in the CNS to blood levels is inappropriate.

In conclusion, we demonstrated an association between the release of 5-HIAA into the CSF during successive stages of pregnancy and labor. The increase in 5-HIAA during pregnancy and parturition may represent the body's natural process of modifying pain. The results of this study should not be taken as evidence that serotonin is the only neurotransmitter responsible for the reduced anesthetic requirements in pregnancy. Other neuropeptides such as dopamine, neurotensin, and substance P also are involved in nociception and analgesic drug potency.¹² Further research should be undertaken so that we may understand the extent to which these substances mediate pain in both pregnant and nonpregnant individuals.

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Does Hyperkalemia Contraindicate the Use of Bupivacaine or the Use of Succinylcholine to Treat Bupivacaine-induced Toxicity in Humans?

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Data from animal experiments indicate that mild hyperkalemia, as compared with the normokalemic state, results in cardiotoxicity at a significantly lower dose of bupivacaine,¹ and that hyperkalemia may be a factor in enhancing bupivacaine's negative chronotropic effects on the heart.² Furthermore, in humans with renal failure and acidosis, slight elevations in potassium levels (but still within normal limits) have been cited as one possible reason for cardiotoxicity associated with bupivacaine administered to a patient receiving brachial plexus blocks.³

Therefore, two questions arise: 1) does hyperkalemia enhance the possibility of a systemic toxic reaction from bupivacaine; and 2) does succinylcholine used in the treatment of convulsions produce hyperkalemia and is it therefore contraindicated for this purpose?

METHODS

To answer the first question, we investigated 10 patients with renal insufficiency in whom dialysis shunts

were to be inserted using bupivacaine for supraclavicular brachial plexus blocks (table 1). Patient consent was obtained, as was approval of our Human Rights Committee. Venous potassium levels were determined in these 10 patients immediately before and 30 min after completion of the block. The 5-ml blood samples were drawn from the arm not blocked after: 1) stopping the intravenous fluids (which were running in a hand or wrist vein) for 30 s; 2) applying a Penrose drain tourniquet on the arm; 3) inserting the needle attached to a 5-ml syringe (single-use) into either the cephalic or the basilic vein in the cubital fossa; and 4) releasing the tourniquet. Postblock sampling times for the plasma levels of potassium were selected to correlate with the maximum plasma levels of a bupivacaine-epinephrine solution following a supraclavicular brachial plexus block.⁴

Then, to approach question two, we reviewed three patients in whom: 1) potassium levels had been determined from blood obtained from a vein in the cubital fossa prior to surgery; 2) bupivacaine was employed for the blocks; 3) convulsions resulted; 4) succinylcholine alone along with oxygen was administered; 5) blood was drawn from the femoral artery during the systemic toxic reaction; and 6) the potassium levels of the blood were determined (table 2).

RESULTS

None of the 10 patients developed signs of systemic toxicity from the bupivacaine solutions, although they had significant hyperkalemia (table 1).

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