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Ammonia Toxicity Resulting from Glycine Absorption during a Transurethral Resection of the Prostate

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Intravascular absorption of irrigating solution leading to hypervolemia, dilutional hyponatremia, and decreased serum osmolality is traditionally regarded as the sole explanation for the hemodynamic and central nervous system changes that may accompany transurethral resection of the prostate (TURP).^{1,2} However, a metabolite of the most frequently used irrigating solution, glycine, is ammonia³⁻⁵ which conceivably could cause central nervous system depression following TURP (personal communication, Richard J. Kahnoski, M.D., Indiana University School of Medicine, Indianapolis, Indiana). We describe a patient in whom an acute elevation of the blood concentration of ammonia may be partly or entirely responsible for delayed awakening from general anesthesia following a TURP.

REPORT OF A CASE

A 72-year-old, 80-kg man with chronic urinary retention was scheduled for an elective TURP. Significant preoperative history included adult onset diabetes mellitus treated with Lente® insulin daily and essential hypertension controlled with timolol and hydralazine. There was no history of ethanol abuse or liver disease. Preoperative laboratory values were hemoglobin 15.2 g/dl, sodium 143 mmol/l, potassium 4.0 mmol/l, BUN 27 mg/dl, blood glucose 85 mg/dl, albumin 3.7 g/dl and SGOT 23 units. BP was 180/90 mmHg and HR 68 bpm. ECG showed a normal sinus rhythm.

Preoperative medication was with oral diazepam (10 mg) and intramuscular glycopyrrolate (0.2 mg). Anesthesia was induced with thiopental (150 mg) and fentanyl (100 µg) iv followed by succinylcholine (80 mg) iv to facilitate intubation of the trachea. Anesthesia was maintained with 60% nitrous oxide and isoflurane. After about 35 minutes of resection utilizing 1.5% glycine as the irrigating solution, there was a sudden change in the ECG characterized by depression of the ST segment, widening of the QRS complex, disappearance of the P wave, and bradycardia to 40 bpm. The systolic BP decreased from 140

mmHg to 90 mmHg. There was no evidence of seizure activity. The resection was rapidly completed and anesthetic drugs were discontinued. PaO₂ was 300 mmHg, PaCO₂ 45 mmHg, and pH_a 7.32. At this time, the serum sodium concentration was 105 mmol/l, chloride 90 mmol/l, serum osmolality 279 mOsm/kg, hemoglobin 12.2 g/dl, and glucose 140 mg/dl. In view of hyponatremia, furosemide, 80 mg, and 150 ml 5% saline were given iv. The abnormal findings on the ECG subsequently disappeared and continuous iv infusion of nitroprusside was required to maintain systolic BP below 180 mmHg. However, the patient remained unresponsive despite administration of 100% oxygen for over 60 min. At this time, ammonia toxicity resulting from intravascular absorption of glycine was considered as an explanation for the delayed awakening. The arterial blood ammonia concentration was 500 µM/l (normal 11 to 35 µM/l). Signs of awakening appeared 12 hours postoperatively, and the blood concentration of ammonia at this time was 45 µM/l. Twenty-four hours postoperatively, the blood ammonia concentration was 40 µM/l, sodium 127 mmol/l, and BUN 41 mg/dl. At this time, the trachea was extubated and the remainder of the hospital course was uneventful.

DISCUSSION

Glycine is a nonessential amino acid that is normally present in the circulation. Oxidative deamination of glycine in the liver and kidneys results in the formation of glyoxylic acid and ammonia.^{3,5,6} Predictably, iv infusion of glycine could lead to increased concentration of blood ammonia.^{4,5} Likewise, intravascular absorption of glycine as occurs during TURP could contribute sufficient substrate to produce excessive ammonia. Nevertheless, increased blood ammonia concentrations did not occur in 14 patients undergoing TURP using glycine as the irrigating solution.⁷ On the basis of these data, Madsen and Madsen⁷ concluded that systemic absorption of glycine did not result in significant accumulation of ammonia in the blood. In another report, Desmond stated that signs of ammonia toxicity (nausea, vomiting, convulsions, and coma) had not occurred in 400 patients undergoing TURP despite absorption of large amounts of glycine as indicated by hyponatremia.⁶

In contrast to these earlier reports, recent observations suggest that ammonia toxicity may be an important, and in some instances, the sole cause of encephalopathy in patients manifesting signs of water intoxication during or following a TURP using glycine as the irrigating solution (personal communication, Richard J. Kahnoski, M.D., Indiana University School of Medicine, Indianapolis, Indiana). Therefore, ammonia toxicity should be suspected in patients undergoing a

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TURP who experience predominant central nervous depression with lesser degrees of systemic symptoms. The mechanism by which ammonia produces central nervous system depression is not known. Encephalopathy resulting from ammonia toxicity typically manifests as delayed awakening in the postoperative period that persists despite correction of intravascular fluid volume and electrolyte balance. Absorption of glycine from periprostatic and retroperitoneal tissues probably provides a continued source of substrate for production of ammonia in the postoperative period leading to persistent central nervous system depression. Indeed, only about 30% of the absorbed glycine directly enters the circulation with the majority of absorbed fluid entering extravascular spaces for later absorption.⁸ In contrast to patients manifesting ammonia toxicity, a second group of patients may develop symptoms due to hypervolemia with associated dilutional hyponatremia and decreased serum osmolality in the absence of excessive blood concentrations of ammonia. Those patients are likely to manifest predominately systemic symptoms. In some patients, both ammonia toxicity and hypervolemia probably contribute to the clinical symptoms characterized as water intoxication.

The predominant mechanism (hypervolemia and/or ammonia toxicity) responsible for signs of water intoxication can be substantiated only by observing the clinical response to infusion of saline and measurement of the blood concentration of ammonia. The documentation of acute hyponatremia only confirms a dilutional effect resulting from excessive intravascular absorption of irrigating solution. It is not possible to predict preoperatively who is vulnerable to excessive production of ammonia due to intravascular absorption of glycine. Furthermore, there is no evidence that coexisting liver disease makes patients more vulnerable to ammonia toxicity following absorption of glycine.⁸

In retrospect, ammonia toxicity resulting from intravascular absorption of glycine may have been an unrecognized cause of delayed awakening following TURP that was attributed to acute hyponatremia.^{9,10} For example, ammonia toxicity was not considered in a patient who became progressively obtunded in the recovery room and remained lethargic despite correction of the serum sodium concentration with saline.⁹ Other authors described 14 patients who developed central nervous system depression after TURP presumably caused by hyponatremia.¹¹ Eleven of these 14 patients become lethargic 2 to 10 hours following TURP, but ammonia toxicity was not considered despite the use of glycine as the irrigating solution.

Methods to prevent or treat ammonia toxicity may be indicated if glycine is used as the irrigating solution

during TURP. In this regard, the possible protective and/or therapeutic role of oral or iv L-arginine should be considered.^{4,5} For example, prior administration of iv L-arginine prevents the rise in blood ammonia levels in patients receiving intravenous glycine.⁴ Furthermore, infusion of L-arginine following the initiation of glycine administration prevented a further increase in the blood ammonia concentration and accelerated the return of the blood ammonia concentration towards normal.⁴ These investigators speculated that previous nutritional deficiencies, particularly for arginine, could increase the susceptibility to the development of ammonia toxicity following increased availability of glycine.⁴ The extent to which preexisting hepatic disease could influence this response is not known. However, deamination of glycine occurs in both the liver and kidneys while L-arginine acts only at the liver to reduce the blood ammonia concentration by prevention of hepatic release of ammonia.⁵

The symptoms demonstrated by our patient most likely represent the effects of both hypervolemia and ammonia toxicity. The magnitude of hyponatremia after only 35 minutes of resection implies substantial intravascular absorption of glycine to produce dilutional effects and supply substrate for production of ammonia. The initial cardiac abnormalities on the ECG most likely represented the acute onset of hyponatremia. Hypotension, although uncharacteristic of water intoxication, also may have reflected negative inotropic effects secondary to hyponatremia.¹² The subsequent development of delayed awakening from general anesthesia was most likely caused by ammonia toxicity. Indeed, previous reports have documented deterioration in cerebral function when the blood ammonia concentration exceeds about 150 $\mu\text{M}/\text{l}$.^{13,14} The return of consciousness in our patient as the blood ammonia concentration decreased from 500 $\mu\text{M}/\text{l}$ to 45 $\mu\text{M}/\text{l}$ suggested a role for this metabolite of glycine in the delayed postoperative awakening.

In the future, consideration of the possibility of ammonia toxicity and measurement of the blood ammonia concentration will serve to quantitate the true incidence of this abnormality in patients undergoing TURP who develop water intoxication. Clearly, hypervolemia with associated dilutional hyponatremia and decreased serum osmolality is not the only cause of adverse responses in patients undergoing TURP utilizing glycine as the irrigating solution.

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High-dose Fentanyl for Neuroanesthesia

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High-dose fentanyl-oxygen anesthesia (HDF), well-established in cardiac surgery,¹ may offer several advantages to the neurosurgical patient. Cardiovascular stability characteristic of this technique would be desirable in neuroanesthesia where hypotension may reduce cerebral blood flow in a brain with poor autoregulation while hypertension may induce vasogenic edema. Since specific antagonists are available, HDF can be reversed in the postoperative period without eliminating its postoperative analgesic effect.² Thus, careful neurologic monitoring to detect complications of surgery in the postoperative period would be feasible. For procedures in the sitting position, omission of nitrous oxide should reduce the severity of venous air embolism.³ We have employed HDF with postoperative naloxone administration in neurosurgical anesthesia.

MATERIALS AND METHODS

This study was approved by the Human Studies Committee of Temple University Hospital. Informed consent was obtained from each patient.

Ten patients without organic heart disease and 35 to 65 years of age were studied. All were scheduled for suboccipital craniectomies in the sitting position for tumor removal or microvascular cranial nerve decompression. The mean length of operation was 262 min (90-360 min). Premedication was 5 to 10 mg diazepam, po, and 0.4 mg atropine, im, 1.5 h prior to induction of anesthesia. After application of the ECG and insertion of a peripheral venous cannula in the operating room, a radial artery catheter was inserted to monitor arterial blood pressure (MAP) and arterial blood gases (ABG). A precordial bubble doppler was positioned and a thermolilution balloon-tipped catheter was inserted into the pulmonary artery to measure changes in pulmonary artery pressure (MPAP) and cardiac output (CO) for the detection and removal of entrained venous air.⁴ The magnitude of neuromuscular blockade was monitored using train-of-four (TOF) stimulation of the ulnar nerve. Temperature, urine output, expired CO₂ levels, and a two-lead EEG also were monitored during the procedure.

After a period of stabilization and measurement of baseline values, fentanyl was infused at a rate of 150

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