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# Ketamine as an Induction Agent for Acute Intermittent Porphyria

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Acute intermittent porphyria is of great concern to anesthesiologists, as fatal crises have been associated with induction of anesthesia by most intravenous induction agents, particularly barbiturates. It is a congenital disease that has a variable phenotypic expression.[1–4] The abnormal metabolic pathways and clinical symptomatology of this condition have been well described.[2–5]

Recommendations for anesthetic management of patients who have acute intermittent porphyria have emphasized the safety of using inhalation anesthetics and muscle relaxants and avoiding, whenever possible, the use of intravenous and regional techniques.[1,4,6,7] Neurologic complications that may accompany acute intermittent porphyria may be wrongly attributed to regional blocks.

## REPORT OF A CASE

A 61-year-old woman, weighing 74 kg, who had been known to have acute intermittent porphyria for 16 years, was admitted to our center with a diagnosis typical of left subclavian steal syndrome and stenosis of the terminal aorta with partial occlusion of the right external iliac arter. Since the need for surgical treatment was urgent, the decision was made to proceed without laboratory reassessment of acute intermittent porphyria. Past medical history include a hysterectomy 16 years previously for which the method of anesthesia was not known, and its coincidence with the onset of acute intermittent porphyria was not certain. Two subsequent minor operations had been performed with local anesthesia.

The patient was familiar with the symptoms of the acute attack, which were classic regarding the pain (colicky, referred to one or both lower abdominal quadrants), respiratory difficulty, and in occasional attacks, muscle weakness, dizziness and blurred vision. Physical and emotional distress predisposed to crises. She was familiar with testing her urine during the crisis by watching the color changes on exposing it to sunlight.

Preoperatively the only abnormal finding was that blood pressure was 150/80 torr in the right arm and 90/0 torr in the left arm.

For the first operation, right-to-left axillary arterial bypass in the hyperbaric chamber was performed. Premedication was with atropine, 0.4 mg, iv. Blood pressures recorded from the right arm and the left thigh were monitored. The patient refused a face-mask induction due to anxiety related to respiratory difficulty during previous attacks of acute intermittent porphyria. Anesthesia was induced with ketamine, 4 mg/kg, iv, and intubation was facilitated with 80 mg succinylcholine. Anesthesia was maintained with 4 mg pancuronium and an oxygen–halothane mixture. The pressure inside the chamber was 2.5 ATA (22.5 psig) during the procedure. During operation and recovery vital signs were stable, and the postoperative period was uneventful.

Three days later the patient underwent aorto-iliac endarterectomy in the hyperbaric chamber. The same anesthetic technique was adopted. The operation and recovery period were also uneventful. In both occasions the patient recovered consciousness immediately after termination of anesthesia (the duration of each procedure was approximately two hours).

## DISCUSSION

Genetically the patient was considered to represent a sporadic case. Three known generations of the family were free of the disease. Many drugs are known to incite acute attacks of porphyria. Those drugs of anesthetic interest are barbiturates, hydroxydione, alphadione, diazepam, and pentazocine.

Meyer and Schmid[5] postulated that in acute intermittent porphyria there is a decrease in uroporphyrinogen synthetase (UPG-S) with a resultant interference with heme production. This decrease in heme production interferes with the negative feedback of heme on delta-aminolevulinic acid synthetase (ALA-S). This gives increased levels of ALA-S, aminolevulinic acid (ALA), and porphobilinogen (PBG). The effect of barbiturates and other drugs mentioned above is to induce formation of cytochrome P-450, a hemoprotein, a process in which excessive consumption of heme occurs, thus interfering more with its inhibitory effect on ALA-S formation.[1,5] This results in increased levels of ALA-S, ALA and PBG. ALA-S induction is currently accepted to be the crisis-triggering factor in acute intermittent porphyria.[1–5] In one case of acute intermittent porphyria in which the patient died after anesthesia (unpublished), the cytochrome P-450

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level in the liver, for unknown reasons, could not be detected.§ This phenomenon might have been a reflection of the so-called Type I optical difference binding spectrum mentioned by Brown.[8]

Parikh and Moore[9] investigated the effects of intraperitoneal injection of different drugs used for intravenous induction of anesthesia in rats, then measured hepatic ALA activity and measured ALA quantitatively in the livers of enzyme-induced rats, and found that ALA-S activity increased significantly after thiopental, methohexital and alphadione, but was not significantly altered after ketamine, propanidid, phenoperidine and droperidol.

Chang *et al.*[10] used chromatography to study the biotransformation of tritium-labeled ketamine in man, monkeys, and rats. They found that ketamine was converted to metabolite I by dealkylation, and then to metabolites III and IV by hydroxylation, being further transformed to matabolite II by dehydration. In the rat, due to a species difference, a larger amount of a less oxidized metabolite III was prevalent in urine. In human and monkey urines, a larger amount of a more oxidized metabolite II was a feature. They also found that 20 per cent of the total tritium in human urine, presumably representing unknown metabolites, cannot be extracted. Some free ketamine was also found in human urine in the first four hours. Their experiments were also carried out to determine whether ketamine could induce the formation of enzymes responsible for its own biotransformation. They administered ketamine intravenously for several doses to rats, separated out the hepatic microsomal fraction, and tested its demethylation activity against control animals. Their results indicated that ketamine probably does not enhance the activity of microsomal enzymes responsible for N-dealkylation in the rat.

In view of the above-mentioned observations ketamine is obviously a substrate for hepatic microsomal enzymes[8] for a major part of its biotransformation, yet it does not appear to enhance the activity of hepatic microsomal enzymes in comparison with other intravenous induction agents.[9,10]

Thus it is theoretically possible to conclude that ketamine and propanidid should be safe induction agents for patients who have acute intermittent porphyria. Based on the uneventful outcome of our case, in which ketamine was used on two occasions within a week, this agent would seem to provide a safe alternative to inhalation induction of anesthesia for patients who have acute intermittent porphyria.

§ Estabrook RW: Personal communication, November 1976.

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