Induction of anaesthesia with ketamine during an acute crisis of hereditary coproporphyria

V. Capouet, B. Dernovoi, J.S. Azagra

An appendectomy operation was undertaken in a 29-year-old patient with signs of an acute crisis of hereditary coproporphyria. Anaesthetic induction with ketamine 75 mg IV was uneventful. The safety of ketamine in patients with coproporphyria is discussed.

Porphyria is a group of diseases which have in common disorders of heme metabolism. Among them, all three hepatic hereditary porphyrias (acute intermittent porphyria (AIP), variegate porphyria and hereditary coproporphyria (HC) can be precipitated or aggravated by drugs.[1,2] All three are transmitted as autosomal dominant traits. They differ each from another biochemically but are clinically similar.

Biochemically, there is a deficient activity of one or other specific enzymes of heme biosynthesis together with reactive hyperactivity at the rate limiting enzymatic stage of heme biosynthesis: formation of amino-laevulinic acid (ALA) from glycine and succinyl coA by ALA synthetase.[1] The measurement of the different porphyrins and their precursors allows detection of the latent phase and confirms the acute phase of the disease.[3] Latent cases are generally not detected before puberty.[4]

Clinically, the patient with an acute attack of hereditary hepatic porphyria can have abdominal pain, vomiting, constipation, autonomic neuropathy and ascending polyneuropathy which may lead to death in respiratory failure. Abdominal pain is the initial symptom in about 85 per cent of the acute attacks and almost always precede peripheral neuropathy. Acute attacks can be spontaneous or may be precipitated by drugs, alcohol, hormones or infection. Death usually results from respiratory paralysis or from cardiac arrythmias secondary to sympathetic overactivity.[4]

Key words
GENETIC FACTORS: porphyria;
ANAESTHETICS, INTRAVENOUS: ketamine.

From the Departments of Anaesthesia and Surgery, Brugmann Hospital, Brussels, Belgium.

Address correspondence to: Dr. V. Capouet, Dept of Anaesthesia, Brugmann Hospital, 4 place Van Gehuchten, B-1020 Brussels, Belgium.

Hereditary coproporphyria is characterized by the deficiency of coproporphyrinogen oxidase which mediates the oxidative decarboxylation of coproporphyrinogen III to porphobilinogen IX. During the latent phase of HC, urinary prophobilinogen (PB) might be slightly increased, urinary uroporphyrin (UP) is normal and urine coproporphyrins (CP) is normal or slightly increased. During the active phase, urinary PB is greatly increased, urine UP is increased and urine CP is greatly augmented.[3]

Case report

A 29-year-old black female, weight 70 kg, height 170 cm, whose hereditary coproporphyria had been diagnosed two years previously, was admitted with abdominal pain which had started in the left iliac fossa and had migrated to the right.

Clinical examination revealed tenderness at McBurney's point. Systolic blood pressure was 120 mmHg, heart rate 80 beats·min^{-1}. On the day of admission the white blood cell count (WBC) was 11,600 (88 per cent polynuclear neutrophils); body temperature was 37.5° C. The urine was red but a microscopic examination was negative. The Watson-Schwartz test[16] was positive for porphobilinogen. The following day, the WBC was 19,600, body temperature still 37.5° C. The urine was still red and urinary uroporphyrins were 27.4 μg·24h^{-1} (normal value: 20) and urinary coproporphyrins were 214 μg·24h^{-1} (normal value: 20–100). There was increased tenderness at McBurney's point. Although an acute crisis of HC may include abdominal pain, it was clinically clear that an operation for acute appendicitis should be undertaken.

The patient was not premedicated. After placement of two intravenous lines, an ECG and blood pressure cuff, induction was achieved using 75 mg of ketamine IV, 0.2 mg of fentanyl and 100 mg of succinylcholine. After tracheal intubation, the patient was ventilated with a mixture of nitrous oxide and oxygen (2/1). Muscle

relaxation was maintained using intermittent bolus doses of succinylcholine: a total dose of 425 mg was given. Analgesia was maintained with fentanyl (total dose 0.85 mg). In addition, the patient received small doses of dehydrobenzperidol (total dose 10 mg). During the operation she received 1000 ml of glucose ten per cent in water and 400 ml of SSPP (stable solution of plasma protein). The appendix was inflamed and signs of peritonitis were present.

After the operation, the patient received two 15 mg doses of piritramide to relieve pain. A fluid program rich in carbohydrates was instituted: 1000 ml glucose ten per cent and 1000 ml glucose five per cent in lactated Ringer's solution. Antibiotic therapy included cefuroxine 3 × 1.5 g and metronidazole 3 × 500 mg a day for two days. On the first postoperative day the urine was clear, the Watson Schwartz test was negative, uroporphyrin and coproporphyrin in the urine returned to normal levels.

Discussion

In the case reported biochemical analysis of the urine confirmed the diagnosis of coproporphyria in the active phase. While it is clear that drugs which have been shown to precipitate acute attacks are absolutely contraindicated in the latent phase (including barbiturates),[5,6] Mustajoki and Heinonen[7] showed that the risk of incurring symptoms after exposure to thiopentone was small but that thiopentone aggravates porphyrics' symptoms in most cases when given during an acute episode. Based on these observations, it is clear that the successful use of a particular anaesthetic in patients with latent porphyria is of relatively little predictive value. Silvay *et al.*[14] and Bancroft *et al.*[15] reported ketamine to be a safe drug for induction of porphyric patients, but none of their patients had symptoms of an acute porphyric crisis. On the other hand, anecdotal reports linking acute attacks to specific medications in small numbers of patients are less easy to interpret when the drugs have previously been used in porphyrics without ill-effect.[5] An anecdotal report linking an acute attack of porphyria to ketamine has been reported only on one occasion.[13]

Various attempts have been made in the laboratory to evaluate the porphyrogenicity of ketamine. The models tested included chemically-induced porphyria in rats[8,9,12] and chick embryo liver cell preparation in tissue culture.[10] Although most reports support the safety of ketamine, the results reported by Lipinska *et al.* do not.[10]

This difficulty of classification of a drug as safe or unsafe arises in part because of differences of sensitivity of the models tested;[8,9,11] induction of ALA-S by drugs is a dose-related phenomenon[8] and large variations in the individual responses of rats to the drugs were observed.[9] Concomittant aggravating factors (starvation, infection, hormones) combine to increase sensitivity to a drug.

Although it is still extremely difficult to extrapolate from the laboratory findings to the clinical setting, experimental models afford the only means for testing the potential dangers of drugs. Keeping these points in mind, it is now accepted that among induction agents propanidid is the most appropriate: propanidid has been reported dangerous by only one author[5] and although it is considered safe in experimental models,[9] its side effects are well-known. Therefore ketamine remains a theoretically good choice, although the reports are conflicting.

Acute attacks of porphyria have been reported after the use of flunitrazepam[5] and experimental results confirm this porphyrogenic activity.[9] Although no clinical reports of acute attacks have been reported with etomidate, experimental results suggest that it is best avoided.[8,12]

The use of ketamine to induce a patient in the acute phase of the disease, when the risk of aggravating the crisis is higher, has not been previously reported. Reports of other similar cases should be sought to reinforce the clinical and laboratory results which support the opinion that ketamine is a safe drug for induction of anaesthesia during acute porphyric crises.

References

1 *Magnus IA*. Drugs and porphyria. Br Med J, 1984; 288: 475.

2 *Jackson SH*. Hereditary Hepatic Porphyrias. *In*: Chapter 1 Genetic and Metabolic disease. *In*: Anesthesia and Uncommon diseases. Pathophysiologic and clinical correlations. J Katz, J Benumof, LB Kadis (Eds). 2nd Edition Philadelphia. W.B. Saunders 1981; 23–9.

3 *Mees JR, Fredreckson EL*. Anesthesia and the porphyrias. South Med J 1975; 68, 29–32.

4 *Tshudy DP, Valsalmis M, Magnussen R*. Acute intermittent porphyria: clinical and selected research aspects. Ann Int Med, 1975; 83, 851–64.

5 *Disler PB, Blekkenhorst GH, Eales L, Moore MR, Straughan J*. Guidelines for drug prescription in patients with the acute porphyrias. S Afr Med J 1982; 6: 656–60.

6 *Dundee JW, Riding JE*. Barbiturate narcosis in porphyria. Anaesthesia 1955; 10: 55–8.

7 *Mustajoki P, Heinonen J*. General anaesthesia in "inducible" porphyrias. Anesthesiology 1980; 53: 5–20.

8 *Parikh RK, Moore MR*. Effect of certain anaesthetic agents on the activity of rat hepatic gamma aminolevulinate synthetase. Br J Anaesth 1978; 60: 1099–103.

9 *Blekkenhorst GH, Harrison GG, Cook ES, Eales L*. Screening of certain anaesthetic agents for their ability to elicit acute porphyric phases in susceptible patients. Br J Anaesth 1980; 52: 759–62.

10 *Lipinska D, Kostrzewka E, Gregor A.* Ketamine in acute intermittent porphyria. Dangerous or safe? Anesthesiology 1978; 49: 376–7.

11 *Ealers L, Blekkenhorst GH.* The use of the rat in the experimental investigation of the porphyrias. J S Afr Vet Assoc 1978; 49: 249.

12 *Harrison GG, Moore MR, Meissner PN.* Porphyrinogenicity of etomidate and ketamine as continuous infusions. Screening in the DDC-primed rat model. Br J Anaesth 1985; 57: 420–3.

13 *Wetterberg L.* Report on an international survey of safe and unsafe drugs in acute intermittent prophyria. *In*: Porphyrins in Human Disease (Vol 2). Supplement to the Proceedings of the First International Meeting on Porphyrins in Human Diseases, Freiburg (M. Doss and P. Nawrocki (Eds). 1976; 191.

14 *Silvay G, Miller R, Tansk C.* Safety of ketamine in patients with acute intermittent porphyria. Case report. Acta Anaesthesiol Scand 1979; 23; 329–30.

15 *Bancroft GH, John IL.* Ketamine induction for cesarean section in a patient with acute intermittent porphyria and achondroplastic dwarfism. Anesthesiology 1983; 59: 143–4.

16 *Watson CJ, Schwartz S.* A single test for urinary porphobilinogen. Roy Soc Exp Biol Med 1941; 47: 393–4.

Résumé

Un patient âgé de 29 ans fut opéré pour appendicectomie en présence de signes de crise aigue de coproporphyrie héréditaire. L'induction avec la kétamine (1 mg·kg^{-1}) fut faite sans incident. La sécurité de la kétamine chez les patients atteints de coproporphyrie est discutée.