Anesthetic considerations of porphyria

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Some anesthetic agents can precipitate acute attacks of intermittent porphyria, a congenital metabolic disorder, with dangerous consequences. The authors review the etiology, pathology, clinical symptomology, and anesthetic management of porphyrias. Emphasis is placed on clinical classifications, characteristics, and features of each variety.

Though the incidence of porphyria is very rare, it is essential that we are aware of the anesthetic management and complications of porphyria; knowledge of porphyria can reduce fatalities in this area. It is the very severity and the complications of this disease which prompted us to report on three cases of porphyria treated in our institution.

Case 1
The first case was that of a 23-year-old woman who presented for a lumbar laminectomy. In her medical history she indicated that her mother had been diagnosed as having acute intermittent porphyria. The patient was diagnosed as having congenital erythropoietic protoporphyria. She denied any history of colic pain, weakness, nausea, palpitation, or hypertension, which would be suggestive of a crisis of porphyria. She did not give a history of change in the color of the urine.

Preoperative medication was droperidol 2.5 mg. Induction was done with Valium® (diazepam), Innovar® (fentanyl and droperidol), nitrous oxide/oxygen, and Ethrane® (enflurane). Intubation was facilitated with pancuronium bromide. Enflurane was chosen for intraoperative maintenance. The patient continuously monitored for temperature, pulse rate, and blood pressure. There was no tachycardia or hypertension.

At the end of the operation, the patient was reversed with Prostigmin® (neostigmine) and Robinul® (glycopyrrolate). She did very well postoperatively, made an uneventful recovery, and was discharged.

Case 2
A second case involved a woman who was diagnosed as having acute intermittent porphyria. She presented for a Marshall Marchetti procedure. Except for the induction, which was done with ketamine, the anesthetic management was the same as described for the first case. There were no problems intra- or post-operatively.

Case 3
A third interesting case concerned a 29-year-old woman who presented for a laparoscopic tubal ligation. Anesthesia was induced with sodium pentothal, nitrous oxide/oxygen, and enflurane.

Postoperatively, the patient developed abdominal pain. A gynecologist, a general surgeon, and an urologist were consulted; nothing was found.
She was suspected of having acute intermittent porphyria. A porphobilinogen test in 24-hour urine was done. Normal values are 2 mg %/24 hours; the patient's values were 22 mg %/24 hours.

She was discharged without any residual symptoms on the sixth postoperative day.

**Classification of porphyria**

*Porphyria* is the genetic name given to a group of diseases in which excessive porphyrin is formed in the tissues.¹ ² There are two main types: *erythropoietic* and *hepatic*. Uroporphyria and protoporphyria are classified as erythropoietic. Acute intermittent porphyria, porphyria variegata, porphyria cutanea tarda, and hereditary coproporphyria are classified as hepatic.

*Uroporphyria* occurs very early in life, sometimes a few days after birth. The disease is characterized by the excessive deposit of porphyrin in the tissue, leading to pronounced photosensitization.³

The early lesions of the photosensitive effects are blisters on skin surfaces exposed to light, especially on the face and hands.² After years of continued photosensitivity, mutilation becomes extensive with the possible loss of fingers and part of the nose. The color of the urine turns from pink to red.

The disease is slow to progress and death is usually due to infections or severe hemolytic anemia. Exposure to sunlight should be avoided and a splenectomy is indicated if there is evidence of erythrocyte destruction.¹ ³

*Protoporphyria* is the most common of erythropoietic porphyrias and is manifested in childhood. It is clinically characterized by skin photosensitivity with intense, painful, and aching edema and erythema of the exposed parts. Biochemically, the disorder causes an increase in the protoporphyrin content of the normoblasts and erythrocytes of the patient and the patient's family. The course of the disease is usually benign with symptoms related only to the skin.² ⁸

The basic disorder is heme metabolism. Each of these different types of porphyrias have distinctive clinical and laboratory patterns. In congenital erythropoietic porphyria, there is no sensitivity to barbiturates.

*Hepatic porphyrias*.

Acute attacks in hepatic porphyrias can be precipitated by drugs and other factors. The mechanism of an acute attack is by enzyme induction. 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 and alpha aminolevulinic acid synthetase (ALA-S). This, in turn, gives rise to increased levels of ALA-S, aminolevulinic acid (ALA), and porphobilinogen (PBG).

Barbiturates induce formation of the enzyme cytochrome P-450. The increased demand for heme results in stimulation in ALA-S in absence of inhibition by the normal negative feedback system. Therefore, in the absence of UPG-S and increased levels of ALA-S, there are increased levels of porphobilinogen and uroporphyrins in the urine.⁴

The significant lesions of hepatic porphyrias are multiple, segmental, scattered areas of demyelination in peripheral nerves, autonomic as well as sensory and motor. Demyelination of the autonomic nerves will lead to symptoms of abdominal pain and bowel upset; demyelination of peripheral, motor and sensory nerves leads to paralysis and sensory loss. Involvement of the cranial nerves in this process may explain bulbar palsy and respiratory failure.

Foci of demyelination are found in the cerebrum, especially around blood vessels in the parietal, temporal, and occipital lobes. This explains psychiatric symptoms found in 65% of the cases of the disease. The demyelination may be indirectly related to porphobilinogen. The liver is probably the site of deranged synthesis of porphyrin.⁵

**Diagnosis**

While uroporphyrins are often found in the urine, in acute porphyria, they may also be found in large quantities in other areas (such as tissues, plasma, and stools) or may be absent during acute exacerbations. Porphobilinogens, on the other hand, are always present during acute exacerbations.¹ ⁵

Examination of the urine gives the most valuable clue to the diagnosis. When first voided, the urine contains porphobilinogens that are usually normal in color, but darken only when left in day light for a few hours. A comparison may be made between unheated specimens and those heated for ten minutes in a water bath.¹ ⁵

Five clinical entities have been described for porphyria: (1) *latent*, no symptoms or signs, but porphobilinogens have been demonstrated to be present in the urine on at least one occasion; (2) *purely abdominal* symptoms with no involvement in the nervous system; (3) *purely neurologic* with no symptoms referable to abdomen; (4) *mixed abdominal and neurological* symptoms; and (5) *terminal comatose* term.
The classical case presents colicky abdominal pain, muscular weakness, paralysis, psychiatric manifestations, and red colored urine. Insomnia is a frequent symptom and may lead to the administration of barbiturates and a subsequent precipitation of an attack.\(^3\)

**Anesthetic management**

When a case of porphyria is present, it is important for anesthetists to know the factors and agents that precipitate an acute attack. It is also important to choose a drug which will be safe. From the preceding discussion, it is evident that any drug known to produce enzyme induction should be avoided.\(^1\) (See Table I.) Barbiturates are known to precipitate an acute attack in hereditary hepatic porphyrias.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td><strong>Drugs contraindicated for porphyrias</strong></td>
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<tr>
<td><strong>Barbiturates (hepatic porphyrias only)</strong></td>
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<tr>
<td>Valium(^\circ) (diazepam)</td>
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<tr>
<td>Librium(^\circ) (chlordiazepoxide hydrochloride)</td>
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<td>Miltown(^\circ) (meprobamate)</td>
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<td>Doriden(^\circ) (glutethimide)</td>
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<td>Dilantin(^\circ) (phenytoin sodium)</td>
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<td>Sulfonamides</td>
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<td>Gantrisin(^\circ) (sulfisoxazole diolamine)</td>
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<td>Estrogen</td>
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<td>All oral contraceptives</td>
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<td>Ergot preparations</td>
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<td>Aldomet(^\circ) (methyldopa)</td>
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<td>Orinase(^\circ) (tolbutamide)</td>
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<td>Diabenase(^\circ) (chlorpropamide)</td>
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<td>Alcohol in any form</td>
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<td>Talwin(^\circ) (pentazocine)</td>
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Other drugs that can precipitate an attack include Valium\(^\circ\) (diazepam) (which was used in the past but is now known to produce an acute attack); Librium\(^\circ\) (chlordiazepoxide hydrochloride); Miltown\(^\circ\) (meprobamate); Doriden\(^\circ\) (glutethimide); Dilantin\(^\circ\) (phenytoin sodium); sulfonamides; and Gantrisin\(^\circ\) (sulfisoxazole diolamine). In addition, estrogen and all oral contraceptives are contraindicated. Ergot preparations; Aldomet\(^\circ\) (methyldopa); Orinase\(^\circ\) (tolbutamide); Diabenase\(^\circ\) (chlorpropamide); and alcohol in any form are also contraindicated. Talwin\(^\circ\) (pentazocine) is one analgesic that porphyric patients cannot take for pain.\(^2,4\)

All regional, spinal, and epidural blocks should be avoided because any paralysis that results may be contributed to the block, even when it could be due to the porphyria.\(^2,4\)

Inhalation agents have been used safely. Halothane is successfully used in porphyric patients. Although the liver is the site of abnormal porphyric production, liver function tests in such patients are generally normal. However, from a medical-legal standpoint, it may be better to use enflurane.

Ketamine is the drug of choice for induction. If ketamine is contraindicated, Innovar,\(^\circ\) nitrous oxide/oxygen, Ethrane,\(^\circ\) or halothane induction will be satisfactory. There are no contraindications for muscle relaxants and narcotics.

Intraoperatively, one has to watch for an increase in pulse rate and blood pressure. Postoperatively, one should observe for any respiratory inadequacy and take appropriate supportive measures.

Treatment of a crisis is mainly accomplished by giving respiratory assistance with a respirator. Abdominal pain can be treated with chlorpromazine or Demerol\(^\circ\) (meperidine hydrochloride). Cortisone and ACTH have been used with apparent good results, but on the whole, they are disappointing.

**Conclusion**

The erythropoietic variety of porphyrias are not sensitive to barbiturates. They are characterized by photosensitive cutaneous lesions, hemolytic anemia, splenomegaly and an absence of porphobilinogen in the urine.

The hepatic porphyrias, (with the exception of porphyria cutanea tarda which is acquired), are sensitive to barbiturates and other enzyme inducing agents. They are differentiated by the absence of photosensitivity and the presence of porphobilinogen in the urine.

The overall picture of anesthetic management of porphyria is not gloomy; in fact, it can be managed well if one realizes the factors and drugs that precipitate acute attacks. It is therefore possible to prevent them.

**REFERENCES**


AUTHORS

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