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General Anesthesia in "Inducible" Porphyrias

Pertti Mustajoki, M.D., and Jussi Heinonen, M.D.†*

To evaluate the risk of inducing acute symptoms after general anesthesia in patients with "inducible" porphyrias, the authors analyzed retrospectively the effects of 78 exposures to anesthesia in 47 patients, 33 with acute intermittent porphyria and 14 with variegate porphyria. On 62 occasions, 29 involving the use of a barbiturate, anesthesia was induced in 37 patients who had no porphyric symptoms at the time. None of these patients had an acute attack postoperatively. Anesthesia was induced 16 times in 14 patients during acute episodes; 12 of these patients also received precipitating drugs other than anesthetics. Porphyric symptoms worsened in seven in the ten patients who received thiopental and in two of the four who did not. In the latent stages of acute intermittent and variegate porphyria in this patient population, the risk of incurring symptoms after exposure to thiopental and/or other anesthetics was small. During an acute episode thiopental may aggravate porphyric symptoms. (Key words: Anesthetics, intravenous: Anesthetics, volatile. Complications: porphyria. Hypnotics: barbiturates.)

ACUTE INTERMITTENT PORPHYRIA, variegate porphyria and hereditary coproporphyria are a group of inherited diseases that occasionally manifest as acute abdominal and neuropsychiatric symptoms. These symptoms are often induced by drugs that, under experimental conditions, are capable of inducing porphyrin biosynthesis. For this reason the porphyrias of this group have been recently named "inducible" porphyrias.[1]

The drugs most commonly associated with induced acute symptoms are barbiturates. Since the introduction of barbiturates into anesthetic practice, a number of cases have been described in which severe porphyric symptoms developed after the patients received one of these agents.[2–5] In some series, most or all patients given thiopental showed symptoms.[2,3,6,7] Other cases have been documented in which thiopental anesthesia caused no harm to patients with porphyria[5,8] but these are generally regarded as so exceptional as to deserve publication.[9]

During a study of porphyrias in Finland,[10] we encountered cases in which thiopental had been administered without adverse effect. This led to a systematic study of the risk in our patients with acute intermittent porphyria and variegate porphyria of incurring symptoms during or after general anesthesia. The results are not in accord with current opinion; provided the patient is in a latent stage of "inducible" porphyria, induction of porphyric symptoms by thiopental or other anesthetics must be exceptional.

Patients and Methods

The population studied comprised 168 patients with acute intermittent porphyria or variegate porphyria; most of them had been included in the previous study of porphyrias in Finland.[10] All traceable exposures of these patients to anesthesia were analyzed retrospectively from hospital records. In addition, 104 patients could be contacted personally or by letter to obtain further information about possible operations and the course of events after them. Thirty patients were not reached or did not respond to the questionnaire, and the remaining 34 had died before the study. Only cases with sufficiently detailed information about drugs given during anesthesia and about the pre- and post-operative courses were included in the study. The cases of 47 patients in whom anesthesia was induced a total of 78 times between 1952 and 1978 met these criteria.

Twenty-five additional operations were known to have been performed on 19 patients, but these cases were not included in the series because information about anesthesia and/or pre- and postoperative courses was lacking or incomplete. The available information in the 25 cases excluded from the study can be summarized as follows. Nine patients underwent a total of 11 exposures to anesthesia during latent stages of porphyria, and no porphyric symptoms were known to have occurred postoperatively. Fourteen episodes of anesthesia induced in ten patients had some association with porphyric symptoms. In eight of these instances, anesthesia apparently was induced during an acute attack. After three of them, abdominal symptoms diminished; after one (in which the anesthetic used was probably thiopental), they remained unchanged; and after three, the symptoms worsened, leading to paresis in two patients (one of the latter patients received diethyl ether); in one instance information about the immediate postoperative course was lacking but the patient recovered. For the remaining six episodes of anesthesia induced in four patients, information about the immediate preoperative symptoms was incomplete, *i.e.*, we do not know whether anesthesia was induced during an acute attack. One of these patients reported worsening of persistent porphyric paresis after two operations (sterilization and an orthopedic operation), but after a third operation symptoms

* Assistant Physician, Third Department of Medicine.
† Associate Professor in Anesthesia, Department of Anesthesia.
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Address reprint requests to Dr. Mustajoki.

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TABLE 1. Anesthetics and Adjuvants Given during Latent Stages of Porphyria

	Number of Exposures*	
	Before Diagnosis of Porphyria	After Diagnosis of Porphyria
Intravenous anesthetics		
Thiopental†	24	3
Hexobarbital†	2	
Propanidid	1	12
Ketamine†		2
Diazepam	2	4
Droperidol	2	5
Analgesics		
Meperidine	16	25
Morphine	9	2
Oxycodone	1	1
Fentanyl	3	7
Pentazocine†		1
Anileridine		2
Inhalational anesthetics		
Diethyl ether	5	1
Divinyl ether	1	
VAM‡	2	
Halothane	4	10
Methoxyflurane†	1	
Nitrous oxide	21	29
Neuromuscular blocking agents		
Succinylcholine	14	18
d-Tubocurarine	4	4
Alcuronium	5	8
Pancuronium	3	5
Other drugs		
Neostigmine	11	14
Atropine	18	30
Scopolamine	8	1
Promethazine	7	12

* The number of occasions on which each drug was used for anesthesia in the 37 patients. On 29 of the 62 occasions, anesthesia was induced before the diagnosis of porphyria was made.

† Drugs known to induce porphyrin synthesis in experimental animals.[27,28]

‡ A mixture of diethyl and divinyl ether, 3:1.

remained unchanged. Two patients had prolonged nonspecific symptoms without paresis or severe abdominal pain after cholecystectomy, and abortion and curettage, respectively. One patient, who had had porphyric paresis a year earlier, died after cesarean section.

The quantitative analytic methods used for the diagnosis of porphyria in this series have been described elsewhere.[10,11] Thirty-three of the 47 patients were diagnosed as having acute intermittent porphyria. Thirty of these diagnoses were based on definitely increased porphobilinogen excretion in the urine. In 11 of the 30 cases the diagnosis of acute intermittent porphyria was confirmed by demonstration that erythrocytic uroporphyrinogen I synthetase activity was subnormal. In the case of one patient, who was a member of a porphyric family but had normal urinary excretion of porphobilinogen, the diagnosis of acute intermittent porphyria was based only on the low activity of the enzyme. In two cases of patients who had died before the commencement of our study, the diagnosis of acute intermittent porphyria was based on a typical clinical picture, qualitative porphyrin analysis, and a positive family history. Fourteen patients were diagnosed as having variegate porphyria, and all of these diagnoses were based on increased fecal excretion of porphyrins. The families of 44 patients were known to include other members with porphyria.

Results

Anesthesia during a Latent Stage of Porphyria

On 62 occasions general anesthesia was induced in 37 patients (23 with acute intermittent porphyria and 14 with variegate porphyria) who had no symptom of porphyria at the time. Eighteen patients were known to have experienced at some time acute porphyric symptoms unrelated to anesthesia, while the others had been asymptomatic all their lives. The anesthetics were given for 19 gynecologic or obstetric operations, seven operations for varicose veins, four cholecystectomies, four appendectomies, six other abdominal operations, five cytoscopies, four operations for hemorrhoids, two hernioplasties, two orthopedic operations, and nine miscellaneous operations. In all 23 abdominal operations (in nine gynecologic operations the abdominal approach was used), the cause of symptoms was found to be a nonporphyric disease.

The drugs given for premedication and the anesthetics and adjuvants administered are listed in table 1. Barbiturates had been given during 29 anesthetic administrations to 18 patients (11 with acute intermittent porphyria, seven with variegate porphyria), whose mean age was 37.6 years, 12 being less than 30 years old. In the majority of cases a barbiturate had been given before the diagnosis of porphyria had been made, but for three operations on two patients thiopental was used inadvertently although the patients were known to have porphyria. Four of the 18 patients had received a barbiturate during anesthesia on two separate occasions, one patient during four and one during five anesthetic administrations. The last-mentioned patient was an 18-year-old woman who received thiopental for the first time when an inflamed appendix was removed. Eight months later a gynecologic examination was performed with anesthesia. After two months the patient underwent

TABLE 2. Anesthetics and Adjuvants Administered, and Pre- and Postoperative Data, for Patients Anesthetized during Acute Episodes of Porphyria

	Age (Years), Sex	Diagnosis*	Preoperative Drugs and Symptoms	Operation	Premedication, Anesthetics and Adjuvants	Postoperative Course and Drugs
Patient 1	23, F	AIP	Abdominal and back pain 6 days; sulfonamides	Appendectomy	Thiopental, droperidol, meperidine, fentanyl, N_2O, succinylcholine, neostigmine, atropine	Sulfonamide, amobarbital; worsening of pain, hysterical symptoms; discharged on 25th postoperative day
Patient 2	19, F	AIP	Abdominal pain 1 day	Appendectomy	Thiopental, meperidine, N_2O, succinylcholine, neostigmine, atropine	Sulfonamide, cyclobarbital; worsening of pain, weakness in legs; discharged on 23rd day
Patient 3	26, M	AIP	Abdominal pain 6 days, epileptic seizures	Laparotomy	Thiopental, morphine, N_2O, succinylcholine, alcuronium, neostigmine, atropine, scopolamine	Abdominal pain 17 days, paresis of abducens nerve; discharged on 26th day
Patient 4	26, F	VP	Abdominal pain 3 days	Curettage and culdocentesis	Thiopental	
			(1 day later)	Laparotomy	Thiopental, meperidine, fentanyl, N_2O, alcuronium, neostigmine, atropine	Sulfonamides; epileptic seizures, peripheral pareses; slow recovery
Patient 5	28, M	AIP	Peripheral pareses 8 days; meprobamate	Tracheostomy	Thiopental, halothane, N_2O, succinylcholine, atropine	Shock and sudden death from unknown cause on 4th day
Patient 6	16, F	AIP	Abdominal pain 12 days, epileptic seizures; diphenylhydantoin	Laparotomy	Thiopental, meperidine, halothane, N_2O, succinylcholine, alcuronium, neostigmine, atropine	Phenobarbital; abdominal and leg pain; discharged on 50th day
Patient 7	32, F	AIP	Abdominal pain 18 days; phenobarbital	Laparotomy	Thiopental, morphine, VAM,† *d*-tubocurarine, scopolamine	Pareses, death on 34th day
Patient 8	24, F	AIP	Abdominal pain 17 days	Laparotomy	Thiopental, morphine, VAM,† N_2O, *d*-tubocurarine, scopolamine	Phenobarbital; abdominal pain continued; discharged on 21st day
Patient 9	30, F	AIP	Pregnancy 1st trimester; abdominal pain 10 days, hyponatremia	Abortion and curettage	Thiopental, meperidine, N_2O, atropine	Abdominal pain subsided slowly; discharged on 10th day
Patient 10	20, M	AIP	Pareses 15 days; phenobarbital	Tracheostomy	Thiopental, halothane, N_2O, succinylcholine	No change in symptoms; slow recovery during several months
Patient 11	20, F	VP	Peripheral pareses 14 days; phenobarbital	Tracheostomy	Halothane, N_2O, atropine	No change in symptoms, slow recovery
			(2 months later)	Appendectomy	Halothane, N_2O	Recovery continued
Patient 12	22, F	AIP	Peripheral pareses 7 days; phenobarbital	Tracheostomy	Droperidol, fentanyl, N_2O, atropine	Pareses continued; death from pneumonia 3 months later
Patient 13	23, F	AIP	Abdominal pain 10 days; phenobarbital, amobarbital	Laparotomy	Diethyl ether	Phenobarbital; abdominal pain continued two weeks; discharged on 30th day
Patient 14	26, F	AIP	Abdominal pain 3 days	Appendectomy	Meperidine, VAM,† atropine, promethazine	Amobarbital; abdominal pain worsened temporarily, discharged on 12th day

* AIP = acute intermittent porphyria; VP = variegate porphyria.
† A mixture of diethyl and divinyl ether, 3:1.

a laparotomy for a suspected genital abscess, and 22 and 24 days postoperatively anesthesia was administered while the wound was debrided. A few years later this patient had a porphyric attack, but it was not associated with anesthesia.

In none of the 37 patients did a porphyric attack

develop in association with anesthesia. On inquiry, two patients reported having experienced an unusual feeling of weakness lasting a few days after the administration of anesthesia. One of them received thiopental with *d*-tubocurarine and ether; the other, nitrous oxide and halothane. However, the hospital records contained no mention of postoperative symptoms, and both patients were discharged in good condition after a usual period of hospitalization. One patient whose inflamed appendix was removed during anesthesia with thiopental–succinylcholine–nitrous oxide–halothane was discharged in apparently good condition on the fifth postoperative day. However, she reported later that she had been confused for a few days during her convalescence. A 22-year-old woman with variegate porphyria, who recovered some months earlier from complete paralysis due to porphyria, was inadvertently given thiopental when her tracheal stricture was corrected, but no symptom developed.

In two patients major complications occurred. In the first, a female patient, cardiac arrest occurred following induction of anesthesia in which nitrous oxide–halothane–succinylcholine was used, but she recovered completely. The second, a 66-year-old woman whose porphyria had been diagnosed 20 years earlier, was operated on because of hematemesis caused by diffuse gastric bleeding. She was operated on again three days later because of peritonitis. In both instances thiopental was administered inadvertently. After the second operation the patient became hypotensive and anuric, and she died on the third postoperative day. These symptoms are not those seen in an acute porphyric attack, and we believe they were complications of gastrointestinal bleeding, peritonitis, and surgery.

Anesthesia during Acute Episodes

In 14 patients, general anesthesia was induced while porphyric symptoms were present. The symptoms and the drugs used are summarized in table 2. Four patients had peripheral pareses with other porphyric symptoms before induction of anesthesia. The ten patients without preoperative pareses had abdominal pain, which lasted from one to 18 days (mean 8.8 days) and was associated with mental symptoms in three, epileptic seizures in two, red urine in two, and severe constipation and vomiting in two. Several patients also had nonabdominal pain, high blood pressure, and/or tachycardia. In one patient the only preoperative symptom was abdominal pain. Ten patients underwent laparotomy or appendectomy, and no cause for the abdominal symptoms was found during any of these operations.

Ten of the 14 patients received thiopental, and in seven of these the porphyric symptoms appeared to have worsened during the postoperative period; in three, abdominal symptoms progressed to pareses. Of the two patients receiving thiopental in the presence of pareses (Patients 5 and 10), one died suddenly from an unknown cause and the other made a slow recovery. Eight of the ten patients given thiopental had also received other drugs known to precipitate porphyric symptoms.

Four patients had not been given a barbiturate, but all of them had received other precipitating drugs during their illnesses. In two of these patients, who had pareses, the condition remained unchanged for several months, but one of them died from pneumonia three months after operation. In the third patient abdominal symptoms continued for two weeks postoperatively, and in the fourth patient the porphyric symptoms worsened temporarily.

Discussion

Dundee and Riding,[6] in their review article based on Dean's[2] earlier observations, were the first to focus attention on the dangers of thiopental anesthesia in porphyria. Since then, several reports of serious symptoms following barbiturate administration have been published.[7,12–16] In the extensive series reported by Eales,[4,5] a quarter of his patients with porphyric attacks had received thiopental before or during acute symptoms. In contrast to this, Ward[8] could not document precipitation of symptoms after any of 36 instances of anesthesia during which barbiturates were administered to patients diagnosed as having porphyria. However, Ward's results have been contested and have not been given serious attention because the classification of his patients was considered not to be clear.[4] In most other reviews of the subject, thiopental has been regarded as extremely hazardous, whether given in the latent stage of porphyria or during an acute attack.[16–20]

The results of our study show that, in our patient population, those who are in a latent stage of "inducible" porphyria incur only a slight risk of development of porphyric symptoms when undergoing operations with any of various anesthetics, including barbiturates. The effects of thiopental and other anesthetics during acute attacks are more difficult to evaluate, both because of the variety of drugs given and because the number of patients was small. However, the apparent exacerbation of porphyric symptoms in most patients after administration of thiopental suggests that this anesthetic is harmful when given to a patient experiencing actual porphyric symptoms. These results are in accord with earlier reports that barbiturate anesthetics given during an acute attack may worsen

the symptoms.[7,13,14] However, our results do not bear out current opinion concerning the danger of thiopental anesthesia in latent porphyria.

To explain the benignity of thiopental in our patients with latent porphyria, we have tried to identify some inherent cause in the series. Special attention was given to validating the diagnoses in these cases, and we believe there is no doubt that all of the patients had either acute intermittent porphyria or variegate porphyria, *i.e.*, one of the "inducible" porphyrias. The mean age of our patients at the time of operation was greater than the age at which patients are most susceptible to symptoms of "inducible" porphyria.[10,21] However, 12 procedures were done with thiopental anesthesia in patients less than 30 years of age, and none of these patients experienced symptoms.

It is now generally accepted that primary abnormalities in porphyrias are specific enzyme deficiencies along the biosynthetic pathway of heme. These deficiencies have been demonstrated by investigators in various countries and, in the case of acute intermittent porphyria, also in Finland,[11] showing the uniformity of porphyrias in different parts of the world. Variegate porphyria is the only porphyria in which such an enzyme defect has not been measured directly, but the excretion patterns of porphyrins with this porphyria are similar in Finland[10] and South Africa.[3] Therefore, we believe that acute intermittent porphyria and variegate porphyria are the same diseases in Finland as in other parts of the world. The possibility cannot be excluded that other genetically determined racial characteristics or even environmental factors may have altered the proneness of our patients to porphyric symptoms. However, it appears unlikely that such differences would have any influence on our results, since half of our patients manifested symptoms on other occasions. We therefore conclude that our results are probably relevant to "inducible" porphyrias in general.

The reported cases in which barbiturate anesthesia in an asymptomatic patient precipitated acute symptoms are mostly from South Africa, where the prevalence of variegate porphyria is very high.[3] In the series of Eales,[5] several patients had received thiopental, apparently in the latent stage. Dean[3] has also described such cases. From other parts of the world reports are few; we could find only half a dozen published cases.[7,12,16] Two points in these reports deserve attention. First, in many instances other precipitating drugs were given,[5,7] which makes it difficult to evaluate the role of the anesthetic. Second, it is probable that only cases of patients in whom symptoms developed have been reported, *i.e.*, the cases are selected, which is likely to distort the general picture. There are only two studies, those of Ward[8] and our own, in which an effort has been made to avoid selection. In these studies altogether 65 episodes of anesthesia with barbiturates were analyzed, and none of them led to a porphyric attack. We therefore conclude that although thiopental may occasionally induce symptoms in latent porphyria, this must be rare.

Because of the apparent rarity of symptoms even after known precipitating drugs, case reports[22] or even larger series[23] describing successful use of a particular anesthetic in patients with latent porphyria are of relatively little value. Other approaches for testing drugs include *in-vitro* systems and experimental animals, in which barbiturates, certain steroids, and several other drugs have been found to induce porphyrin synthesis.[24,25] Moore and Parikh[26,27] performed systematic tests of different anesthetic agents in rats and determined levels of δ-aminolevulinic acid synthetase as a measure of the induction of porphyrin synthesis. Of the great number of agents tested, two barbiturates (thiopental and methohexital), Althesin®, and etomidate were found to strongly induce porphyrin synthesis, and moderate responses were found with chlordiazepoxide, pentazocine, enflurane, and methoxyflurane. Ketamine was without effect in rat,[26,27] but has been found to induce δ-animolevulinic acid synthetase formation in the liver of the chicken embryo.[28] These results are difficult to relate to porphyria, because the porphyrinogenic effects of chemicals in experimental animals probably differs from those in the human body.[24,29] However, experimental systems afford the only means for testing the potential dangers of drugs. Therefore, although anesthetics that induce porphyrin synthesis in experimental animals seem usually to be harmless when given in therapeutic concentrations to patients with latent porphyria, it may be wise to avoid these drugs if alternative agents are available.

It is reassuring and of some interest that drugs that do induce porphyrin synthesis are not usually capable of causing clinical manifestations in a latent stage of "inducible" porphyrias. Although our results do not exclude the possibility that drugs other than anesthetics may be more dangerous in porphyria, we believe that in general the role of precipitating agents in the induction of porphyric symptoms has been overestimated. The beginning of an acute attack is obviously a complex event and it is probable that drugs may be harmful only in association with other factors precipitating the development of symptoms.

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