Medical Intelligence

Porphyria and Its Relation to Anesthesia

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Hospital admissions in Seattle over an 11-year period were reviewed to determine the risk of precipitating respiratory paralysis by barbiturates in patients with undiagnosed porphyria. There were 66 cases of porphyria with 163 hospital admissions, an incidence of 1 in 7,088 admissions. The group received 44 anesthetics, and barbiturates on 110 occasions. Three patients receiving barbiturates developed complications, but not those typical of these drugs. Anesthetics other than barbiturates were well tolerated. Two patients outside the scope of the study were found to have suffered respiratory paralysis after receiving barbiturates. The data suggest that barbiturates should be avoided in patients with porphyria, but not abandoned for anesthesia in the general population on the remote possibility that paralysis might be induced in a patient with undiagnosed phorphyria.

Symptoms of porphyria, primarily an hereditary metabolic disorder, have been known to be precipitated by barbiturate administration. Schultz described the disease in 1874, presenting the case history of a 33 year old man with dermal photosensitivity and dark red urine. In 1906, three years after the introduction of the barbiturates to clinical medicine, Dobrschansky described a typical case of acute intermittent porphyria apparently caused by prolonged administration of diethylbarbituric acid. Earlier, in 1889, a drug similar in action to the barbiturates, sulphanal, had been implicated in the death of a woman whose urine had turned red.

Recently, Dundee and Riding found 32 cases in the literature from 1948 to 1953, in which porphyria was associated with administration of anesthetics. In this series, 13 patients received thiopental and subsequently developed respiratory paralysis, which was fatal in 5 cases. In 1962, Dundee, McCleery and McLaughlin described 3 cases of porphyria apparently precipitated by thiobarbiturate administration. Two of the three patients died.

The acute intermittent form of porphyria is most commonly aggravated by barbiturates in which typical findings are usually those of nervous system derangement. These include abdominal pain, constipation, vomiting, tachycardia, arterial hypertension, mental symptoms and, less frequently, motor or sensory disturbances. Death is usually due to respiratory paralysis. Hepatic changes are of no consequence. The basic abnormality in porphyria is as yet unknown, nor can the clinical manifestations of the disease be explained wholly on the basis of over-production of porphyrinomers by the liver.

The incidence of porphyria is equally obscure. Waldenstrom found an incidence of 1 in 1,000 in Lapland, while in southern Sweden he found it to be 1.5 in 100,000. In South Africa, the incidence among both the Bantu and whites is 1 in 100. In western Australia it is 2.4 in 100,000. In the Irish Free State the incidence is 1 in 80,000, while in Northern Ireland the ratio is much higher, being 1 in 5,000.

There is no report on the frequency with which patients with porphyria are hospitalized or anesthetized. In addition, no information is available on the frequency of complications following anesthesia administered to patients with porphyria. However, Goldberg in a study of 50 patients with porphyria noted that respiratory paralysis was three times more frequent in those who had received barbiturates. Eales states that "Pentothal sodium anesthesia is frequently followed by catastrophic attacks." If this statement is true, por-

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Porphyria is of special interest in anesthesia, since barbiturates are frequently used for induction. Furthermore, patients with undiagnosed porphyria may require anesthesia for any of several reasons, including laparotomy for abdominal pain or cystoscopy for "blood in the urine." To determine the frequency of complications following barbiturate administration in patients with porphyria, the following study was undertaken.

Survey

The records of all patients admitted to hospitals in the greater Seattle area between January 1, 1952, and December 31, 1962, were reviewed. Yearly admissions, excluding newborn infants, were totaled along with the number of anesthetics administered, excluding local anesthetic infiltrations. The name of every patient who had a recorded diagnosis of porphyria was listed. If the diagnosis of porphyria was confirmed by adequate urinary analysis, that patient was included in the survey. During the time span covered, most of the laboratories changed from a qualitative to a quantitative urinary analytic procedure for porphyrins. A positive diagnosis of porphyria was considered adequate in either case. Individuals were eliminated from the survey in whom only traces could be found in the urine, and several patients in whom the diagnosis was made only on clinical grounds. Patients' names were cross-referenced through all hospitals to include every hospitalization. Especially noted in the records were administration of barbiturates, frequency and types of operation, anesthetic procedure and agents used, and subsequent complications.

Results

There were 1,155,411 admissions to hospitals in the greater Seattle area and 622,412 anesthetics administered. The overall percentage of anesthetics in relation to admissions was 54 per cent. Sixty-six patients, 32 men and 34 women, were found with proven porphyria. This group had 163 hospital admissions, providing a rate of 1 in 7,088 admissions. The men had 55 admissions, or 1.7 admissions per patient. The women had 108 admissions, or 3.2 admissions per patient. The youngest patient was 9, the oldest 68.

Caudal, spinal, extremity blocks and general anesthesia were used. Anesthetic agents and adjuncts included halothane, cyclopropane, ether, succinylcholine, d-tubocurarine, nitrous oxide, thiopental and thiamylal. Twenty-one of the 66 patients received a total of 44 anesthetics, 36 of which were induced with barbiturates. In 25 instances, an additional barbiturate was given, either preoperatively or postoperatively. Five of the 8 patients who received non-barbiturate anesthetics were given barbiturates at some other time during hospitalization. Only 3 of the 21 patients were not given barbiturates during a hospitalization.

Forty-five patients with porphyria were not anesthetized. During their hospitalizations, 15 of these patients were given barbiturates on 44 occasions. In none of these instances were complications recorded. In 3 cases, a barbiturate was given to precipitate porphyrimuria for diagnostic purposes.

Thus, 36 patients with porphyria were given barbiturates on 110 occasions. Most of these patients received barbiturates more than once.

Complications: Patients with porphyria apparently tolerated all types of anesthesia and anesthetic agents other than barbiturates in a normal manner. Complications following anesthesia were reported in only 3 cases. A 40 year old white woman had mild leg pains for 2 days after receiving thiopental nitrous oxide anesthesia for uterine dilatation and curettage. A 68 year old white man, seriously ill with cirrhosis of the liver, was given thiopental nitrous oxide and d-tubocurarine for a laparotomy. On the third postoperative day he became confused, developed a wound dehiscence, and died of cirrhosis and multiple abdominal wound abscesses 40 days later. A 49 year old white man was given thiopental-nitrous oxide-ether cyclopropane and succinylcholine for an appendectomy. On the fifth postoperative day he developed hepatic failure, which cleared in two months with supportive care.

There were 4 deaths in the nonanesthetized group. One patient with porphyria and a history of barbiturate administration was admitted with a stroke, fatal within 24 hours of onset. Three other patients were admitted with fatal respiratory paralysis. The onset of symptoms first was noticed in one of these.
patients following a thiopental anesthetic, given for a shoulder manipulation in another city two years prior to the present admission. Since these patients had been admitted to, but received no anesthetics in, hospitals participating in this study, they were not included as complications.

In addition, one patient was admitted for treatment of paralysis which originally occurred after a thiobarbiturate anesthetic for an appendectomy in another city. The paralysis gradually and partially cleared with supportive treatment. During her Seattle hospitalization she was given cyclopropane d-tubocurarine anesthesia for a hysterectomy without complication. She is included in the group of 3 who had anesthesia without barbiturate during a Seattle hospitalization.

Thus, within the scope of the survey, there were only two serious complications, possibly due to barbiturate anesthesia in patients with porphyria, for an overall incidence of 1 in 311,206 anesthetics. If one excludes the patient with prior cirrhosis as not a true instance of barbiturate-porphyrin incompatibility, the incidence is 1 in 622,412. Among the patients with known porphyria the incidence of complications was 2 in 110 barbiturate administrations.

Discussion

It is probable that a number of patients with porphyria may have been hospitalized without the diagnosis being made. The exact number of cases of porphyria that were missed is therefore unknown. However, the records of the hospitals surveyed permitted easy identification of all of the patients with a positive diagnosis.

Barbiturates are apparently capable of precipitating respiratory paralysis in patients with porphyria. This is substantiated to some extent by the fact that two patients outside the scope of this study were found to have suffered respiratory paralysis immediately after receiving barbiturate anesthesia. However, the reaction must be rare, since it did not occur once in 622,412 consecutive anesthetics administered over an 11-year period in Seattle. Nor was it found in 110 instances when barbiturates were administered for anesthetic or sedative purposes to patients with known porphyria. It can reasonably be assumed that all major complications were noted in the patients studied. A complication so severe as respiratory paralysis could not have occurred postoperatively without being noted. Thus, in this study, Eales' statement, "Pentothal sodium anesthesia is frequently followed by catastrophic attacks," could not be confirmed.

The two serious complications which occurred in patients anesthetized with barbiturates were hepatic failure. One occurred in a man dying of cirrhosis of the liver; his death probably bore no relation to anesthesia. The other patient, a 49 year old man, had a strongly positive porphobilinogenuria on his fifth postoperative day, the very day that liver function tests were found to be markedly abnormal. This may be an instance of hepatic cellular damage and increased urine porphyrin excretion, as demonstrated by Nesbitt and Snell in 1942. The patient may not have had true acute intermittent porphyria. In any event, hepatic failure is not a complication of porphyria, alleged to be frequently caused by barbiturates.

The rarity of paralysis following barbiturate administration to patients with porphyria does not mean the problem should be ignored. A logical course of action in treatment of patients with porphyria is avoidance of the barbiturates. But it is not logical to abandon the use of these drugs in anesthesia generally, on the remote possibility that paralysis might be induced in a patient with undiagnosed porphyria.

Summary

Eleven years of hospital admissions in the greater Seattle area were surveyed. Hospital admissions, number of anesthetics, patients with porphyria, and anesthetic complications in these patients were noted. There were 1,155,411 hospital admissions and 622,412 anesthetics administered. Sixty-six patients with porphyria were found. Twenty-one of these patients were given 44 anesthetics, 36 of which were barbiturate-induced. In addition, 5 patients were given supplemental barbiturates. In 15 instances, patients were not anesthetized, but were given barbiturates during hospitalization. Thirty-six patients, therefore, were given barbiturates on 110 occasions.
No patients developed paralysis following barbiturate administration. Two patients developed hepatic failure postoperatively. Two patients with porphyria were observed who had developed paralysis after a barbiturate anesthetic administered elsewhere.

Barbiturates may precipitate an acute porphyric attack in the susceptible patient, but the complication seems to be extremely rare.

References

LOCAL VASOCONSTRICTION The local ischemic effects of three types of vasoconstrictor substances were compared. Octapressin, a cyclic polypeptide of the neuro-hypophyseal type, epinephrine and norepinephrine, and hypertensin were infiltrated into the cutis or subcutis. Four parameters were studied: (1) Radioactivity of excised abdominal skin after intravenous injection of Rb$^{85}$Cl. The vasoconstrictor drugs and controls were injected intracutaneously five minutes before the injection of the rubidium isotope. Octapressin produced the greatest decrease in radioactivity, e.g., the greatest vasoconstrictor effect, hypertensin the least, and epinephrine an intermediate decrease as compared with saline control wheals. (2) Prolongation of local anesthetic effect of procaine after addition of the three vasoconstrictor substances. Octapressin was considerably more potent (33 times) than epinephrine which, in turn, was 100 to 1000 times more effective than hypertensin. Dose response curves were significant for octapressin and epinephrine, but quite shallow in case of hypertensin. (3) Inhibition of bradykinin-induced edema. Octapressin was more potent than norepinephrine, with epinephrine showing intermediate potency. Hypertensin was practically without effect. (4) Delay of onset of strychnine convulsions. The potency in this parameter was in the order octapressin, epinephrine, norepinephrine, hypertensin. The results contrast with the potency of these drugs in respect to systemic effects. This may be explained by their different site of action: hypertensin acting mostly on resistance vessels, octapressin mostly on capacitance (post-arteriolar) vessels, while the catecholamines seem to constrict both vascular areas. (Berde, B., Schalch, W. R., and Docquier, W.: Local Vasoconstrictor Activity of Octapressin, Epinephrin and Hypertensin, Helv. Physiol. Pharmacol. Acta 22: 110 (Aug.) 1964.)