A REPORT ON PROPANIDID, AN INTRAVENOUS ANAESTHETIC, IN PORPHYRIA VARIEGATA*

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The first account of acute porphyria after taking barbiturates was described in 1906 by Dobrschansky.[1] Since then barbiturates, particularly the pentobarbitones, have been the commonest drug to cause attacks of acute porphyria in all 3 Mendelian-dominant hepatic porphyrias, intermittent acute porphyria, porphyria variegata and coproporphyria. Acute porphyria may result in the paralysis and death of the patient.

Among the South African White population porphyria variegata is common.[2] In the adult who has inherited porphyria variegata there is usually, but not always, a high excretion of proto- and coproporphyrin in the stool.[3] At the Eastern Cape Provincial Hospital before 1959 we would diagnose, on average, 12 cases of acute porphyria each year. Acute attacks of porphyria were so regular an occurrence and so frequently followed a thiopentone anaesthetic that it was decided in 1959 to examine the stools of all patients admitted to hospital in Port Elizabeth for excess porphyrin before an intravenous thiopentone anaesthetic was administered. Following the introduction of routine stool testing, it became possible to estimate the prevalence of porphyria in the White population of the Eastern Cape and later in South Africa as a whole. The prevalence of porphyria variegata in the Eastern Cape is 1 in 250 and for the whole of South Africa it is estimated to be 1 in 400 of the White population. Over 9,000 of the White population of South Africa have inherited porphyria variegata.[4] It is also fairly common among the Coloured people of South Africa. I have attended 54 patients who have developed acute porphyria after a thiopentone anaesthetic, although thiopentone was not the only barbiturate used in every case. Thiopentone does not always precipitate an acute attack of porphyria variegata when the disorder has been inherited. In children and old people acute attacks are rare, but in adults between the ages of 16 and 60 years thiopentone will usually precipitate at least a mild attack of acute porphyria.

The routine screening test of the stool for porphyria variegata is very simple.[3] A small fragment of stool, such as can be obtained, if necessary, on the gloved finger on rectal examination, is dissolved in a solvent consisting of equal parts of amyl alcohol, glacial acetic acid and ether; after the solution has been decanted it is examined in ultraviolet light.[4] In adults with porphyria variegata there is usually a high excretion of porphyrin in the stool and the decanted solution will show a brilliant pink fluorescence in ultraviolet light. Chlorophyll will also show a pink fluorescence, but when N/1 hydrochloric acid is added to the solution and the mixture is shaken the porphyrin will settle in the acid solution at the bottom and the chlorophyll will stay in the ether solution at the top. If the diagnosis is in doubt, it can then be confirmed by examination of the urine for porphyrin and by a quantitative analysis of the stool porphyrin using the method of Holti and Rimington.[5] There are other conditions besides porphyria variegata which can cause an increase in stool porphyrin, such as, for instance, carcinoma of the stomach, and therefore not every patient with increased stool porphyrin has necessarily inherited porphyria variegata. However, it is usually fairly simple—by repeating the screening examination, carrying out quantitative analysis of the stool porphyrin and by obtaining a personal and family history of a sensitive skin on the back of the hands or attacks of acute porphyria—to confirm the diagnosis. Porphobilinogen, which can be detected by the Watson-Schwartz test using Ehrlich's aldehyde reagent, will only be positive in porphyria variegata during an acute attack. The Watson-Schwartz test, therefore, cannot be used for screening for porphyria variegata in the quiescent phase. The urine should also be examined for excess porphyrin.

After the introduction of routine testing for porphyria variegata before operation in the Eastern Cape, patients who had positive stools on screening and who might therefore have been porphyric were given an alternative anaesthetic to thiopentone, such as gas, oxygen and ether, although only a proportion of these patients had inherited porphyria variegata. In the others there was usually only a slight transient increase in porphyrin or there was pathology in the gastro-intestinal tract.

Porphyria occurs relatively frequently in South Africa because a small nucleus of early settlers have become a people so that over one-third of South Africa's 3½ million White population hold 40 family names which they have derived from 40 original Free Burghers.[5] One of the early Free Burghers happened by chance to carry the gene for porphyria variegata. Porphyria variegata in South Africa has been traced back to either Gerrit the son of Jan, or his wife Ariaantje the daughter of Jacob who married at the Cape in 1688.[6]

Routine testing for porphyria variegata in Port Elizabeth and in other Eastern Cape towns greatly reduced the number of patients who developed acute porphyria each year, but nevertheless every year 2 or 3 patients are still seen with a severe attack of acute porphyria, often after a thiopentone anaesthetic, because for some reason the routine test had been neglected or occasionally because the increased porphyrin excretion was so slight that it was not considered likely that the patient had porphyria variegata. Many thousands of thiopentone anaesthetics are given in South Africa each year and the possibility that the patient has porphyria variegata has created a most serious problem for anaesthetists. It is not always easy to obtain a specimen to carry out a routine test before operation, and with a large number of patients the routine testing does create considerable additional effort for the hospital staff.

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TABLE I. PATIENTS WITH PORPHYRIA VARIEGATA ANAESTHETIZED WITH PROPANIDID

Case No.	Sex	Age	Propanidid (mg.)	Operation	Urine: Porphobilinogen Watson-Schwartz test	Urine: Porphyrin UVL screen	Stool: UVL screen	Stool: Copro-porphyrin µg./G dry wt.	Stool: Proto-porphyrin µg./G dry wt.	Family history	Personal history
1	F	39	400	Curette	Neg.	+++	+++++			+	Sister had acute porphyria after thiopentone.
			400	Abscess in ear	Neg.	++	+++++				
2	F	18	400	Curette	Neg.	+++	+++++			+	Father acute porphyria after thiopentone.
3	F		350	Dental clearance	Neg.	+++	+++++		186	+	Father died acute porphyria after thiopentone.
4	F	31	400	Curette	—	+++	+++	223	378	+	Acute porphyria after thiopentone.
			500	Hysterectomy	Neg.	+++	+++				
			300	Cystoscopy	Neg.	+++	+++				
5	F	42	400	Insertion radium	Neg.	++	+++++	496	1,134	+	Previous acute porphyria after barbiturates.
			400	„ 2 weeks later	Neg.	++	+++++				
			400	„ 2 weeks later	Neg.	++	+++++				
6	F	32	400	Curette	Neg.	++	++	81	287	+	
7	M	52	300	Haemorrhoidectomy 6/6/67	Neg. 10/6/67 20·8 µg./litre (Pos. 1/5/67)	+++ Copro. 2,959 µg./litre Uro. 419 µg./litre	++++	424	521	+	Acute porphyria (*a*) 1958 (*b*) One month before propanidid both after barbiturates.
			300	Liver biopsy	Neg.		++++				
8	F	19	500	Appendicectomy	Pos.	+++++ like Coca-Cola	++++	484	700	+	Acute porphyria after barbiturates.
	F		350	Tonsillectomy	Neg.	+	++	250	451	+	Stool porphyrin raised. Confirmed by Rimington. X-porphyrin 91 µg./G.
10	M	38	400	Hernia repair	Neg.	++	++			+	Acute porphyria 1956, thiopentone.
11	F	13	250	Antrum wash-out	Neg.	++	+			+	
12	F	27	500	Bartholin cyst removed	Neg.	++	++			+	Previous acute porphyria thiopentone (*a*) 1961, (*b*) 1964. Mother had acute porphyria Groote Schuur. Aunt died acute porphyria Watford Hospital, England, 1962.
			350	Curette cervix	Neg.	++	++				
13	F	38	500	Abscess jaw	Neg.	—	—			+	Acute porphyria 1956 after thiopentone. Skin lesions previously. Now porphyria quiescent.
			350	Dilatation cervix	Neg.	—	+				
			500	Operation on jaw	Neg.	—	+				
			350	Operation on jaw	Neg.	—	+				
14	M	19	350	Dental extractions	Neg.	+	+	31	68	+	Father has had acute porphyria.
15	F	18	400	Draining pilonidal abscess	Neg.	+	+	43	170	+	
16	M	69	350	Bronchoscopy Ca. lung	Neg.	+	++++			+	Skin lesions of porphyria when a young man.
17	M	31	300	ECT 7/12/67	Neg.	++	+			+	No ill-effects from repeated propanidid anaesthetic.
			300	14/12/67	Neg.	++	+				
			300	19/12/67	Neg.	++	+				
			300	21/12/67	Neg.	++	+				
			300	3/1/68	Neg.	++	+				
			300	4/1/68	Neg.	++	+				
18	F	49	350	Cholecystectomy	Neg.	++	+	32	74	+	High stool porphyrin 1960.
19	F	49	400	D & C	Neg.	++	++			+	Previous acute porphyria barbiturates, Groote Schuur, 1955. Sister acute porphyria after thiopentone.
20	F	44	350	Hysterectomy	Neg.	+	+			+	Known porphyric.
			350	Vaginal repair	Neg.	+	+				
21	F	15	350	Dental attention	Neg.	+	+			+	Delay in doing Watson-Schwartz test. No ill-effects from anaesthetic.
22	M	15	350	Dental attention	Neg.	+	+++			+	
23	M	55	350	Haemorrhoidectomy	Neg.	+	+++	295	383	+	
24	F	28	350	Curette	Neg.	++	++++	366	731	+	Mother died acute porphyria after thiopentone.
25	F	17	350	Tonsillectomy	Neg.	—	+++	349 192	314 203	+	Father died acute porphyria after barbiturates.
26	F	34	350	Removal of scar	Neg.	+++	+++++	953	702	+	
27	F	36	300	Angiogram	Neg.	+				+	
			300	Laparotomy	Neg.	—	+	47 58	140 26		
28	F	41	300	Colporrhaphy	Neg.	++	+	222	118	+	
29	M	44	350	Removal cartilage knee	Neg.	+	+			+	Sister died acute porphyria after thiopentone.
30	M	49	400	Resection of polyp	Neg. 10·1 µg./litre	+++ Uro. 53 µg./litre	—			+	Previous acute porphyria after thiopentone. Skin lesions as a young man. Porphyria now quiescent. Daughter acute porphyria.
			400	Tympanoplasty	Neg.	+	—				
31	F	30	350	Curettage	Neg.	+	++++	816	655	+	Previous acute porphyria after thiopentone. Paralysed 6 months.
32	F	27	350	Thyroidectomy	Neg.	++	+++++	481	735	+	Became partly paralysed after pentobarbitone. D & C 1965.

The range of normal for quantitative porphyrin in stool is taken as coproporphyrin 0–36, protoporphyrin 0–113 µg./G dry weight. A total porphyrin about 80 µg./G is suspicious of porphyria.

PROPANIDID

In the early 1960s a short-acting non-barbiturate intravenous anaesthetic, Fabantol, was introduced (Epontol in the United Kingdom—generic name propanidid). It is a pale yellowish oil, insoluble in water.

The usual anaesthetic dose of propanidid for adults is between 5 and 10 mg./kg. of body-weight, given in a 5% solution. It is given at an injection speed of 1 ml./2 seconds and produces a rapid, smooth anaesthetic induction, consciousness being lost after 1 arm-brain circulation time. As with thiopentone, excitatory phenomena are sometimes seen during induction when atropine only is used as a premedicant, but this is very rare when an opiate premedicant is used. Recovery of consciousness is related to dosage and begins 3 - 6 minutes after a single injection and is usually complete within 5 or 10 minutes. After induction with propanidid it is practical to continue the anaesthetic with gas and oxygen and other anaesthetics. There is a very rapid recovery time when propanidid is given alone, and the majority of patients are able to leave hospital within 20 minutes of the anaesthetic. Propanidid is therefore excellent for minor operations. It is generally well tolerated, and nausea and vomiting are rare when it is used as the sole anaesthetic agent.[7,8]

Dowdle studied the effects of the drug on the porphyrin production of embryo chicks and concluded that the drug did cause some slight increase in porphyrin production.[9]

The Present Study

Because of the unknown effects of propanidid in patients with porphyria variegata, it was not possible to recommend that the drug be tried out in an experimental form. The anaesthetists in Port Elizabeth and Dr A. C. Anderson of Bloemfontein took part in this study by informing me when any patient who was suspected to have porphyria variegata had, at their discretion, been given propanidid. These patients were usually studied in hospital after the operation. Their personal and family history was taken, and they were examined for a sensitive skin on the back of the hands. Their stools were examined for excess porphyrin, and when there was any doubt about the diagnosis a quantitative porphyrin analysis was carried out by the South African Institute for Medical Research, Johannesburg. The urine was examined for porphyrin and porphobilinogen on a number of occasions after the anaesthetic. After full study, about half of the suspected patients who had a positive stool test on routine screening were found to have inherited porphyria variegata.

RESULTS

Thirty-two patients, 9 men and 23 women, with proved porphyria variegata who had been given 50 propanidid anaesthetics, have been studied over a period of a year. Twenty-eight of these patients with porphyria variegata were given the propanidid anaesthetic in Port Elizabeth (Table I). The other 4 patients were treated in Bloemfontein. Only one patient, who was almost certainly in an acute attack at the time of the anaesthetic, had any symptoms suggestive of acute porphyria after the propanidid anaesthetic. They all made uneventful recoveries. In no patient did the Watson-Schwartz test become positive when it was previously negative, and in the case of the patient with acute porphyria, where the Watson-Schwartz test was positive on the day following the anaesthetic, it became negative after a week. Six of these patients had suffered from attacks of acute porphyria in the past after a thiopentone anaesthetic, and a further 4 had had acute porphyria after other barbiturate drugs. Most of these patients had relatives who had developed acute porphyria following thiopentone or barbiturate drugs.

One patient (No. 7) was treated by me for an attack of acute porphyria only 4 weeks before the propanidid anaesthetic. During the acute attack, which followed barbiturate sleeping tablets, the Watson-Schwartz test was strongly positive. The patient suffered severe abdominal pain and had attacks of vomiting. Four weeks later, at the time of the propanidid anaesthetic, the Watson-Schwartz test had become negative. In spite of the recent acute attack of porphyria the propanidid caused no flare-up of porphyric symptoms and the Watson-Schwartz test for porphobilinogen remained negative. Patient No. 8, who knew she had inherited porphyria, developed abdominal pain after taking barbiturate sleeping tablets. Her doctor made a presumptive diagnosis of acute appendicitis and removed her appendix, using propanidid to induce anaesthesia. On the following day the Watson-Schwartz test was strongly positive and for a few days the abdominal pain persisted. The appendix appeared to be normal. Over the period of a week the patient made a good recovery and the Watson-Schwartz test for porphobilinogen became negative. In my opinion the patient was in an acute attack of porphyria at the time of operation.

SUMMARY

A retrospective study of 32 patients with porphyria variegata who were given 50 propanidid anaesthetics showed no adverse reactions to the anaesthetic and in no patient was an attack of acute porphyria precipitated. Furthermore, acute porphyria after a propanidid anaesthetic has not been reported in Port Elizabeth or elsewhere in South Africa.

When propanidid is used as an anaesthetic in porphyria variegata great care must be taken that no barbiturate sedative is given either pre-operatively or postoperatively.

Propanidid appears to be a safe intravenous anaesthetic for patients who have inherited porphyria variegata.

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