

PORPHYRIN METABOLISM AND BARBITURATE POISONING: OBSERVATIONS ON CASES OF ACUTE AND CHRONIC POISONING

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The connexion between acute porphyria and barbiturate poisoning was pointed out by Waldenström (1939), who stated that practically all fatal cases of acute porphyria had been treated with large doses of barbiturates; on the other hand, the less severe cases as a rule received no such treatment, and further (Waldenström, 1940) in the majority of cases of acute porphyria large quantities of, for example, isophen, veronal, luminal, or dial, had been taken immediately preceding an attack of severe porphyria with pareses, and he mentioned further that cases with paralytic attacks of this disease without a history of taking barbiturates were in his experience very rare. In his two brief communications Waldenström presented no material in support of these important statements, but his monograph (1937) on acute porphyria includes some cases where attacks of porphyria were provoked by barbiturates. No systematic studies on the connexion between the drugs taken and the acute attacks of porphyria were carried out on the clinical material of 103 cases presented in Waldenström's classic monograph.

Later several writers presented clinical observations supporting Waldenström's statements (e.g., Hug, 1945; Jørgensen and With, 1945, 1947; Dalseth, 1955), and moreover animal experiments have shown that barbiturates and allied substances may cause conditions much like acute porphyria in rodents and chick embryos (Schmid and Schwartz, 1952; Goldberg, 1954; Talman, Case, Nevé, Labbe, and Aldrich, 1955). The reports of Nielsen (1953) and Plum (1954) from a Danish mental hospital, where several cases of acute porphyria developed among the patients during a short period, are, however, brief and preliminary and not entirely satisfactory from a clinical point of view (cf. With, 1953, 1955).

On the other hand some investigators have questioned Waldenström's hypothesis. Thus Nilsson (1946) was unable to find any connexion

between attacks of acute porphyria and barbiturate intake, and Jørgensen and Voldby (1949) report a case of acute porphyria where high doses of barbiturates were tolerated both during attacks and free periods for years, apparently without influence on the porphyria.

Because of this controversial evidence it seemed important to study the influence of acute and chronic barbiturate poisoning on the porphyrin excretion in man, and especially to decide whether barbiturates are capable of producing acute porphyria in normal subjects as they seem to do in certain rodents. If this were correct one would expect a significant rise in the porphyrin excretion or an excretion of porphobilinogen in acute and chronic barbiturate poisoning in man, and failing such an increase one would be inclined to regard the occasional cases of acute porphyria provoked by barbiturates and allied substances as instances of latent porphyria rendered manifest by the poisoning.

Material

Twenty-three cases of acute barbiturate poisoning and four cases of acute carbon monoxide poisoning from the poisoning centre of Copenhagen at Bispebjerg Hospital were studied. Twenty-five male patients from the State Mental Hospital at Middelfart provided the material for the study of chronic barbiturate poisoning; four cases of chronic alcoholism were also included in the study. The age of the patients was 25–70 years. The urine of the acute cases was subjected to analysis every day or with a few days' interval, but in the chronic cases the urine was only studied at weekly intervals. The 24-hour urine was analysed whenever possible; in the chronic cases the first urine voided after the patient was admitted to the hospital was also studied.

The data are given in Tables I and II. It was not always possible to obtain reliable information concerning the doses of barbiturate, but in all

cases the clinical diagnosis of barbiturate poisoning was established with reasonable certainty, and in most of the acute cases was confirmed by blood barbiturate analysis. Many of the patients with chronic barbiturate poisoning suffered from other conditions besides the poisoning, e.g., chronic encephalitis, mental depression, schizophrenia, and various narcomanias.

Methods

The method of porphyrin analysis was the same as described in an earlier paper (With and Petersen, 1954) with the exception of some modifications of the extraction procedure for coproporphyrin. Instead of washing the ether with water it was washed once with a 3% sodium acetate solution, thereafter once with a diluted iodine solution, and finally with distilled water. The iodine solution was prepared by diluting a 1% alcoholic iodine solution 1:200 with distilled water fresh every day. Further, the coproporphyrin was extracted from the ether with 1.5 N HCl instead of 0.1 N HCl. In this way coproporphyrin and its chromogen were determined together. These modifications of the procedure were introduced because of the findings of Schwartz, Zieve, and Watson (1951) and found to give the same figures for coproporphyrin as their ethyl acetate extraction procedure.

TABLE I
OBSERVATIONS ON CASES OF ACUTE POISONING

Observation No.	Sex	Observations on Days after Poisoning	Barbiturate	Dose (g.)	Blood Barbiturate Level (mg. per 100 ml.)	Coproporphyrin Excretion (μ g. per 24 Hours)
1	F	2nd to 5th	Dial	Unknown	8.3	71-149
2	F	1st ,, 3rd	Isonal*	"	11.4	139-240
3	F	1st ,, 3rd	Luminal	10	21.0	43-70
4	F	1st ,, 2nd	Isonal and veronal	10	6.1	25
5	F	2nd ,, 10th	Isonal	8	10.7	190, decreasing to 36
6	F	1st ,, 3rd	"	4	9.5	39-121
7	F	3rd ,, 25th	Amytal	5	6.0	102-191
8	M	1st ,, 5th	Isonal and veronal	6	14.4	123-493
9	F	1st ,, 5th	Isonal	2.8	9.3	134-267
10	M	2nd ,, 10th	Dial	5	10.4	30-116
11	M	1st ,, 8th	Isonal	2.2	3.3	38-124
12	M	1st ,, 5th	"	2.0	3.0	30-111
13	F	1st ,, 2nd	"	2.5	3.5	26
14	M	1st ,, 2nd	"	Unknown	2.5	61-149
15	F	3rd ,, 4th	Dial	"	8.4	49-56
16	F	2nd ,, 3rd	Isonal	"	2.8	35-89
17	F	1st ,, 2nd	Amytal	5	3.6	52
18	M	1st ,, 3rd	Isonal	3	5.8	55
19	M	5th ,, 9th	Dial	2.5	5.7	41-63
20	M	1st ,, 2nd	Isonal	3	4.0	25-33
21	F	1st ,, 2nd	Dial	1	5.0	43
22	F	1st ,, 6th	Isonal, veronal and amytal	7	14.0	23-74
23	M	3rd ,, 4th	Isonal	1	2.2	30-48
24	M	2nd ,, 3rd	CO	"	"	35
25	M	3rd ,, 4th	"	"	"	40-133
26	F	2nd ,, 4th	"	"	"	24-42
27	F	1st ,, 3rd	"	"	"	29-65

* Isonal = allyl-isopropyl barbituric acid.

TABLE II
OBSERVATIONS ON CASES OF CHRONIC POISONING

Observation No.	Barbiturate	Dose (per Day)	Coproporphyrin	
			μ g./100 ml.*	μ g./24 Hours*
28	Phenobarbital	Unknown	11.7	113; 150
29	Isonal	30 cg., 3 years	4.5	85; 36
30	Phenobarbital	At least 10 cg., $\frac{1}{2}$ year	10.0	32; 65; 35
31	Isonal and phenobarbital	Unknown	13.9	51; 36
32	Isonal	"	1.7	23; 19
33	Isonal and veronal	40 cg.	4.9	
34	Amytal	30 "	5.1	
35	"	30 "	2.8	17; 53; 23
36	Phenobarbital	Unknown	3.2	33; 40
37	Amytal	30 cg.	2.7	15
38	Amytal and phenobarbital	At least 50 cg. amytal and 10 cg. phenobarbital for 1 $\frac{1}{2}$ years	29	160
39	Phenobarbital	Unknown	55	35; 57; 138
40	"	"	2.6	73; 45
41	"	"	13.7	117
42	"	"	8.6	37
43	Amytal and isonal	100-150 cg. amytal and 40-50 cg. isonal	8.0	150
44	Amytal	Unknown	6.2	62; 37
45	"	100 cg.	9.3	110; 162
46	Phenobarbital	Unknown	11.2	74; 88.5; 62
47	Isonal and veronal	"	5.6	95; 109; 105
48	Phenobarbital	"	17.1	116; 105
49	"	"	7.7	
50	Amytal	40 cg.	37	224; 90
51	"	30 "	10	121
52	Phenobarbital	Unknown	21	202
53	Chronic alcoholism	"	4.8	143
54	"	"	14.5	84
55	"	"	7.5	123
56	"	"	22.3	108; 120

* μ g. per 100 ml. refers to the first urine voided after the patient was admitted to the hospital; μ g. per 24 hours refers to the various 24-hour urines from the observation period; the interval between the latter analyses was about one week.

Examination for porphobilinogen was carried out by performing the Ehrlich reaction on the urine and, if positive, repeated on urine extracted twice with 10% acetic acid in ether to exclude urobilinogen.

The barbiturate analyses were performed in the central laboratory of Bispebjerg Hospital by the method of Lous (1954).

Results

The results are presented in Tables I and II. The normal values for urinary coproporphyrin in man, determined with a method found to give similar figures as that described above, were studied on about 800 subjects by Zieve, Hill, Schwartz, and Watson (1953), who found the mean coproporphyrin excretion for normal men to be 189 ± 59 and for normal women 134 ± 42 μ g. per 24 hours and proposed the upper normal limit of 300 μ g. per 24 hours and the lower 100 μ g. per 24 hours. Many of our cases are seen to

fall below the lower limit and only a single observation (No. 8) exceeds the upper limit. This low excretion of coproporphyrin may be due to renal damage during the acute barbiturate poisoning, and in the chronic cases its cause may be complicating disease.

There was no correlation between the coproporphyrin excretion and the dose of barbiturate, and in the cases where a series of determinations of the porphyrin excretion was carried out it showed no regular variation with the time after the poisoning.

In three of the patients with acute barbiturate poisoning non-coproporphyrin porphyrins were demonstrated while such porphyrins did not occur in any of the chronic cases. The cases with excretion of non-coproporphyrin porphyrins were the following: Case 7 where the 24-hour excretion was 191 μg . coproporphyrin and 216 μg . non-coproporphyrin porphyrin; Case 8 where the coproporphyrin for six days in succession showed the 24-hour values 123, 297, 493, 383, 359, and 381 μg . and the corresponding values for non-coproporphyrin porphyrins were 0, 0, 0, 0, 215, and 585 μg .; and Case 22 where the coproporphyrin values were 23, 48, 74, and 49, and the corresponding non-coproporphyrin porphyrins were 0, 0, 42, and 120 μg . in 24 hours. This occasional excretion of minor amounts of non-coproporphyrin porphyrin cannot be taken as a sign of porphyria, as With and Petersen (1954) found similar amounts in the urine of several patients with a wide variety of diseases and without signs of porphyria.

Determination of porphobilinogen was not carried out on all the patients but only of the acute cases Nos. 1-12 and the chronic cases Nos. 28-40. As the reaction was never found positive

it was omitted in the remaining cases. This failure to find porphobilinogen goes against the occurrence of serious disturbances of porphyrin metabolism in these patients.

Conclusion

These studies on the porphyrin excretion in the urine in patients with acute and chronic barbiturate poisoning showed no evidence of a disturbed porphyrin metabolism, and the porphyria caused by barbiturates must therefore be attributed to an activation of a latent porphyria.

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