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ARTICLES

THE EFFECT OF BARBITURATES IN PORPHYRIA TURCICA

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Hexachlorobenzene-induced porphyria has aroused wide interest in medical circles and numerous reports have been published on this syndrome.[1, 2, 3, 4] In view of its toxic etiology, the fact that not every person exposed to hexachlorobenzene acquired the disease has led to an interest in the the possibility of genetic predisposition to this form of porphyria. This subject has been studied and reported on previously.[5]

Since the barbiturates are numbered among the drugs that are known to be highly effective in inducing porphyria in certain individuals it was decided to investigate the effect of these drugs in porphyria turcica to determine whether or not individuals sensitive to hexachlorobenzene would also prove to be sensitive to the barbiturates. It was hoped in this way to gain a better understanding of the effect of both hexachlorobenzene and the various barbiturates on porphyrin metabolism.

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Two patients with porphyria turcica, in whom the active disease had subsided, volunteered for experimental treatment with barbiturates. No new clinical or chemical manifestations of porphyria were noted in either patient during this treatment. A third volunteer, with acute manifestations of the disease, was also given barbiturates. No deterioration in symptomatology and no increase in urinary porphyrin excretion were noted.

Case Reports

1. **B. K.:** a 35 year old white housewife, admitted to Hacettepe Medical Center on 9/19/61, discharged on 2/11/63. Chief complaints on admission were hypertrichosis and hyperpigmentation. The patient's illness commenced shortly after she consumed wheat which had been treated with hexachlorobenzene (C_6Cl_6). She recalled that the first symptom was the appearance of very small, pin-head sized blisters which enlarged rapidly and later ruptured, causing great pain. Cramping abdominal pain and the passage of red urine were noted almost simultaneously, followed by the development of hypertrichosis and hyperpigmentation.

On physical examination the hypertrichosis and hyperpigmentation were observed together with bullae and partly healed scars of bullous lesions. Bilateral otitis media and chronic mastoiditis were also discovered but were considered to be non-contributory.

Laboratory reports revealed normal blood count and urine findings and the blood chemistry was also found to be within normal limits.

Roentgenological examination of the joints showed some narrowing of the joint spaces and swelling in the soft tissue of the periarticular regions. Examination of a biopsy specimen from the liver indicated the presence of a precirrhotic condition.

The patient was treated with ethylene diamine tetraacetic acid, administered intravenously, for the first five days after her admission to the hospital and this treatment was continued orally for about a year. The clinical picture improved on this regime and the patient was considered ready for discharge early in 1963. Shortly before her discharge she agreed to participate in the barbiturate experiment and was given 150 milligrams of seconal, by mouth, for eight days. At the end of the eight days no deterioration in the patient's clinical condition could be detected nor was there any change in the urinary excretion of porphyrins. (Table 1.)

2. **Z. K.:** an 18 year old white girl, admitted to Hacettepe Medical Center on 9/1/62 and discharged on 2/11/63. Chief complaints were hyperpigmentation and loss of weight. The patient's illness had started five years previously subsequent to the eating of hexachlorobenzene treated wheat. She reported the development of bullae shortly after having eaten the treated wheat. The bullae ruptured or became infected and left deep scars. Simultaneously she noted that her urine had turned red and reported abdominal cramps and a gradually increasing hypertrichosis. She noted an exacerbation of her clinical symptoms during the summer months and a relative decrease in severity during the winter. Discussion of her

TABLE 1

PORPHYRIN EXCRETION BEFORE AND AFTER ADMINISTRATION OF SECONAL

URINARY PORPHYRIN VALUES (micrograms/day)			
On Admission :	*B.K.*	*Z.K.*	*G.S.*
Coproporphyrin	440	232	112
Uroporphyrin	1500	1744	618
Before Seconal :			
Coproporphyrin	24	313	93
Uroporphyrin	60	1375	39
After Seconal :			
Coproporphyrin	53	55	61
Uroporphyrin	79	1132	23

FECAL PORPHYRIN VALUES (micrograms/100 Gm.)			
On Admission :	*B.K.*	*Z.K.*	*G.S.*
Coproporphyrin	1750	1166	300
Protoporphyrin	500	71	70
Uroporphyrin	1250	78	80
Before Discharge :			
Coproporphyrin	320	790	250
Protoporphyrin	750	250	200
Uroporphyrin	120	80	40

family history elicited the fact that a brother died following the appearance of clinical symptoms similar to the patient's and that two other siblings manifested similar symptoms.

On physical examination hypertrichosis was noticed together with freshly developed bullae and scars of past bullae which had caused deformation of her fingers. Hepatomegaly was noted, the liver being palpable 3 - 4 centimeters below the right costal margin on the midclavicular line.

Laboratory reports indicated that the blood count and urinary findings were normal; serum proteins, blood cholesterol and cholesterol esters, transaminase activity and bromosulphopthalein excretion were within normal limits. Examination of a skin biopsy specimen (taken from an uninvolved region) showed no deposition of porphyrins. The histologic appearance of the specimen was normal. A liver biopsy specimen, however, revealed chronic hepatitis and a precirrhotic appearance.

Like the patient in case 1, this patient was given 150 milligrams of seconal by mouth every day for eight days before her discharge. Again, no clinical or laboratory disturbances were reported and the urinary porphyrin values, before and after the administration of seconal, are given in table 1.

3. G. S.: a 13 year old white girl, admitted to Hacettepe Medical Center on 9/1/62, discharged on 2/11/63. Chief complaints were the presence of bullae and hypertrichosis commencing after the eating of hexachlorobenzene treated wheat. Cramping abdominal pain and red urine marked the onset of the disease followed by hyperpigmentation of the exposed parts of the body; hypertrichosis, mainly manifest on the face and forehead; development of bullae on arms and legs and the scarring of some of these lesions which commenced about a year after exposure to the treated wheat.

The patient had been previously admitted for these complaints to Hacettepe Medical Center between 8/31/58 and 5/29/59. The readmission was for the purpose of carrying on more detailed investigation of her disease. Three siblings are reported to be afflicted with the same disease.

Physical examination revealed that she had both hyperpigmentation and vitiliginous spots. Hypertrichosis was apparent on her forehead. Her liver was palpable 3 - 4 centimeters below the right costal margin and she indicated tenderness on palpation of the left hypochondrium.

Laboratory findings were within normal limits.

Radiologic examination revealed multiple calcified spots in her chest; osteoporosis in both hands and feet; and the possible presence of ulcerative colitis.

The adrenal cortex responded to the administration of ACTH and urinary excretion of 17 ketosteroids was found to be normal.

The patient improved during her second stay in the hospital and shortly before her discharge was treated with 100 milligrams of seconal, by mouth, daily for eight days. There was no aggravation of clinical symptomatology nor any increase in urinary porphyrin excretion.

Discussion

The three patients presented here all developed porphyria following ingestion of hexachlorobenzene.

Various drugs have been accused of causing porphyria. The oldest drugs with a reputation for causing porphyrinuria are sulfonal and trional. Garrod reported patients who developed porphyria after the use of such drugs, and referred to other cases previously reported. At that time the inadequacy of the technics used, and the lack of knowledge about the various porphyrins, prevented identification of the porphyrins involved. It is possible that sulfonal and trional were merely the agents which precipitated a mild or severe porphyria in constitutionally liable subjects. Waldenström observed that administration of trional to apparently healthy near-relatives of patients with congenital porphyria was followed by the appearance of uroporphyrin in urine.[6] It has been very hard to reproduce this type of porphyria in experimental animals. Administration of near lethal amounts of these drugs to rabbits failed in most cases to produce manifest disease symptoms[7] and in the mild cases that occurred occasionally the workers could not obtain enough porphyrin to examine its character.

Much more striking changes in porphyrin metabolism have been attributed to sedormid (allylisopropylacetylcarbamide)[8] a barbiturate analogue. It was found that, upon feeding sedormid to rabbits for several consecutive days, the daily urinary excretion of ether-insoluble porphyrins increased from 0.02 to 60 milligrams. This was paralleled by an increase in porphobilinogen excretion. In studying the organs of sedormid-poisoned rabbits, a marked increase in porphyrin and porphobilinogen was found in the liver.[9] In contrast to the liver findings, no porphobilinogen and no increase in porphyrin concentration was detected in the erythropoietic system. The urinary pattern of excretion was characterized by increased excretion of porphobilinogen and uroporphyrin; increased coproporphyrin and protoporphyrin were noted in bile and feces. Schmid and his group made the very interesting observation that the administration of sedormid produced a rapid and progressive fall in liver catalase activity.[9] This is not due to inhibition of catalase activity, as occurs with another porphyria-causing drug : 3-amino, 1, 2, 4-triazole, which inhibits catalatic activity non competitively.[10] Sedormid probably interfered with the formation of the enzyme, or increased the breakdown of catalase, as indicated by the marked reduction of inclusion of labeled

glycine into catalase heme in sedormid - treated rats.[9] Sedormid apparently had little effect on the catalase formed in red blood cells, because administration of the drug for as long as 42 days did not produce an appreciable decrease in the catalase activity of bone marrow and red blood cells. The exact mechanism leading to decreased catalase activity is not known, however, such a blockage does exist and no other effect of this drug on other heme enzymes can be demonstrated.[9]

The reader is referred for detailed information to a previous article by one of us (P.Ö.) for extensive discussion of the chemical findings in various porphyrias.[11]

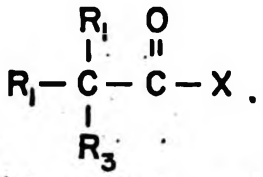
Pharmacological studies have been carried out with drugs related to sedormid, which led to the discovery of a basic structure that gave rise to the development of experimental porphyria in animals. This structure has been confirmed by at least two groups of workers,[12],[13] and is described by the basic formula presented in figure 1.

Certain barbiturates can also precipitate or produce attacks of porphyria. Stich *et al.*[12] have found that allylethyl barbituric acid, allylisopropyl barbituric acid, allylbutyl barbituric acid, allylisobutyl barbituric acid, and diallyl barbituric acid are particularly effective in this regard. The formula of these compounds is also shown in figure 1; their effect is comparable to that of sedormid. The barbiturate used in our test was allyl 1-methylbutyl barbiturate which conforms to the structure described by Stich *et al.*

Laboratory investigations using experimental animals gave supportive evidence for the toxicity of hexachlorobenzene.

Working with rabbits, Kantemir[14] demonstrated increased urinary porphyrin excretion and skin lesions induced by feeding hexachlorobenzene to the animals.

Ockner and Schmid produced experimental porphyria in rats.[15] Biochemical changes observed in these animals included : increased urinary excretion of δ - aminolevulinic acid, porphobilinogen, uroporphyrin and coproporphyrin; slight to moderate increases in fecal excretion of copro-and protoporphyrin; and increased uroporphyrin and porphobilinogen, slightly increased copro-and protoporphyrin, in the liver. Liver damage was noted but there was no change in liver catalase activity. Fluorescence appeared only in the cortices of the long bones, not in the marrow. It was found that the disturbance could be reversed by discontinuing the drug in cases where



R_1 = CH_2= CH — CH_2—

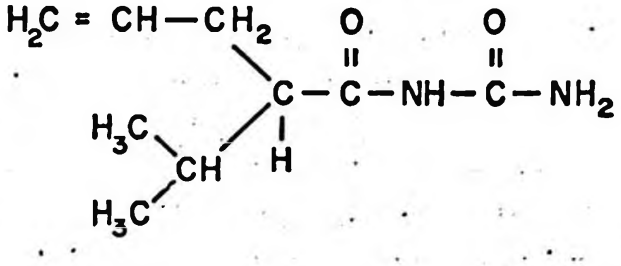
R_2= Alkyl —

R_3= H— (or Alkyl—)

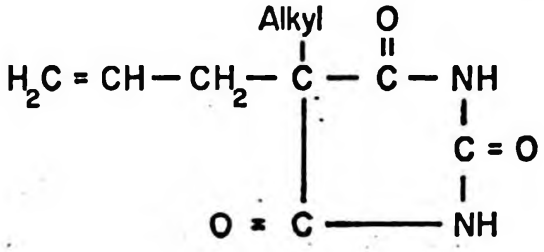
X = — NH_2
or

R_3+ X = — CO — NH — CO — NH

chemical structure of porphyrogenic compounds.



chemical structure of sedormid.



chemical structure of porphyrogenic barbiturates.

Figure 1. The chemical structure of various porphyrogenic compounds.

the animals had been fed hexachlorobenzene for short periods of time. In animals who had been exposed to hexachlorobenzene for as long as 2 - 3 weeks, porphyrinuria persisted despite discontinuance of the drug.

Matties *et al.* reported similar results in rats and confirmed the conclusions of Ockner and Schmid.[16] In working with rabbits, however, these investigators achieved results closer to the conditions seen in human porphyrias. They found, in rabbits with hexachlorobenzene-induced porphyria, that urinary porphyrin was predominantly uroporphyrin and that porphobilinogen was consistently absent. Massive deposits of uroporphyrin III were found in the liver, in several other organs, and in bone cortices. Pseudo-uroporphyrins, hexa-and pentacarboxylic porphyrins were also detected but no increase in the excretion of glucuronic acid, as had been reported by Parke and Williams subsequent to the administration of hexachlorobenzene,[17] was noted.

Although both hexachlorobenzene and the barbiturates (and barbiturate analogues such as sedormid) can precipitate porphyria in susceptible subjects, the etiology of these diseases seems to differ.

This is evidenced by the findings summarized here and by our failure to produce porphyria symptoms with barbiturates in three cases of porphyria turcica. The underlying lesion in the latter disease is not similar to the one produced by barbiturates in other susceptible subjects. We do not have, as yet, sufficient information to resolve this dilemma and must wait for the accumulation of further data on the physiopathology of the porphyrias.

Summary

Case histories of three patients with porphyria turcica are presented. Two patients manifested the disease in a quiescent state, one was acutely ill. All three volunteered for experimental treatment with a porphyria-inducing drug : seconal, an allylbarbiturate. In no case did the drug aggravate existing symptoms or induce new ones nor did it produce any change in the excretory pattern of porphyrins.

The biochemical pathology of the drug-induced porphyrias, in particular the effect of the barbiturate analogue, sedormid, on porphyrin metabolism, is discussed in some detail.

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