lymphocytes and 2 per cent eosinophiles and 1 per cent basophiles); heterophile, negative; urine-bile, positive; total bilirubin, 3.4 mg and direct bilirubin, 2.0 mg per 100 ml; serum glutamic oxaloacetic transaminase (SGOT) 550 units; prothrombin time, 76.5 per cent. All medication except desiccated thyroid and therapeutic multivitamins (Optilets®) was discontinued and complete bed rest and dietary restrictions were prescribed. By 31 August 1965 she was much improved and liver function showed decided improvement: Urine-bile, negative; total bilirubin, 1.9 mg and direct bilirubin 0.9 mg per 100 ml; SGOT, 188 units; prothrombin time, 91 per cent; plasma proteins, normal; cephalin flocculation, 2+ (48 hours). She was allowed to return to her studies on 16 September 1965, at which time laboratory findings were virtually normal. The diagnosis at that point was felt to be mild viral hepatitis.

In August 1965, mestranol plus chlormadinone acetate (C-Quens®) was added by the dermatologist as a possible aid to the skin problems. At first the response was good but on 22 January 1966 she was again given sulfadimethoxine 0.5 gm twice a day by the dermatologist to control an exacerbation. The following day nausea and vomiting developed, along with pruritus, dark urine and light stools. The sulfonamide was immediately discontinued and when seen 27 August the patient appeared clinically well.

Laboratory studies on that date gave the following significant findings: Leukocytes, 2,850 per cu mm (segmented 14 per cent, stabs 1 per cent, lymphocytes 85 per cent); urine-bile, positive; total bilirubin 1.8 mg and direct bilirubin 0.8 mg per 100 ml; SGOT, 168 units; prothrombin time, 90 per cent; cephalin flocculation, 2+ (48 hours); alkaline phosphatase, 5.6 Bodansky units; thymol turbidity, 3.6 units. Bed rest was again prescribed and two weeks later all previously abnormal laboratory findings were within normal range.

Comment

Recent contributions to the literature[1,2,3] have served to point up the fact that sulfonamides can cause hepatic dysfunction, however rarely. The present case is the first reported in which hepatitis followed the use of sulfadimethoxine (Madribon®). The relationship was established by a prompt return of earlier symptoms and laboratory findings when the drug was used a third time. The laboratory findings suggested a mixed cholestatic-hepatitis response, as evidenced by increased alkaline phosphatase and transaminase. The reaction was clearly mild and readily reversible, and it was more likely a hypersensitivity response than a direct toxic effect of the sulfadimethoxine.

GENERIC AND TRADE NAMES FOR DRUGS

Sulfadimethoxine—*Madribon.*®
Lidocaine—*Xylocaine.*®
Methohexital—*Brevital.*®
Pentobarbital—*Nembutal.*®
Hydroxyzine pamoate—*Vistaril.*®
Promethazine hydrochloride—*Phenergan.*®
Trimeprazine tartrate—*Temaril.*®
Therapeutic multivitamins—*Optilets.*®
Mestranol + chlormadinone acetates—*C-Quens.*®

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Diphenylhydantoin Toxic Psychosis with Associated Hyperglycemia

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NEARLY 30 YEARS AFTER its introduction, diphenylhydantoin (DPH) (Dilantin®) remains a mainstay in the therapy of epilepsy.[11] During this period, its side effects have been well documented. In addition to the well-known, largely dose-related neurologic toxicity,[8] a number of other complications have been observed, reported and reviewed.[10]

The purpose of this report is to describe an episode of transient hyperglycemia and glycosuria associated with DPH toxicity in a non-diabetic patient. No similar cases could be found in a search of the literature.

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Report of a Case

A 47-year-old businessman was first seen 8 September 1965 because of "peculiar behavior" of several weeks' duration. Pertinent medical history consisted of a cerebral concussion at the age of 22, and the onset three years later of grand mal epileptic seizures, which were controlled by treatment with DPH in a dose of 100 mg three times daily. After several years the patient discontinued medical supervision but continued to take DPH. In May 1965, however, he began to feel "peculiar," and fearing that the grand mal seizures were about to recur, gradually increased the amount of DPH taken daily. At the time the present symptoms began, he was taking 700 mg of DPH daily; 500 mg of the daily dose was taken at bedtime. Initially, he noted tinnitus associated with impaired hearing, then ataxia ("shakiness and lurching") and finally delusions regarding his wife's marital fidelity. He began to have visual hallucinations, seeing his wife's alleged lover lurking behind trees and rocks or peering at him from passing cars. At that time he began to carry a loaded pistol, causing his alarmed wife to bring him in for evaluation. The patient's medical and social history was otherwise unremarkable. His appetite had remained good and his diet was normal. He had no family history of diabetes mellitus.

On physical examination, the patient appeared to be in no distress but showed aberrant affect, such as smiling inappropriately or giggling. The blood pressure was 155/85 mm of mercury; the pulse rate was 76 beats and respirations 12 per minute. The only significant abnormalities were found by neurologic examination. He had bilateral fine nystagmus on lateral gaze. Cranial and peripheral motor and sensory nerve function was otherwise normal. Pronounced truncal ataxia was present. The deep tendon reflexes were brisk but equal bilaterally, and the plantar responses were flexor.

Laboratory studies included a hemogram within the normal range. The urine gave a strongly positive reaction for glucose, and a trace of acetone was present. A blood specimen obtained approximately two hours after the patient had eaten lunch showed a glucose level of 230 mg per 100 ml (Table 1).

The dosage of DPH was immediately reduced to 200 mg daily. When the patient was seen two days later, the symptoms and neurologic abnormalities had all but disappeared. Glycosuria was no longer present, and the fasting blood glucose level was normal at 100 mg per 100 ml. These findings suggested that the hyperglycemia and glycosuria were related to DPH toxicity. Blood glucose determinations including a cortisone glucose tolerance test to detect mild carbohydrate intolerance[2] were performed during the subsequent eight months. The results (Table 1) documented the recovery of normal carbohydrate regulatory function.

Within one week of the first office visit, the patient became free of symptoms and neurologic abnormalities and has remained so to the present. Blood pressure levels have ranged between 145/85 and 160/90 mm of mercury. He has continued to take DPH in a dosage of 300 mg daily.

Discussion

As is apparent from Table 1, the patient's blood glucose level became normal in the fasting and two-hour post-glucose state after his recovery from DPH toxicity. A cortisone glucose tolerance test was then performed because of the possibility that he might have "pre-clinical" diabetes. Although the results were abnormal by the original criteria of Fajans and Conn,[2] the patient ranked in the 25th percentile of the nomogram constructed by Pozefsky and co-workers[6] to allow comparison of the test values in a given patient with those of his age cohorts, which is well within

TABLE 1.—*Results of Blood Glucose Determinations*

Date	Determination	Blood Glucose Levels* (mg per 100 ml) Fasting	30 Min.	1 Hr.	2 Hr.	3 Hr.
9/ 8/65	Random, 2 hours after lunch	....	....	....	230	....
9/10/65	Fasting	100	....	....	....	....
9/15/65	Partial glucose tolerance test†	80	....	....	120	....
10/28/65	Cortisone-glucose tolerance test‡	114	236	240	180	140
5/ 5/66	Random	....	....	....	118	....
5/11/66	Standard glucose tolerance test†	70	120	140	100	88

*Folin-Wu; normal fasting level, 80-120 mg.
†Glucose, 100 gm orally, after fasting sample is taken.
‡Hydrocortisone, 50 mg orally, 8½ and 2 hours before administration of glucose.[2]

their normal range. Finally, eight months after the initial episode a standard glucose tolerance test gave normal values.

It thus appears that the hyperglycemia and glycosuria observed in this patient were related to the DPH toxicity and were mediated by a mechanism other than that operating in the stressed "pre-diabetic" subject. Several possibilities seem to exist. Release of ACTH has been reported to be inhibited[3] and plasma 17-hydroxycorticoid levels low or normal[1] in patients receiving DPH, so it seems unlikely that the pituitary-adrenal axis mediated the observed effect. Epinephrine infusion has been shown to inhibit release of pancreatic insulin,[4,5] thereby potentiating the hepatic glycogenolytic hyperglycemia also induced. Not to my knowledge, however, has the production of sustained hyperglycemia via this mechanism been documented in acutely stressed patients.

Finally, a direct effect of DPH on the pancreatic release of insulin can be postulated. Woodbury[12] suggested that DPH exerts its anticonvulsant action by diminishing the intracellular sodium content of the brain, thereby lowering excitability. He also noted the stimulating effect of DPH on cellular sodium-extruding processes in cardiac and skeletal muscle. This observation is of interest in view of the well-known hyperglycemic effect of the thiazide diuretics.[9] The mechanism of their hyperglycemic action remains unclear, but intracellular potassium depletion appears to be a possible explanation, at least in part.[7] It is thus tempting to speculate that the effect of DPH in the present case was similarly mediated via an induced alteration in the electrolyte concentration of the pancreatic islet cells, thereby inhibiting insulin secretion.

Summary

The occurrence and remission of hyperglycemia and glycosuria in conjunction with diphenylhydantoin (DPH) toxicity in a non-diabetic patient is described. No similar cases were found in the literature. An inhibitory effect of DPH on insulin secretion by the pancreatic islet cells is one of several possible explanatory mechanisms.

GENERIC AND TRADE NAME OF DRUG

Diphenylhydantoin—*Dilantin.*®

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Gynecomastia Associated with Vincristine Therapy

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Vincristine (Oncovin®), a chemotherapeutic agent derived from the periwinkle plant (vinca rosea Linn), has been demonstrated to induce remissions in various neoplastic diseases including myeloproliferative and lymphoproliferative syn-

This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendations of such products as may be named.

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