Case Reports

HYPOPLASTIC ANAEMIA—AN UNUSUAL COMPLICATION OF CHLORDIAZEPOXIDE HYDROCHLORIDE THERAPY

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CHLORDIAZEPOXIDE hydrochloride, "Librium", was discovered in the Roche Research Laboratories a few years ago. It is 7-Chloro-2-methylamino-5-phenyl-3H-1, 4-benzo diazepam and is structurally unrelated to any other psychotropic drug. It has been found to be an effective drug with a general lack of severe side effects in the treatment of anxiety, either occurring alone, or complicating a variety of other conditions. Results of studies have suggested its effectiveness in the treatment of anxiety and tension (Tauber, 1960), anxiety neuroses (Tobin and Lewis, 1960), anxiety and agitation in psychotic patients (Smith, 1960), and as an adjunct to psychotherapy (Toll, 1960). In angina pectoris, by relieving fear, anxiety and tension (Hirshleifer, 1960), in patients suffering from dermatoses influenced by emotional fluctuations (Robinson, 1960), and in allergic disorders (McGovern, 1960), its beneficial effects have been demonstrated. Minor side effects such as drowsiness, ataxia, nausea, constipation and skin eruptions are infrequent and readily controlled by reduction in dosage. The only more troublesome complication of chlordiazepoxide hydrochloride therapy reported so far in medical literature is a temporary, reversible agranulocytosis (Kaelbling and Conrad, 1960; Wilcox, 1962). The pertinent details of two cases of hypoplastic anaemia attributable to the drug are recorded below. They are believed to be the first recorded cases.

Case Reports**Case No. 1**

A thirty-year-old married woman with two children was admitted to hospital, as an emergency, with a five-day history of a swelling in the right submandibular region associated with a moderate pyrexia and a generalized petechial rash. She also complained of a poor appetite and malaise. She was taking chlordiazepoxide hydrochloride 20 mg. daily, started by her own doctor for "anxiety", the cause of which had not been determined. The total duration of therapy was two years. The only other drug that had been prescribed for her was tetracycline 250 mg. every 6 hours for 48 hours prior to admission. The patient firmly denied taking any drugs other than those prescribed for her.

On Examination she was an ill-looking, pale lady with a temperature of 102°F, a generalized petechial rash simulating purpura and a small, soft, tender, fluctuant swelling in the right submandibular region. Her spleen was not palpable and no other abnormal physical signs were detected.

Investigations. Hb. 7.6 g./100 ml.; RBC 3.36 million/cu. mm., orthochromic with slight anisocytosis; WBC 2000/cu. mm.; polys 12%, eosinos 2%, monos 6%, lymphs 80%; platelets 24,000/cu. mm.; serum iron 240 µg./100 ml.; serum iron binding capacity 250 µg./100 ml.; ESR 30 mm./hour (Westergren); liver function tests normal; radiograph of chest and right submandibular region, normal; four blood cultures, sterile; urine—chemically and microscopically normal; ECG: sinus tachycardia. A sternal bone marrow biopsy showed a moderately cellular marrow with a normoblastic erythropoiesis. Lymphocytes were relatively increased, myelocytes and promyelocytes were numerous, but metamyelocytes or segmented polymorphonuclears were greatly reduced. Megakaryocytes were scanty and there appeared to be no excess of blast cells. The haematologist (Dr. J. H. Jones) concluded that the picture was of a maturation arrest at the myelocyte stage and was compatible with the diagnosis of drug toxicity.

Chlordiazepoxide hydrochloride was discontinued and the patient treated initially with prednisolone 15 mg. every 8 hours and ampicillin 500 mg., every 6 hours. A week after withdrawal of chlordiazepoxide therapy, the patient's initial symptoms and signs had disappeared. Ampicillin was stopped after 10 days and the dose of prednisolone gradually decreased over a period of three weeks. During her hospitalisation for a month she was also transfused two pints of Gp. A rhesus-positive blood. Daily blood cell counts showed a gradual return to normal. The blood picture and bone marrow were normal within a month of stoppage of chlordiazepoxide therapy and remained so thereafter.

Case No. 2

A forty-two-year-old single woman was referred to the medical clinic for investigation of anaemia. She gave a history of increasing pallor, dyspnoea on accustomed exertion, lack of energy and interest for a month. A generalized petechial rash was noticed a day before being referred to the medical clinic. She had been given chlordiazepoxide hydrochloride 30 mg. daily for 3 months followed by 20 mg. daily thereafter. The total duration of therapy was nine months. In addition, she had oral iron for a fortnight. The patient had *not* taken any other drugs.

Clinical examinations revealed a thin, pale lady with a generalized petechial rash simulating purpura. The spleen was not palpable and the rest of the physical examination was negative.

Investigations. Hb. 8.4 g./100 ml.; erythrocytes 3.08 million/cu. mm., orthochromic with slight anisocytosis and poikilocytosis; retics. 0.6%; WBC 1800/cu. mm.; polys. 16%, lymphs. 84%; platelets less than 10,000/cu. mm.; ESR 44 mm. in one hour (Westergren); liver function tests, normal; urine

chemically and microscopically clear; radiograph of the chest, normal; ECG, normal; sternal bone marrow examination showed features of a myeloid maturation arrest identical to the picture in Case 1.

Chlordiazepoxide hydrochloride was discontinued and the patient advised not to take it in view of the possible ill effects. Treatment was started with two pints of Gp. O rhesus-negative blood and prednisolone 15 mg. every six hours. The petechial rash gradually faded and totally disappeared within a fortnight of stoppage of chlordiazepoxide therapy. The patient had a normal full blood count and bone marrow four weeks after withdrawal of the drug. This was maintained and there was no recurrence of the hypoplastic anaemia as confirmed during subsequent attendances at the medical out-patient clinic. The dose of prednisolone was gradually decreased over a period of four weeks.

Discussion

Two cases of reversible agranulocytosis associated with chlordiazepoxide therapy have been previously reported (Kaelbling and Conrad, 1960; Wilcox, 1962). The present paper records two cases of definite hypoplastic anaemia presumably attributable to the same drug, but distinguishable from the two previous ones by certain features, namely, (a) low haemoglobin (b) relatively low erythrocyte count and (c) thrombocytopenia. The other possible causes of hypoplastic anaemia were considered but the reversal to normal of the bone marrow and peripheral blood pictures within a few weeks of stoppage of the drug in both cases left little doubt about the direct relationship between the psychotropic therapy with chlordiazepoxide hydrochloride and the hypoplastic anaemia. Moreover, both cases when seen as out-patients at periodic intervals did not show the slightest evidence of a relapse of the hypoplastic anaemia. How the marrow hypoplasia occurs is uncertain. Kaelbling and Conrad stated that the bone marrow, in the case recorded by them, had the appearance of a myeloid maturation arrest. Wilcox's patient was too unwell and so he could not venture a bone marrow examination at the appropriate time. In the present cases the picture was of a maturation arrest at the myelocyte stage and in both of them it took four weeks for the effects of chlordiazepoxide hydrochloride to wear off. The relationship of the biochemical effects of the drug to its psychotropic action and the exact mechanism by which it causes hypoplastic anaemia need to be studied.

In conclusion, I submit that there is evidence to regard chlordiazepoxide hydrochloride as a

potential, though probably infrequent, cause of hypoplastic anaemia. It represents an uncommon constitutional sensitivity to this widely used psychotropic drug. Perhaps, as previously suggested by Kaelbling and Conrad in 1960, it would be advisable for patients on this drug to be cautioned to report any departure from their customary state of physical health, such as development of fever, sore throat, local sepsis, or pallor. In addition, only interim supplies of the drug should be prescribed between periodic check-ups when haematological examinations should be carried out.

Summary

Definite features of hypoplastic anaemia developed in two patients receiving chlordiazepoxide hydrochloride therapy.

In both of them, the anaemia completely disappeared within four weeks of stoppage of the drug and did not recur.

It is suggested that a definite causal relationship existed between the chlordiazepoxide hydrochloride and hypoplastic anaemia.

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REFERENCES

- HIRSHLEIFER, I. (1960): The Use of Chlordiazepoxide in Cardiovascular Disorders, *Curr. ther. Res.*, **2**, 501.
- KAELBLING, R., and CONRAD, F. G. (1960): Agranulocytosis due to Chlordiazepoxide Hydrochloride, *J. Amer. med. Ass.*, **174**, 1863.
- MCGOVERN, J. P. (1960): Studies of Chlordiazepoxide in Various Allergic Diseases, *Ann. Allergy*, **18**, 1193.
- ROBINSON, R. (1960): Adjunctive Therapy of Dermatoses with Librium, *Dis. nerv. Syst.*, **21**, 43.
- SMITH, M. E. (1960): A Comparative Controlled Study with Chlordiazepoxide, *Amer. J. Psychiat.*, **117**, 362.
- TAUBER, C. G. (1960): Librium, ein Neues Psychotropes Pharmakon, *Schweiz. med. Wschr.*, **90**, 1065.
- TOBIN, J. M., and LEWIS, N. D. C. (1960): New Psychotherapeutic Agent, Chlordiazepoxide, *J. Amer. med. Ass.*, **174**, 1242.
- TOLL, N. (1960): Librium as an Adjunct to Psychotherapy in Private Psychiatric Practice, *Dis. nerv. Syst.*, **21**, 264.
- WILCOX, W. W. (1962): A Case of Agranulocytosis, *Alaska Med.*, **4**, 31.