Quinidine-induced systemic lupus erythematosus

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SYSTEMIC LUPUS erythematosus (SLE) is a chronic, progressive inflammatory disorder of unknown aetiology affecting connective tissue and producing a disease of great complexity. It probably results from a combination of a predisposition, which may be genetically determined, and recognized or unrecognized precipitating factors (Alarcon-Segovia, 1969). Several precipitants are known, such as sunlight, X-rays and infection (Sternberg & Bierman, 1963), but drugs are one of the most important. When predisposition is strong and SLE starts spontaneously in childhood the prognosis is relatively poor, whilst the drug-induced disease often carries a good prognosis if the drug is stopped (Alarcon-Segovia, 1969). This paper describes a case due to quinidine where the drug had to be continued in large doses to prevent dangerous tachycardias.

Case history

In January 1965, a 70-year-old woman was admitted with a 9-day history of palpitations. She had been on digoxin for 3 years following an episode of mild cardiac failure, thought to be ischaemic in origin, at the time of a cholecystectomy; her previous health had been good.

On admission she had a tachycardia with a rate of 172/min, refractory to small doses of quinidine, so she was reverted by DC shock and discharged on procainamide. After reversion there were no abnormal signs: BP 150/90, ECG showed sinus rhythm, rate 70/min and right bundle branch block.

She had three further admissions in 1965 and three more in 1966 with recurrent attacks of tachycardia with ventricular rates of 150–180/min needing 8 DC shocks because digoxin, procainamide and propranolol failed to control them. Between admissions she suffered short episodes of palpitations but each major attack caused cardiac failure. Her ECG showed the Wolf-Parkinson-White syndrome and during the palpitations was often difficult to interpret, but there appeared to be a supraventricular tachycardia with abnormal intraventricular conduction (Fig. 1).

In October 1966 she was again admitted with tachycardia and severe cardiac failure. Her haemoglobin was 12.4 g/100 ml, ESR 10 mm/hr, urea 45 mg/100 ml and the electrolytes and liver function tests were normal. As drug therapy had failed, an endocardial pacemaker catheter with a triggered multiple pulse device was implanted, but was unsuccessful. She was therefore given quinidine 200 mg tds. She remained well for 9 months but was readmitted with a tachycardia in July 1967. This could only be controlled by increasing the dose of quinidine to 500 mg/qds. and by adding Kinidin Durules (long acting quinidine) 400 mg at night. This kept the serum quinidine at 5.5–6.7 mg/l, below which level the tachycardia would recur. She was discharged on this large dose and has now been two and a half years without requiring admission for uncontrolled tachycardia.

In March 1968 she developed disseminated

FIG. 1. ECG leads I, II and III in sinus rhythm and during a tachycardia.

eczematous dermatitis, pallor, lymphadenopathy and hepatosplenomegaly. She had a haemolytic anaemia, haemoglobin 10.2 g/100 ml with 5% reticulocytes, and bilirubin 1.2 mg/100 ml, a leucopenia 3200/mm³ and thrombocytopenia 51,000/mm³ (Fig. 2).

The skin improved with topical betamethasone valerate and she refused to allow any reduction in the dose of quinidine.

She remained relatively well for the next 18 months but came in again in October 1969 with a rash which had been present for a month. It was pruritic, erythematous and scaly covering the exposed surfaces of the body, with areas of skin atrophy and patches of follicular plugging. A diagnosis of lupus erythematosus was made and confirmed by skin biopsy. The liver was enlarged as before, though the spleen and lymph nodes were not palpable. Her haemoglobin was 10 g/100 ml, WBC 5000/mm³, platelets 87,000/mm³, bilirubin 1.2 mg/100 ml, albumin 3.8 and globulin 2.1 g/100 ml. Her ANF was weakly positive but no LE cells were seen.

Prednisone 5 mg tds was started and quinidine 1.4 g/day continued. This improved the skin and

blood count to: haemoglobin 11.6 g/100 ml, WBC 7000/mm³, platelets 159,000/mm³. Her urea was then 47–52 mg/100 ml.

Now, 75 years old, she has been on quinidine for three and a half years and has had over 1.5 g daily for two and a half years. She feels well and is relatively untroubled by occasional mild episodes of tachycardia. The liver is still palpable and the rash is present, though not troublesome. Investigations in February 1970 showed haemoglobin 10 g/100 ml, reticulocytes 3.6%, WBC 9200/mm³, platelets 162,000/mm³, albumin 4.0 g/100 ml, globulin 2.2 g/100 ml, bilirubin 2.4 mg, and urea 54 mg/100 ml. The ANF test remains weakly positive and the Coombs' test is positive.

Comment

Quinidine is known to cause hypersensitivity reactions and thrombocytopenia (Bishop, Spencer & Bethel, 1959) but has not hitherto been shown to cause SLE, although quinine, which is closely related chemically, has been incriminated. It is surprising that our patient had had procainamide without complications, since this drug frequently causes SLE (Fakhro, Ritchie & Lown, 1967) and is the most potent drug capable of activating lupus (Alarcon-Segovia, 1969). It was not the precipitating factor in our patient because the features of lupus did not appear until 18 months after the drug had been stopped. Previous series (Fakhro *et al.*, 1967) have emphasized that the lupus syndrome develops during chronic therapy (3–22 months) with procainamide and regresses when the drug is stopped and that arthralgia is present in every instance, with pleurisy occurring in the majority.

Although SLE had developed, quinidine had to be continued since it was the only drug which controlled the tachycardia that on several occasions caused severe heart failure. When corticosteroids were added both her skin and general health improved, the white cells and platelets increased, though the haemolytic anaemia has persisted.

Drug-induced SLE is becoming well recognized. It resembles the spontaneous form clinically, serologically and histologically, and is probably more common in females. It occurs in an older age group who are more likely to be given the responsible drugs, and differs from the spontaneous form in that renal complications are less common. The prognosis, after withdrawal of the drug, is usually good. Theoretically the aetiology of SLE might be clarified from a knowledge of the drugs which cause this variant. However the many drugs responsible do not have anything in common except that many can cause hypersensitivity reactions and some may occasionally cause leucopenia, thrombocytopenia and haemolytic anaemia.

Fig. 2. Results of investigations shown in relation to drug therapy. The upper scale is for haemoglobin in g/100 ml, reticulocytes as % and bilirubin in mg/100 ml. The lower scale is for the white cells $\times 10^3$ and platelets $\times 10^4$.

The reported cases of drug-induced lupus probably represent the tip of an iceberg. A positive ANF occurs in all instances of procainamide-induced lupus but serological abnormalities have been recorded in up to 65% of patients taking procainamide (Dubois *et al.*, 1968) and in 67% of tuberculous patients on isoniazid (Alarcon-Segovia, 1969). Until the mode of action is understood, any drug might be suspect and presumably also any food additive. Some preparations shown to be responsible are no longer in common use but the risk should be remembered when considering long-term therapy with any of the following:—

- (1) Anticonvulsants: phenytoin, troxidone, primidone.
- (2) Antibacterial and fungal agents: sulphonamides, penicillin, tetracycline, griseofulvin.
- (3) Antituberculous therapy: streptomycin, PAS and isoniazid.
- (4) Antirheumatic preparations: phenylbutazone, gold, long-term steroids.
- (5) Cardiac depressants: procainamide, quinidine.
- (6) Antithyroid drugs: methyl and propyl thiouracil.
- (7) Hypotensives: hydralazine, methyldopa, reserpine.

(8) Others: antihistamines, chlorpromazine, oral contraceptives and quinine.

Any of these drugs may precipitate an exacerbation of SLE or explain the development of rashes, hepatosplenomegaly, arthropathies or blood dyscrasias. Awareness of this is important for the drug can then be stopped. Although the prognosis of drug-induced SLE is usually good, fatalities have been reported (Holley, 1961).

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Accident proneness in hypothyroidism

SIR—It is not generally realized that patients suffering from hypothyroidism have more accidents at home than can be accounted for by chance alone. This became apparent during a recent survey of the psychiatric aspects of hypothyroidism, in which I had the opportunity of examining thirty consecutive patients referred for investigations to the Department of Nuclear Medicine, Liverpool University which provides a regional diagnostic service.

Six of the thirty patients interviewed were brought to medical attention as a result of accidents at home. One was overcome by fumes, one fainted and the remaining four had a fall. None of them had cerebellar signs as reported by Jellinek & Kelly (1960), and only two of the six were sufficiently forgetful for this to account for the accident. Lloyd & Goldberg (1961), in their survey of hypothyroidism, found that nine out of every ten proven cases had not been recognized as examples of hypothyroidism by their own doctors, but were referred because of suspected heart failure, cerebral thrombosis, bronchitis, or anaemia, and some were simply labelled 'senile'.

Accidents at home are well-known hazards of the elderly and as a majority of hypothyroid patients are elderly one might suspect a chance association. The ages of patients who

had accidents were 48, 61, 66, 67, 79 and 87 as compared with the total sample of 30, where the range was 20–87 years with a mean of 57.9. A random selection of medical out-patients matched for age and sex, showed only two had accidents at home as compared with six in the hypothyroid group.

It is hoped that publication of this report will lead to recognition of accident proneness as one of the methods of presentation of this condition.

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