

Serum sickness-like syndrome associated with minocycline therapy

J. PUYANA*, V. UREÑA*, S. QUIRCE, M. FERNANDEZ-RIVAS, M. CUEVAS* & J. FRAJ

Departments of Allergy and *Immunology, Ramon y Cajal Hospital, Madrid, Spain

A 19 year-old youth was taking oral minocycline and after 8 days he presented all four cardinal symptoms of serum sickness (urticaria, fever, lymphadenopathy and joint symptoms). C_3 , C_4 and CH_{50} evolution imitate experimental serum sickness complement evolution. We exclude other causes of this syndrome. Although other hypersensitivity reactions have occurred with minocycline usage, to our knowledge serum sickness-like syndrome has not been previously reported with this drug.

Key words: complement; minocycline; serum sickness; tetracycline.

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The tetracyclines are closely congeneric derivatives of the polycyclic substance naphthacenecarboxamide. Minocycline is a semi-synthetic drug obtained from tetracycline. Minocycline inhibits protein synthesis by reversibly binding to the 30 S ribosomal subunit of susceptible microorganisms. It has a broad spectrum of antimicrobial activity being effective against a large number of Gram-positive and Gram-negative pathogenic bacteria, including some that are resistant to Penicillin (8). About 95 % of minocycline is readily absorbed from the gastrointestinal tract (11). It is widely distributed in body tissues and fluids (8). Plasma half-life is about 14 h.

Minocycline is normally given orally but may be given by slow intravenous infusion. The usual dose by either route is 100 mg every 12 h. The main adverse effects are: gastrointestinal irritation, vestibular damage, teeth staining, bone growth interference and superinfections (11).

Frequent immunologic reactions are: exanthematous eruptions, urticaria, angioedema, fixed drug eruptions, exfoliative dermatitis, hemolytic anemia, vasculitis and antinuclear antibodies with or without systemic lupus erythe-

matosus. Systemic anaphylaxis has also been described (9). Pulmonary infiltrates and eosinophilia are exceptional (7).

The following case report is about a patient who developed serum sickness-like reaction induced by this drug.

CASE REPORT

A 19-year-old youth, with neither personal nor familial history of atopy, was taking Minocin (minocycline hydrochloride) at the usual dose (100 mg twice a day) for acne treatment. After 8 days, he presented generalized urticaria which was predominantly on the legs and trunk. Some hours later, he also presented angioedema of eye-lids, hands and feet, some petequeal lesions on the legs, fever (38.3°C), tender cervical, inguinal and axilar lymphadenopathy and intense arthralgia of both ankles associated with slight swelling, local heat and redness. Mobility limitation was not present. He was not taking any other drug. He had no intercurrent infection.

The following laboratory tests were normal or negative: complete blood cell count, including differential cell count, blood biochemistry,

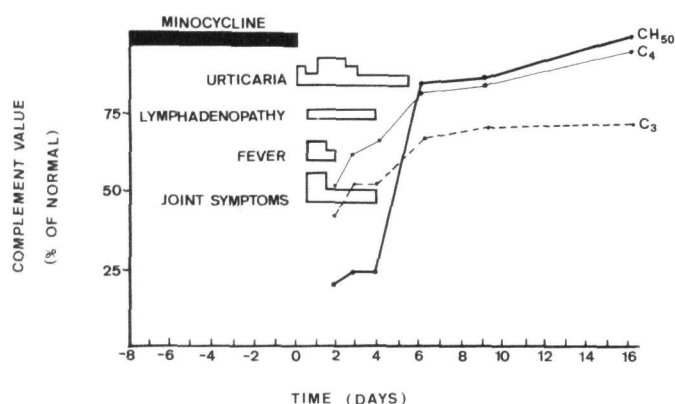


Fig. 1. Clinical and complement (CH_{50} , C_3 and C_4) evolution after 8 days on minocycline. Clinical symptom score is represented on a 0 to 3 scale. Complement values are represented as a % of normal value.

platelet count, prothrombine time, urine analysis, HBSAg, VDRL, Epstein-Barr virus serology, anti-streptolysin O test, respiratory virus serology, 3 blood cultures, antinuclear, anti-mitochondrial and anti-smooth muscle antibodies, rheumatoid factor, direct and indirect Coombs test, ECG, spirometry, chest X-ray and ankle X-rays. ESR was 16 mm, IgE = 86 μ g/l, serum protein electrophoresis was normal except for a slight increase in gamma-globulins (17 g/l). Circulating immune-complexes were not detected by laser nephelometry using polystyrene particles coated with C1q (Behring). Haemolytic complement titer (CH_{50}) was quite low (minimum value was 23 % of normal value).

Minocycline was withdrawn and the patient was treated with hydroxicine (25 mg/8 h) and AAS (500 mg/8 h). The evolution can be seen in Fig. 1. The four cardinal symptoms are presented here. We have used the symptom score in 0 to 3 scale (3 = severe, 2 = moderate, 1 = slight and 0 = none). We can see that urticaria preceded the other symptoms by about 12 h and was present until 36 h later. Urticaria score peaked on the 2nd and 3rd day. The patient's symptoms lasted < 6 days. However, dermographism was present for 6 days more. CH_{50} was determined on days 2, 3, 4, 6, 9 and 16 of illness. It was slow on days 2, 3 and 4. On the 6th and 9th day, when symptoms had disappeared, CH_{50} was almost normal. C_3 and C_4

values show a parallel evolution which was less intense.

DISCUSSION

Serum sickness is a clinical syndrome resulting from the injection of foreign protein and the individual's subsequent immune response. There is agreement that this is the human equivalent of immune complex-mediated experimental serum sickness observed in animal models (1, 2). With adequate immunization procedures, the development of effective antimicrobial therapy, and the use of human antitoxins serum sickness has declined. Serum sickness-like reactions that are secondary to the administration of non-protein drugs are clinically similar, if not identical, to classic serum sickness (1). Currently, penicillin is the drug most frequently implicated.

Clinical manifestations typically occur 6 to 21 days after antigen administration. The four cardinal manifestations are fever, skin eruption, lymphadenopathy and joint symptoms. The majority of serum sickness-like reactions are mild and usually resolve spontaneously within a few days to weeks. In serum sickness-like reactions there is no universally present abnormality or single laboratory test that is definitively diagnostic. When an individual has received foreign proteins or non-protein drugs and, within the appropriate time lag, the classic findings of serum sickness are manifested, the diagnosis should be readily apparent (3).

Our patient was taking minocycline and with a time lag of 8 days, he presented all four cardinal symptoms. Clinical evolution after drug withdrawal and antihistamine and AAS treatment was excellent. All symptoms disappeared in less than 6 days. Laboratory investigations failed to demonstrate any other etiology of his symptoms. CH_{50} largely decreased before the 6th day, which is coincident with the symptomatic period. We did not find circulating immune complexes, but these are not detected in a significant proportion of patients with serum sickness (5, 6, 10). C_3 and C_4 decrease was parallel but less intense than CH_{50} , which is in agreement with classic pathway activation.

C₄ and CH₅₀ evolution imitates experimental serum sickness complement evolution.

In our patient clinical and laboratory findings point to a serum sickness-like reaction induced by minocycline.

We think this case report is interesting because:

- 1) to our knowledge serum sickness-like reactions have not previously been reported with minocycline,
- 2) it is unusual to find serum sickness-like reactions paralleling complement evolution and so clearly imitating experimental serum sickness syndrome.

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Address:

Jesus Puyana, M.D.

C/ Virgen de Aranzazu 33, 3^o C.

Madrid 28034

Spain

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