Letter to The Editor

LOW-DOSE METHOTREXATE POTENTIATES PLATELET AGGREGATION IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Low dose methotrexate (MTX) is used as a second line drug for the aggressive therapy of rheumatoid arthritis (1). It is also used in high doses to treat various neoplastic disorders, as well as being used as an immunosuppressive agent. The use of this drug though may be fraught with many dangers. Although its side effects have been well established in higher doses (2), it has been observed that treatment with low-dose may also cause significant toxicity. The Committee on Safety of Medicines has recently alerted users of low-dose MTX to reports of blood dyscrasias and other adverse outcomes. WHO reports 83 cases of dyscrasias and 36 fatal outcomes in the last 2-3 years (3,4). The reasons for this fatal outcome are not completely understood. It is known that the release of chemical mediators during the inflammatory process in RA trigger platelet activation not only locally at the site of the inflamed joint but also perhaps systematically. This study sought to determine whether the plasma of RA patients influenced platelet aggregation, and whether this was enhanced by the use of low-dose MTX. The low-dose MTX associated amplification of platelet aggregation in RA patients has not been previously reported.

Patients for this study were selected from the Rheumatology outpatient clinic at the Aga Khan University Hospital, Karachi. All patients were diagnosed as having RA on well-defined criteria (5). A total of 16 samples were collected which were divided into two groups. The first group (n=7) was the control group and comprised of patients taking an NSAID (diclofenac sodium 50 mg/BD) for the past two months. The second group (n=9) was composed of patients who were treated with NSAID's for two months and then switched to methotrexate (7.5 mg/week) for a minimum of two months. Blood from patients was drawn by venipuncture, mixed with sodium citrate 3.8%, and centrifuged at 1200 rpm for ten minutes to prepare platelet poor plasma (PPP) for use in the platelet aggregation studies. Blood was then drawn from normal healthy adult volunteers, and platelet rich plasma (PRP) was prepared by centrifugation at 2600 rpm for 15 minutes. All aggregation studies were carried out at 37°C with the PRP having platelet counts of 2.5 x 10^8 /ml.

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To investigate the effects of plasma, two complimentary test methods were used (6,7). In the first, plasma obtained from patients in group I (RA alone) did not induce aggregation when added directly to PRP (aggregation was 2% ± 5, N = 7). However, the plasma of group II patients (RA + MTX) showed a dose-dependant increase in aggregation when added directly to PRP (aggregation 90% ± 5, N = 9). The results were analyzed by Students t-test and the p value against the control group was found to be <0.001. In another experiment, it was found that plasma of group II patients induced a profound potentiation of aggregation (aggregation 80% ± 5, N = 9) when added to sub-threshold doses of platelet agonists such as adrenaline, arachidonic acid, collagen and platelet activating factor. This potentiation was absent when tested on plasma from group I. In addition, MTX alone (0.01 - 100 mM) had no effect on platelet aggregation.

In light of these results, we can conclude that use of low-dose MTX in patients with RA does in fact enhance the platelet aggregation phenomenon, and that this should be considered as a potential adverse affect in patients on this treatment, which may in fact be a contributing factor to the fatal outcome. This is an observation that requires study in further detail.

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