LEADING ARTICLE

THE MEGA SHOT

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The big top has come here to stay. Recently, the mega top arrived - more powerful, more fuel efficient, more comfortable, etc. All these refer to Boeing aircraft, of course. Almost 13 years ago, there was an editorial in the Lancet titled 'The Big Shot' (1), which surveyed the uses and usefulness of large intravenous doses of steroids in disease states. Methylprednisolone (MP) given as 1-2 grams boluses over 5 to 30 minutes was fashionable. Side effects were few - transient weakness, flushing, a metallic taste in the mouth and transient hypotension. The half life of the drug is only 2 1/2 hours. Its purported therapeutic benefits? - a complex action on the lymphoproliferative system. Pulse dosing lowered blood lymphocyte counts temporarily, altered their function with little effects on polymorphs. Its clinical indication was mainly to treat organ transplant rejection episodes - mainly kidneys. It was to eradicate "passenger" lymphocytes in donated kidneys and also to protect them from the harmful effects of ischemia, probably by preventing the release of lysosomal enzymes. Then, cyclophosphamide was given with MP to improve their objectives but today, cyclosporin A is the successfully used drug of choice (2).

In this Journal issue, Howe et al (2) analysed, in a retrospective study, 39 patients with systemic lupus erythematosus (SLE) given MP in pulse fashion. The dose was 10 mg/kg body weight intravenously over an hour daily for three consecutive days. 27 had lupus nephritis and 12 had non-renal lupus. 17 (63.0%) and 7 (58.3%) respectively responded in each group. No acute complications were noted. These 24 survived the acute episode of SLE but 15 died (a mortality of 38.5%), 8 of whom died within a week of the pulse therapy and another 3 in the second week.

There are various ways of administering the mega shot but the bolus pulses appear fashionable as mentioned in Howe's article. Doctors use it when conventional therapies appear to have failed and life-threatening situations are on hand. There is a significant lack of well-controlled trials in the use of this drug for SLE. It was in 1976 that the beneficial effects of MP pulse therapy on diffuse proliferative lupus nephritis appeared (4). The rationale for the mega shot was the higher therapeutic effect while minimising toxicity. In similar trials, 12 out of 34 (almost 33.0%) patients with lupus nephritis improved (5) and 8 out of 20 (40.0%) of active SLE patients showed partial improvement 12 weeks after the pulse MP treatment (6). All these were uncontrolled trials.

In 1982, there was reported a small double blind placebo controlled trial of monthly pulses of MP in SLE patients (7). 9 patients with biopsy-proven diffuse proliferative glomerulonephritis were in the trial. One gram of intravenous MP was administered on 3 consecutive days on a monthly basis for one year. The authors concluded that the treated group had a better maintenance of renal function. A larger study (8) with 21 patients failed to show therapeutic efficacy.

The largest double blind placebo controlled trial reported to date (1988) had 25 active SLE patients given intravenous MP as additional therapy to conventional oral steroid treatment (9). The dose was 1 gram over 4 hours in 500 ml of normal saline on 3 consecutive days for one course only. In the first 2 weeks after the treatment, there was overall improvement with faster resolution of hypocomplementemia. Other monitored parameters showed no difference. By one month of follow-up, there was no difference between the groups.

Thus, while in uncontrolled trial situations the response for individual very ill SLE patients may be gratifying, under more stringent scientific scrutiny, the way physicians have used intravenous pulse MP has not given the expected clear-cut benefit expected of the drug.

Perhaps the dose is wrong. In the kidney transplant situation, a common regimen was 1 gram every 12 to 24 hours and up to 25 grams was used in a single course but prolonged high doses predispose to septic complications and death (1). In Howe's article, 11 of her 39 patients had infection and 7 died from the infection so that in SLE patients, the trade-off using too many mega doses seems unacceptable. Perhaps one course of 3 grams per course is inadequate and the pulses need to be continued for several courses.

The mega shot has also been tried in rheumatoid arthritis (RA) patients where the result was also equivocal (10). 20 patients with active RA were randomised to receive MP or placebo. 10 patients received intravenously 1 gram MP over 40 minutes as an infusion on an outpatient basis. Only one dose was given and patients were reassessed six weeks later. All their clinical variables improved - grip strength, finger measurements, morning stiffness, pain and mobility. But the 10 patients given placebo also improved!

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As with the renal transplant rejection experience, too mega a dose of MP is counterproductive. In 1977, the recommendation was to give no more than 6 to 8 grams and if it proved ineffective, the kidney was removed (1). For severely ill SLE patients, it may be feasible to double the present 1 gram bolus doses to give a pulse of 6 grams over 3 days and to use four or six weekly maintenance doses. However, the present report shows that by the end of the second week, 11 of the 15 patients had succumbed, 8 within the first week so that the big shot of yesteryears may presumably be increased to the mega shot of today as a means of saving these desperately ill SLE patients.

The other approach is to prevent such patients arriving at the threshold of death by initiating more promptly immunosuppressive regimens with cytotoxic drugs other than steroids of any kind. Oral daily cyclophosphamide has been in use for a long time, then replaced by azathioprine to a large extent because of unacceptable long term cyclophosphamide side effects. The trend today is leaning towards intravenous pulse cyclophosphamide especially for renal lupus patients. If by such regimens renal function can be preserved, the mega shot would be less frequently used as a life-saving measure because to date its efficacy remains suspect.

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