A different look at pulsed glucocorticoid protocols; Is high dose oral prednisolone really necessary just after initiation of pulse therapy?

Mona GhaseMian1, Mohammad Bagher Owlia2
1Faculty of Pharmacy; 2Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

ABSTRACT

Pulse glucocorticoid therapy is pivotal in severe and life threatening forms of rheumatic and immune-mediated conditions. High dose oral prednisolone has numerous adverse effects and should be balanced with the advantages. Minimal effective dose of most drugs warrants minimal systemic and local side effects. There are limited controlled trials to validate optimal or minimal effective dose, duration and interval of pulse therapies. Considering the relative high biologic half-life of pulsed methylprednisolone, we hypothesize that oral high dose prednisolone could be changed to rather low oral dose during monthly pulse intravenous methylprednisolone.

Key words: glucocorticoids, corticosteroids, pulse therapy, immunosuppression, biologic half-life, pharmacology, high dose oral prednisolone

Glucocorticoids (GCs) or corticosteroids that are biologically similar to adrenal cortical hormones have created revolution in remission of widespread diseases especially in rheumatic and immunologic disorders. Timing of administration and therapeutic dose of this class of medicine varies widely depending on the type of disorder and stage of disease from as little as 1 mg every other day to as high as 1000 mg/day intravenous infusion. This dose variability is one of the specific features of GCs. However, daily and routine use of these drugs in clinical practice makes them very important regarding safe dosing of the drug. This variability warrants choosing optimal treatment protocol and dose schedule.

Practically our goal is to provide a medicine with the highest efficacy and the least short and long term adverse effects. Among those various treatment protocols, pulse glucocorticoid therapy is pivotal in severe and life threatening forms of rheumatic disease and immune-mediated conditions, such as lupus nephritis, Goodpasture syndrome, crescentic glomerulonephritis, and most kinds of systemic necrotizing vasculitides. Pulse therapy is defined as the rapid intravenous infusion of ≥ 250 mg of prednisolone or its equivalent (10-15mg/kg Solu-Medrol/methylprednisolone) per day for 1 or a few days. In spite of the fact that 1 g methylprednisolone (MEP) daily for 3-5 days has been approved as pulse therapy protocol, some clinical studies have shown that 100 mg MEP daily for 3 days is enough for saturating most of GC receptors and as efficacious as 1000 mg per day for 3 days (Fig. 1). There are limited controlled trials to validate optimal or minimal effective dose, duration and interval of pulse therapies. It seems that the most pharmacologic studies working on ‘maximum tolerable’ doses of most drugs rather than ‘Minimal effective’ doses and this warrants careful attention in clinical drug usage. In a clinical trial, the author of this report showed that half doses of depot methylprednisolone could be as effective as standard and routine dose of 80 mg of this drug in epidural steroid injection for lumbar radicular pain.

Methylprednisolone is frequently preferred to other GCs for pulse therapy because of its acceptable water and salt retention and strong non-specific, non-genomic effects (which are appeared within seconds to minutes after infusion) on human cells in higher doses. In clinical practice, simultaneous use of oral prednisolone with doses of 0.5 -1 mg/kg/d [high dose oral prednisolone (HDOP)] is standard of care as concomitant therapy to achieve maximum immunosuppressive effect. Considering the exponential increment of the acute and long term side effects with cumulative doses of GCs, and the potential long biologic half-life of pulsed GCs, we hypothesized that concomitant high dose oral prednisolone not only might be un-necessary but also it may impose more and more unwanted side effects. Among them, volume overload (clinically evident by accelerated hy-
pertension or congestive heart failure and pulmonary edema), incidental overt diabetes mellitus as well as opportunistic infections (which directly correlate with hypoalbuminemia and the cumulative dose of GCs) are the most dread complications.

Our initial observations (un-published data) showed that eliminating this section of early high dose oral prednisolone (HDOP) has not a major impact on optimal immunosuppression induced by pulsed GC therapy with remarkable decrease in observed adverse effects.

The major advantage of pulse therapy is maximizing the immunosuppression via non-genomic effects of GCs and reducing almost all adverse effects including hypothalamus-pituitary-adrenal axis suppression. However, HDOP may offset this advantage by adding unacceptable side effects. Early infections (oro-gastrointestinal candidiasis or other hospital acquired infections) may badly impact early and long term outcome, hospital stay and more importantly the mortality.

Investigations have demonstrated that in the rheumatic disease flare up, the number of membrane GC receptor (mGCR) positive monocytes is increased.

Figure 1, Outcomes after 1000 mg/day MEP infusion for 3 days in 11 patients with systemic lupus erythematosus (SLE) compared with 100 mg/day MEP in 10 SLE patients in same duration. With courtesy of Dr. Iglehart IW (1990) and Dr. Edwards (1987).

Figure 2, comparison of IgG, IgA and IgM variations after 96 mg MEP daily for 3-5 days in 14 healthy subjects and 10 untreated control volunteers. Each colour indicates an individual patient (diamond) or a control (triangles). (Extracted results from Dr. Butler study, 1973)
In other words, mGCRs are up-regulated following stimulation of immune system and the count of mGCR goes back to the basal level after returning to baseline state. The exact role of mGCR is not clearly known, but possibly they may play a pivotal role in disease pathogenesis. As half-life of monocytes is about 1 -3 days, so theoretically, remission induced by pulse therapy, could persist after 3 days or more. In addition, protein binding of methylprednisolone is about 77%, it means that just 23% of the MEP plasma concentration is pharmacologically active and the rest of them play role as a reservoir, thereby after the end of pulse therapy and GC disposition, the drug molecules which have been bound to plasma protein, are gradually released and the plasma concentration of GCs reaches at an acceptable level.

Another important point is that GCs have lipophilic nature which leads to accumulation in adipose tissue as additional reservoir. In several textbooks it has been proposed that the biologic half-life of MEP is 18 -36 h, however, cumulative tissue exposure occurred in patients who have received high doses of intravenous MEP, may lead to longer lasting effect of MEP on immunity for up to 2 -3 weeks and in some cases up to 3 months (Fig. 2) supporting our idea. Although the necessity of HDOP have been addressed in near all rheumatology guidelines, however, well-designed randomized controlled trials are required in order to investigate the risk-benefits of HDOP after pulsed corticosteroid therapy.

ACKNOWLEDGEMENTS
We would like to express our gratitude for all the valuable comments and graphical assistance we have received from Mr. Sina Owlia, student of medicine.

REFERENCES