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High-dose Oral Corticosteroids for Relapses of Multiple Sclerosis

Access:

professional

Article type:

drug information

Reprise: Plenty of prednisone – high-dose oral corticosteroids for relapses of multiple sclerosis

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In October 2004, the BC Drug and Poison Information Centre published an article in the *Tablet* discussing the use of high-dose oral prednisone for relapses of multiple sclerosis (MS).(1) It appears timely to visit the subject again, considering the number of calls DPIC's Drug Information Service continues to receive on this subject. This article summarizes the literature available to date, and also reviews current practice.

Background in brief

MS is an inflammatory disease of the central nervous system that damages the myelin sheath surrounding nerves in the brain and spinal cord. This damage results in characteristic plaques or sclerosed (scarred) areas, and neurologic symptoms including weakness, vertigo, gait impairment, and optic neuritis. The cause of MS is not yet known, though it is thought to be an autoimmune disease.(2)

High-dose intravenous (IV) methylprednisolone is commonly used to manage relapses of MS. A typical regimen is 500-1000 mg once daily for 3-5 days.(3) Compared to placebo, these doses have been shown to improve disability scores measured 5 or 7 days after start of treatment, and subjective improvement has been described within 3 days.(4,5) More recently, high-dose oral corticosteroids have been used in place of intravenous regimens to improve accessibility and convenience for patients. Two studies (6,7) assessing efficacy of high-dose oral corticosteroids for the treatment of MS relapses were reviewed in detail in the previous article, (1) and brief summaries of these studies are presented here.

Clinical trials

In a randomized, double-blind, controlled trial assessing high-dose oral corticosteroids for the treatment of acute relapses in MS patients, equivalent doses (500 mg) of both oral and IV methylprednisolone were compared.(6) The results suggest that oral methylprednisolone is

similar in efficacy to IV therapy, but problems such as small sample size (n=35) and possible unblinding due to metallic taste in the IV group limit the validity of these findings.

A subsequent double-blind study compared oral methylprednisolone to placebo for the treatment of MS relapse.(7) This study used oral methylprednisolone 500 mg daily for 5 days followed by a 10-day taper. The results favored use of methylprednisolone, although some of the outcome measures did not reach statistical significance and others were of uncertain clinical significance. The study also had a small sample size (n=51).

To date, clinical trials have provided limited evidence supporting the efficacy and safety of oral corticosteroids for the treatment of MS relapses. The larger OMEGA trial mentioned in the previous Tablet article is still underway. Its goals are to enroll 120 patients and compare efficacy of methylprednisolone 1000 mg IV with 1400 mg oral for MS relapses.(8) It is hoped that results from this study will help clarify questions regarding dosing, efficacy and safety of high-dose oral corticosteroids. It will, however, not provide direct evidence for the high-dose prednisone prescriptions (e.g., 1250 mg daily for 3 days) most commonly seen by pharmacists in British Columbia. Studies specifically examining the efficacy of high-dose prednisone regimens in this setting have not been published. One randomized study has been published which examined the area under the curve of oral prednisone compared to IV methylprednisolone.(9) Adult patients beginning steroid treatment for an MS relapse received either 1250 mg oral prednisone (n=8) or 1000 mg IV methylprednisolone (n=8). Serum levels of prednisolone (the active metabolite of prednisone) and methylprednisolone were measured over the subsequent 48 hours, and AUC values were calculated after adjusting for higher potency of methylprednisolone. Wide confidence intervals were noted with both routes, indicating large interpatient variability. Mean AUC measured at 8 hours was significantly greater for IV methylprednisolone, but there were no differences at 24 and 48 hours. Although the authors were measuring two different substances, by factoring in relative potencies they concluded that the two regimens delivered what should be equivalent doses. Neither tolerability nor effectiveness were measured outcomes.

Tolerability

In addition to efficacy, tolerability of oral therapy is a concern. While serious problems have not been reported, adverse effects in this setting have not been adequately evaluated. Reported problems with high-dose oral corticosteroids include insomnia, mood changes (e.g. irritability, euphoria, psychosis), gastrointestinal upset (e.g. nausea, heartburn), flushing and weight gain.(6,7,10) Hyperglycemia and increased susceptibility to infection are also possible and have been reported with 5 days of methylprednisolone 1 gram IV for MS.(11) The use of corticosteroids is uncommonly associated with osteonecrosis (damage to bone due to loss of blood supply).(12) It is not possible to assess the risk of a 3-5 day MS relapse treatment with currently available data.(13)

Clinical practice

Despite limited published evidence supporting the use of oral corticosteroids for MS relapses, specialized clinics in a number of provinces commonly prescribe high-dose oral prednisone for their patients. According to a recent survey of these centres performed by DPIC, it was found that regimens vary from 1250 mg prednisone every 2 days for 5 doses, to 1000 - 1250 mg prednisone daily for 3-5 days. The MS Clinic located at UBC Hospital in Vancouver has used a regimen of oral prednisone 625 mg twice daily at breakfast and lunch for 3 days with no tapering doses. This particular regimen is used because twice daily dosing is believed to improve gastrointestinal tolerability, while giving the second dose at lunchtime is thought to minimize insomnia compared to giving the dose later in the day. Individualization of relapse

therapy based on patient- and disease-specific factors may influence decisions about the specific corticosteroid route and regimen the patient receives. These factors include previous responses to oral corticosteroids, prior history of adverse effects, severity and nature of relapse symptoms, and the number of corticosteroid courses received over the previous year.

With accepted therapeutically equivalent anti-inflammatory doses (14), a 1250 mg dose of prednisone should be equivalent to 1000 mg methylprednisolone, although the impact of different routes of administration is not clear. None of the MS clinics across Canada surveyed use oral methylprednisolone, though it is available in Canada as Medrol® 4 mg and 16 mg tablets (16 mg tablets were on back-order when this article was written).(15) Using oral methylprednisolone 500 mg daily would be more expensive (approximately \$175 more for a 5-day course) and require a larger number of tablets than using oral prednisone 1250 mg daily if commercially available products were used.

Summary

For patients suffering from MS relapses, the desire for improved treatment accessibility and convenience has led to use of high-dose oral corticosteroids as an alternative to the IV route. Limited published evidence suggests oral treatment has beneficial effects in MS relapse and it appears well tolerated, although there is little consensus about the optimal course of therapy. Individualization of corticosteroid regimens (route, dose, duration) is important to optimize benefit and minimize adverse effects. Clinical trials of high-dose oral prednisone to determine efficacy, safety and optimal dosing regimens would be welcomed.

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Originally published in BCPHA Tablet. 2007;16(5):6

Keywords: prednisone
methylprednisolone
multiple sclerosis

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