

MS Patients Report Excellent Compliance with Oral Prednisone for Acute Relapses

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ABSTRACT: Background: Multiple Sclerosis is characterized by relapses separated by periods of relative quiescence. High dose intravenous corticosteroid pulses for three to five days is the current standard for the treatment of acute relapses, but recent evidence supports the use of equivalent doses of oral therapy as an alternative. The highest single dose preparation of oral prednisone is a 50mg tablet, requiring patients to take 25 tablets a day. Questions regarding compliance with this oral regimen have been raised. **Objectives:** To determine whether MS patients are compliant with 1250mg of oral prednisone daily for acute relapses. **Methods:** Between November 2008 and December 2009, all patients diagnosed with an acute relapse in the London (Ontario) MS clinic were prospectively identified. If treatment with oral prednisone was initiated, subjects were given a survey to be mailed anonymously to the clinic. **Results:** Sixty-eight MS relapses were diagnosed and treated with corticosteroids in 66 patients of which 60 (58 subjects) were treated with 1250mg prednisone. Fifty-three (91.4%) surveys were returned. The reported compliance rate was high at 94.3% (50/53) with only one patient reporting being unable to take all the required pills due to intolerance. Most subjects (43, 86.0%) encountered at least one side effect, most commonly insomnia, mood changes and increased appetite. Two thirds of subjects (69.8%) indicated a preference for oral medication for future relapses. **Conclusion:** High dose (1250mg) oral prednisone is an acceptable therapy to MS patients for the treatment of acute relapses with a high rate of compliance.

RÉSUMÉ: Les patients atteints de SP rapportent une excellente fidélité à la prednisone administrée par voie orale lors d'une poussée aiguë. **Contexte :** La sclérose en plaques (SP) se caractérise par des poussées alternant avec des périodes de stabilité relative. La corticothérapie à haute dose en perfusion intraveineuse rapide pendant trois à cinq jours est le traitement standard actuel des poussées aiguës. Cependant, il existe des données récentes en faveur de l'utilisation de doses équivalentes de stéroïdes par voie orale. La dose unique la plus élevée de prednisone par voie orale est de 50 mg par comprimé, ce qui implique que les patients doivent prendre 25 comprimés par jour. Ceci a soulevé des inquiétudes quant à la fidélité au traitement par voie orale. **Objectifs :** Le but de l'étude était de déterminer si les patients atteints de SP sont fidèles au traitement lorsqu'ils doivent prendre 1250 mg de prednisone par voie orale quotidiennement lors d'une poussée aiguë. **Méthode :** Tous les patients chez qui on a posé un diagnostic de poussée aiguë entre novembre 2008 et décembre 2009 à la clinique de SP de London en Ontario ont été identifiés de façon prospective. S'ils recevaient la prednisone par voie orale, on leur remettait un questionnaire qu'on leur demandait de remplir et de poster à la clinique de façon anonyme. **Résultats :** Soixante-huit poussées de SP ont été diagnostiquées et traitées par corticothérapie chez 66 patients, dont 60 (58) patients qui ont été traités par la prednisone à 1250 mg. Cinquante-trois (91,4%) des sondages ont été retournés. Le taux de fidélité au traitement tel que rapporté par les patients était de 94,3% (50/53) et seulement un patient a rapporté qu'il n'avait pas été capable de prendre tous les comprimés prescrits parce qu'il ne les tolérait pas. La plupart des sujets (43, soit 86,0%) ont eu au moins un effet secondaire, les plus fréquents étant l'insomnie, les changements d'humeur et l'augmentation de l'appétit. Les deux-tiers des sujets (69,8%) ont indiqué une préférence pour le traitement par voie orale lors d'une éventuelle poussée de SP. **Conclusion :** La prednisone à haute dose (1250 mg) par voie orale est un traitement acceptable chez les patients atteints de SP pour le traitement de poussées aiguës et le taux de fidélité au traitement est élevé.

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Multiple Sclerosis (MS) is the most common disabling neurological disease of young adults, especially in Canada, where the overall prevalence is 240/10,000¹. Most (85%) patients are diagnosed with relapsing remitting (RR) MS at presentation² and up to 40% of secondary progressive (SP) MS patients continue to have relapses³. Corticosteroid treatment may improve the speed of functional recovery with acute MS relapses but does not provide any long-term functional benefit⁴. There is currently no compelling evidence that the clinical benefit of high dose corticosteroids is influenced by the route of administration, the particular corticosteroid prescribed, or the dosage of corticosteroid^{5,6}. Traditionally, intravenous (IV) administration of corticosteroid preparations has been used, but oral therapy is less expensive and more convenient for the patient⁷. Recent

studies have supported the bioequivalent and clinical equivalence of high dose oral corticosteroids for MS relapses^{8,9}, and a recent Cochrane review found no evidence to support one regimen as superior¹⁰. Furthermore, studies support the gastric safety of high dose oral steroids¹¹. Oral administration is considered more suitable by MS patients, as it avoids traveling

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to an IV site and the risk associated with IV placement⁷. The dose and formulation of oral corticosteroid given in our clinic is 1250mg of prednisone per day, based on a pharmacokinetic study comparing this dose to the standard IV dose of 1000mg of methylprednisolone⁹. The highest strength in a prednisone oral tablet is 50mg; thus, patients must swallow 25 relatively large tablets of chalky consistency each day to achieve full compliance. If the patient was unable to tolerate this oral dosing regimen, the benefit associated with an oral prescription would be diminished or abrogated. Unlike IV therapy where compliance can be objectively monitored, there is no guarantee that the patients will be compliant with the oral corticosteroid prescription. Compliance is an important issue in all areas of medicine, even for short courses, such as the regimen used for an acute demyelinating event. Thus, the purpose of this study was to assess compliance of MS patients to high dose oral prednisone prescribed for the treatment of a relapse as well as to potentially identify any barriers to compliance with this regimen.

METHODS

Between November 1 2008 and December 31 2009, any patient of the London MS clinic, in London, Ontario, Canada assessed for a potential relapse, either by telephone contact or clinic visit, was identified by the treating clinician. Once a relapse has been confirmed and the treatment plan initiated, patients treated with oral prednisone as an outpatient were offered participation in this prospective survey study. Patients who required hospitalization or were treated with IV corticosteroids were not approached to participate; however, a tally was kept of the total number of patients treated for a relapse. A one page (two-sided) questionnaire was given to patients with the oral prednisone prescription. The questionnaire was anonymous; he/she was given an unmarked postage-paid return envelope. Each subject was only included in the study once. If he/she had more than one relapse treated with oral corticosteroids during the study, the patient was approached to participate during the first relapse only. One week after the initial contact, a clinic staff member called to remind the participant to return the questionnaire, without addressing the patient's compliance to the medication or coercing the patient to participate. Data collected included demographic information, type of MS, and data regarding the patient compliance with the medication as well as any reasons why he/she could not comply with the medication instructions. This study was approved by the university's research ethics board.

RESULTS

Sixty-eight relapses in 66 patients were treated for an acute relapse during the study, of which eight were treated with IV corticosteroid. Thus, 58 subjects were invited to participate in the study. All patients treated with oral corticosteroids agreed to participate and were given the survey, however, only 53 (91.4%) surveys were returned. There were 34 (64.2%) women in this sample, with the following age distribution: two (3.8%) < 20 years, 9 (17.0%) 21-30 years, 19 (35.8%) 31-40 years, 17 (32.1%) 41-50 years and 6 (11.3%) >50 years old. Most of the patients identified themselves as relapsing remitting MS (46, 86.8%) while three (5.7%) had a diagnosis of clinically isolated syndrome. The average disease duration was 7.0 years.

Almost all subjects (49, 92.5%) were treated with five days of 1250mg oral prednisone without a tapering dose. The reported compliance rate was high at 94.3% (50/53). Only one patient reported being unable to take all the required pills due to intolerance and thus was switched to IV corticosteroids; two subjects did not return the survey. The majority (45, 90.0%) of patients reported taking the 25 pills all at once, while 7 subjects (14.0%) divided the pills into two doses and one subject divided the pills into three doses throughout the day. Most subjects (43, 86.0%) encountered at least one side effect. The most common side effects reported were insomnia (36, 83.7%), mood changes, described as irritability, agitation or euphoria (28, 65.1%), and increased appetite (15, 34.9%) (Table 1).

More than half the cohort had been treated with corticosteroids in the past for a previous relapse (32, 60.4%) and of those subjects, 18 (56.3%) had received oral corticosteroids at least once. When asked regarding preference of route of administration of corticosteroids for future relapses, 37 (69.8%) indicated a preference for oral medication, four (7.5%) preferred IV medication while another four (7.5%) indicated no preference (eight subjects did not respond).

DISCUSSION

Corticosteroids have been used to treat acute demyelinating events for many years, improving the speed of functional recovery, but without any clear long-term impact on degree of recovery or disease course¹². This study demonstrates that compliance with high doses of oral prednisone is not an issue when treating acute demyelinating events such as MS relapses. Administration of corticosteroids intravenously became the standard of practice based on the results of the Optic Neuritis Treatment Trial (ONTT)¹². In this study, the IV methylprednisolone group had a higher rate of return of vision than the placebo group while the oral prednisone group did not. Additionally, treatment with oral prednisone was associated with a higher risk of new episodes of optic neuritis than both the IV and placebo group. However, the treatment groups were not equivalent. The IV group received 1000mg of methylprednisolone daily for three days followed by an oral taper over 11 days, while the prednisone group received a much lower daily dose: 1mg/kg daily for 14 days. Yet, these results have influenced how physicians treat optic neuritis, as demonstrated

Table 1: Reported Adverse Events Associated with oral prednisone for relapse treatment

Adverse Event	N	% of subjects who reported adverse events	% of total cohort
Insomnia	36	83.7	67.9
Mood changes	28	65.1	52.8
Increased Appetite	15	34.9	28.3
Nausea or GERD	9	20.9	17.0
Horrible taste of pills	3	7.0	5.7
Fatigue	3	7.0	5.7
Headache	2	4.7	3.8
Diarrhea or Constipation	2	4.7	3.8
Limb Edema	2	4.7	3.8
Worsening hypertension	1	2.3	1.9
Worsening Blood glucose	1	2.3	1.9

by a survey performed six years after the publication of the ONTT study: 95% of neurologists had reduced the use of oral prednisone, with 65% and 53% stating high dose IV methylprednisolone was the most effective way to hasten visual recovery and to reduce future neurologic events of MS, respectively¹³.

Recent evidence supports the use of high dose oral corticosteroids as an alternative to IV therapy, as oral therapy is less expensive, more convenient and generally preferred by patients¹⁴. Morrow et al demonstrated bioequivalency of 1250mg of oral prednisone and 1000mg of IV methylprednisolone⁹. A survey study found MS specialists in Canada use both high dose oral and IV for relapse treatment¹⁵. A 2009 Cochrane review found no significant differences between short term outcomes (\leq 6 weeks) of MS relapse treatment with oral vs. IV corticosteroids but did feel the review was limited by the small subject pool and methodological limitations¹⁰. Our current study further supports the use of oral corticosteroids; not only did the majority of our subjects prefer oral corticosteroids, but also 94.3% were fully compliant, despite a high rate of side effects.

Compliance with oral medications is an issue that permeates all areas of medicine. Compliance is lowest in patients with psychiatric diseases such as depression and schizophrenia^{16,17} with more than half of patients considered non-compliant. However, it is also an issue in other chronic illnesses with compliance in developed countries only at 50%¹⁸. Compliance has also been poor in acute illnesses, requiring only a short course of treatment. For children with otitis media, compliance with antibiotics has been found to range from 18-95% and for adults discharged with a short course of medication from emergency departments, compliance ranges from 50-78%^{19,20}. Thus, our compliance rate of 94.3% is excellent and is not a deterrent to oral prednisone treatment.

There are many limitations to this study. To begin, the London MS clinic uses 1250mg oral prednisone per day for relapse treatment as the first line therapy; subjects who prefer IV therapy may have sought treatment elsewhere, such as with his/her primary care physician, walk in clinics or in the emergency department. Secondly, many of the subjects had received oral corticosteroids before and this may have biased the sample towards subjects who already tolerate or prefer oral administration of corticosteroids. Both of these limitations may have biased the sample towards MS patients who prefer oral administration prior to enrollment in the study. However, almost 2/3 of the cohort (35, 66.0%) had either not received corticosteroids or had only received IV formulations, in the past. Further, this study was based on self-reported compliance which can only be assumed to be fully accurate. Additionally, efficacy was not addressed in this study, only compliance and adverse events, and thus no comment can be made regarding the efficacy of oral corticosteroids for acute demyelinating events. However, other studies previously mentioned do address this issue^{8,9}. Finally, any subject who had a relapse severe enough to be hospitalized was not included, limiting the sample to mild or less disabling relapses.

CONCLUSIONS

There is little concern regarding adverse events and compliance with high doses of oral corticosteroids for the

treatment of acute demyelinating events. However, should the patient be intolerant to the oral treatment, IV therapy can be considered as an alternative.

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