

Tolerance of intravenous methylprednisolone for relapse treatment in demyelinating CNS disease

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Summary

BACKGROUND: In Switzerland, the first course of intravenous steroids for treatment of episodes of demyelinating CNS disease is usually administered in an inpatient setting. We prospectively evaluated short term tolerance of treatment with special emphasis on sleep quality.

METHODS: Patients with a first event of presumed demyelinating disease (CIS), multiple sclerosis relapses (MS) or sub-acute disease progression were treated with a 5-day regimen of intravenous methylprednisolone (IVMP) in our inpatient clinic. Patients' experience was documented by self-report questionnaires including a standardised depression scale (ADSL). Laboratory tests were performed on a routine basis. Fasting glucose, blood pressure and pulse were measured before every infusion. Activity and sleep patterns were analysed by wrist actigraphs during the 5 day infusion period and at follow-up after 1–2 months.

RESULTS: A total of 66 patients participated in the study. Of these, 55 were steroid treatment naïve, and 11 patients, who had received intravenous steroid relapse treatment before, were admitted because of disabling symptoms. Mood disturbances were reported before steroid treatment, however significantly less often at the end of the steroid pulse and during follow-up. Sleep efficiency as measured by wrist actimetry was high before, during and after steroid treatment.

CONCLUSION: Therapy was well tolerated without severe side effects in CIS and MS patients. Sleep efficiency was not disturbed. In conclusion there are no obstacles to change from an inpatient to an outpatient setting for the steroid treatment of relapses in MS and CIS, but rare psychotic reactions to steroid treatment are not predictable.

Key words: multiple sclerosis; intravenous steroid treatment; sleep / activity pattern

Introduction

Intravenous corticosteroids are the mainstay for treatment of relapses of demyelinating CNS diseases [1–6]. It hastens

recovery and seems to prevent relapse progression [7]. To date, there is no sufficient evidence for long term preventive strategies with corticosteroids [8–11]. A recent trial of monthly pulses of methylprednisolone in combination with interferon beta-1a revealed no effect on disability progression [12]. In another recent trial, oral methylprednisolone given in pulses every 4 weeks as an add-on therapy to subcutaneous interferon beta-1a in patients with relapsing-remitting multiple sclerosis (RR-MS) led to a reduction in relapse rate [13]. However, the study involved a small number of patients, had a high dropout rate, and sleep disturbance and neurological and psychiatric symptoms were frequently recorded as adverse events in the methylprednisolone group. Bone mineral density had not changed after 96 weeks. Another study showed slowing of progression of atrophy as seen with MRI in RR-MS patients by monthly steroid-therapy [14].

Oral application of high dose prednisone seems to be equally effective, but involves a higher risk of side effects [3, 5, 15].

The first cycle of high dose intravenous pulse therapy is usually administered in hospital for safety reasons. Potentially severe side effects include epileptic seizures, psychotic reactions, cognitive decline, venous thrombosis, anaphylactic reactions and cardiac arrhythmias [2, 4, 5, 16–21]. If the first therapy cycle is well tolerated, subsequent cycles are usually applied with intravenous methylprednisolone (IVMP) in an outpatient setting unless patients require hospitalisation for disabling relapse symptoms. A British trial evaluated home application of IVMP by specialised nurses to be superior as compared to outpatient administration in terms of patient satisfaction [22]. Therapy was generally well tolerated in this trial of patients with definite multiple sclerosis (MS).

Patients with first episodes of demyelinating disease were usually referred to our in-patient clinic for diagnostic work-up and had not been treated with intravenous steroids before. Our aim was to evaluate the safety of steroid therapy with regard to potential application in a day care unit.

Methods

Patients

Patients were recruited after emergency or elective admission to the neurological in-patient clinic of the University Hospital in Berne from October 2004 to February 2006. Patients with clinically isolated syndrome (CIS), RR-MS, and secondary (SP) or primary progressive (PP) MS were eligible for this study, if IVMP therapy was planned for treatment of acute exacerbation (CIS and RR-MS) or accentuated progression of symptoms (SP and PP-MS). The local ethics committee approved the study and all patients gave written informed consent for study participation. All patients were treated in an in-patient setting. Follow-up evaluation after 4 to 8 weeks was obtained from 48 patients. Clinical follow-up data were collected from 12 patients in remission up to 3 months. Follow-up data could not be obtained in 6 patients.

Procedures

Patients received IVMP 500 mg per day for five days. Infusions were administered over one hour during the daytime, preferably in the hours before noon. The IVMP course was followed by oral tapering of prednisone as follows: prednisone 100 mg for 3 days with a reduction to 50 mg, 25 mg and 12.5 mg for 3 days each. Proton pump inhibitors to prevent gastric side effects and calcium tablets to prevent osteoporosis were routinely administered during IVMP treatment. We created a questionnaire for patients' self-evaluation regarding the impact of the relapse, sleep disturbance, use of sleeping pills and day time fatigue before, during and after treatment. Fatigue included both physical and mental fatigue, which specifically meant fatigue perceived as muscle

weakness and fatigue perceived as loss of attention or sleepiness. Furthermore systemic adverse effects were evaluated. In addition, we evaluated for depressive decline with the ADS-L questionnaire, the German version of the CES (Centre of epidemiological studies Depression scale) at baseline, after the IVMP therapy and at the follow-up visit. Sleep-wake patterns were analysed by wrist actigraphs during the infusion period ($n = 31$) and at follow-up ($n = 17$). An actigraph is an acceleration-sensitive, watch-like device that is typically carried on the non-dominant arm and generates a voltage each time the wrist with the actigraph is moved. By using an actigraph, motor activity can be monitored continuously over a prolonged period during wakefulness and sleep.

Laboratory tests were performed on a routine basis. Fasting glucose, blood pressure and pulse were measured before every infusion.

Upper extremity function was measured before treatment, at day five and at day 30 by a brief, standardised, quantitative test called the Nine-hole peg test [23].

Statistical analysis

Longitudinal analysis of ordinal and metric data was performed using the Wilcoxon-Signed-Rank-Test (p -value, median differences with 95% Confidence Interval (CI)). Statistical analysis of longitudinal categorical data was performed using the McNemar-Test (p -value)

Results

A total of 66 patients were included in the study. Table 1 shows the patient characteristics. The majority were CIS and RR-MS patients. Concomitant disease and vascular

Table 1: Baseline characteristics.

	CIS (n = 36)	MS (n = 30)	Total (n = 66)
Women	28 (77%)	20 (66%)	48 (73%)
Age in years (median and range)	33 (16.–53.)	41 (26–74)	36 (16.–74)
Disease course			
Relapsing-remitting	–	20 (66%)	–
Secondary progressive	–	5 (16%)	–
Primary progressive	–	5 (16%)	–
First steroid course	36	19 (63%)	55 (83%)
Previous steroid courses	–	11 (37%)	–
Delay between first relapse symptoms and steroid infusion, days median (min;max)	7.0 (1; 40)	12.4 (3; 28)	7.5 (1; 40)
EDSS median (min; max)	2.5 (1; 6.5)	3.8 (1.5; 7)	3 (1; 7)
ADS-L median (min; max)	11 (3; 37)	12 (5; 41)	12 (3; 41)

Table 2: Adverse effects indicated by the patients during steroid infusion days 1–5.

	CIS	MS	Total
Taste alteration	24/34 (71%)	14/29 (48%)	38/63 (60%)
Dizziness	10/35 (29%)	9/29 (31%)	19/64 (30%)
Facial flush	16/35 (46%)	16/29 (55%)	32/64 (50%)
Sweating	11/35 (31%)	7/29 (24%)	18/64 (28%)
Palpitations	8/35 (23%)	2/29 (7%)	10/64 (16%)
Dry mouth	15/35 (43%)	12/29 (41%)	27/64 (42%)
Tremor	3/35 (9%)	4/29 (14%)	7/64 (11%)
Hearing problems	4/35 (11%)	2/29 (7%)	6/64 (9%)
Visual disturbance	4/35 (11%)	1/29 (3%)	5/64 (8%)
Hallucinations	0/35	0/29	0/64

risk factors were present as follows: Hypertension (11 patients), diabetes (2 patients), hypercholesterolemia (2), history of hepatitis (2), migraine (1), factor V Leiden mutation (1), hypothyroidism (1), and folic acid deficiency (1). The majority of patients (83%) received their first steroid treatment, 36 patients with CIS and 19 patients with RR-MS.

Median EDSS (Expanded disability status scale; a method of quantifying disability in MS) was lower in CIS (2.5) compared to RR-MS patients (4.0) as expected. At baseline, five patients (2 CIS, 2 RR-MS, 1 PP-MS) scored higher than 23 on the ADS-L questionnaire, indicating depression. On day 5, three patients scored higher than 23; two (one CIS, PP-MS) better and one (CIS) worse, than at baseline. ADS-L scores at follow-up visits did not indicate depression in all patients.

Systemic adverse effects based on self-reporting during infusions are depicted in table 2. Mood disturbances were mentioned by 56% of all patients at baseline, but during the five-day infusion period and at the follow-up visit depressive complaints were significantly less frequent compared to the pre-treatment situation (table 3b). Analysis of CIS and MS patients separately revealed a significant improvement of depressive symptoms only for MS patients from baseline to the infusion period. Analysis of ADS-L z-scores revealed significant improvement for MS patients during the infusion therapy. Significant improvement of ADS-L z-score at follow-up was shown for the entire group.

Fatigue, sleep quality and use of sleeping pills were also analysed separately for CIS and MS patients.

Fatigue was present in almost 78% of CIS patients before steroid therapy and was reported by all patients during the infusion period. Fatigue was significantly less frequent in CIS patients at the follow-up visit as compared to the 5 day infusion period.

Poor sleep quality was mentioned in 59% of CIS patients at baseline, and 26% used sleeping pills before and during IVMP therapy. Sleep quality had significantly improved at the follow-up evaluation as compared to the infusion period. At follow-up, 50% of the CIS patients mentioned fa-

tigue and 13% still reported sleep problems, but none were taking sleeping pills.

For MS patients data concerning fatigue showed no significant change before and during steroid therapy. At follow up, MS patients reported fatigue more often than CIS patients (87% vs. 50%). At the follow-up visit, sleep quality had significantly improved in MS patients. The measurement of nocturnal inactivity by wrist actigraphy demonstrated a significantly reduced time spent in bed during the follow-up period at home as compared to the in-hospital infusion period in CIS patients. Presumed sleep efficacy as measured by % inactivity during bedtime did not show a significant difference between the infusion period and the follow-up days. More details are given in tables 4 and 5

Clinical outcome measures improved after steroid therapy. For CIS patients the mean EDSS at baseline was 2.8 and 1.86 at follow up.

The mean EDSS at baseline for MS patients was 3.93 and 3.46 at follow-up.

Mean baseline values of the Nine Hole Peg Test (NHPT), a brief quantitative test of hand dexterity, were as follows: CIS patients, right hand: day 1: 28s, day 5: 24s, follow-up: 17s; left hand: day 1: 23s, day 5: 26s, at follow-up 17s.

For MS patients the mean values of the NHPT for the right hand at baseline were: day one: 28s, day 5: 27 s, follow-up: 21 s; for the left hand: day one: 24 s, day 5: 23 s, at follow up: 21s.

Discussion

This study was undertaken to investigate the tolerance and adverse effects of IVMP treatment in patients with clinical isolated syndrome or relapses in multiple sclerosis. To date there is no evidence that IVMP is more effective than oral administration [3]. However, given the small number of patients studied and methodological problems the equivalence is still questionable. Most departments including our department continue to use the conventional intravenous (i.v.) route. There are mainly two reasons that we have not

Table 3a: Mood disturbance, ADS-L scores before, during and after steroid therapy.

	CIS	MS	Total
Before steroid therapy			
Mood disturbance	15/30 (50%)	16/25 (64%)	31/55 (56%)
ADS-L (z-score, median, n)	-0.22 (31)	0.600 (24)	0.02 (55)
During i.v. steroid therapy			
Mood disturbance	10/32 (31%)	11/26 (42%)	21/58 (36%)
ADS-L (z-score, median, n)	-0.0200 (23)	0.200 (22)	0.02 (45)
After steroid therapy			
Mood disturbance	2/14 (14%)	3/12 (25%)	5/26 (19%)
ADS-L (z-score, median, n)	-0.625 (12)	0.5800 (13)	0.58 (25)

Table 3b: Longitudinal analysis of mood disturbance (*p* value).

Steroid Therapy	CIS	MS	Total
Before – During	0.343	0.041	0.024
Before – Follow-up	0.248	0.131	0.027
During – Follow-up	1.000	0.221	0.131

Table 3c Longitudinal analysis ADS L-z-score (*p* value/median difference/ 95%CI).

Steroid Therapy	CIS	MS	Total
Before-During	0.628 (-0.1; -0.575, 0.340)	0.020 (0.29; 0.060, 0.495)	0.340 (0.1075; -0.140, 0.335)
Before-Follow-up	0.375 (0.3; -0.43, 0.83)	0.148(0.71; -0.165, 1.085)	0.072 (0.5125; -0.045, 0.830)
During-Follow-up	0.067 (0.6375; -0.08, 1.20)	0.289(0.23; -0.56, 1.25)	0.029 (0.51; 0.020, 0.935)

yet categorically changed our inpatient regimen to an outpatient setting with i.v. or oral medication: 1. Too many patients complain of sleep disturbance and mood disorder and, 2. a small number of patients become psychotic while

receiving steroids. In this study steroid therapy was well tolerated. About half of the symptoms which patients complained about were well known side effects.

CIS	Fatigue	Poor sleep quality	Use of sleeping pills
Before steroid therapy	25/32 (78%)	20/34 (59%)	9/35 (26%)
Steroid therapy day 1	33/33 (100%)	20/34 (59%)	11/35 (31%)
Day 2	33/33 (100%)	20/34 (59%)	10/35 (29%)
Day 3	33/33 (100%)	20/34 (59%)	12/35 (34%)
Day 4	33/33 (100%)	21/35 (60%)	7/35 (20%)
Day 5	33/33 (100%)	Not assessed	Not assessed
After steroid therapy	9/17(50%)	2/15(13%)	0/18(0%)

MS	Fatigue	Poor sleep quality	Use of sleeping pills
Before steroid therapy	23/27 (85%)	19/29 (66%)	6/29 (21%)
Steroid therapy day 1	26/28 (93%)	15/29 (52%)	11/29 (38%)
Day 2	26/28 (93%)	13/29 (45%)	11/29 (38%)
Day 3	26/28 (93%)	20/34 (59%)	12/29 (41%)
Day 4	26/28 (93%)	17/28 (61%)	10/29 (34%)
Day 5	26/28 (93%)	Not assessed	Not assessed
After steroid therapy	13/15 (87%)	4/14 (29%)	2/13 (15%)

		p value	Median differences	95% CI median differences
Fatigue				
CIS	Before- during	0.495	-0.25	[-1.5 , 0.5]
CIS	Before-Follow-up	0.208	0.75	[-1 , 2]
CIS	During-follow-up	0.011	0.75	[0 ,2]
MS	Before-During	0.607	-0.5	[-1 , 1]
MS	Before-Follow-up	0.965	-0.25	[-1.5 , 1.0]
MS	During -Follow-up	1.000	0.25	[-1.5 , 1.0]
Impaired Sleep quality				
CIS	Before-During	0.920	0.125	[-0.5 , 0.5]
CIS	Before-Follow-up	0.055	0.75	[-1 , 2]
CIS	During-Follow-up	0.020	0.875	[0.0, 1.5]
MS	Before-During	0.761	0.125	-0.5 1.0
MS	Before-Follow-up	0.031	0.75	0 2
MS	During-Follow-up	0.027	1.125	0 2
Sleeping pills				
CIS	Before-During	0.134		
CIS	Before-Follow-up	1.000		
CIS	During-Follow-up	0.134		
MS	Before-During	0.016		
MS	Before-Follow-up	1.000		
MS	During-Follow-up	0.041		

Day		1	2	3	4	5	31	32	33	34	35
CIS patients	Hours in bed median (min; max)	8.3 (4.9; 10.4) n = 31	8.5 (6.4; 15.4) n = 31	8.5 (5.9; 13.9) n = 30	8.9 (6.1; 11.7) n = 25	8.5 (5.6; 10.3) n = 11	8.0 (4.4; 10.7) n = 17	7.5 (5.7; 10.6) n = 16	7.1 (5.3; 13.3) n = 16	7.8 (4.3; 12.6) n = 15	7.9 (6.1; 10.7) n = 13
	% inactivity median (min; max)	93.8 (64; 98)	93.4 (79; 99.8)	93.5 (65.6; 100)	93.1 (50.4; 99.8)	97.4 (90.7; 100)	94.7 (49.6; 98.9)	93.3 (85.1; 98.6)	96.3 (70.9; 98.3)	96.1 (90.2; 98.5)	94.9 (78.9; 97)
MS patients	Hours in bed median (min; max)	7.9 (5.1; 11.4) n = 29	8.4 (4.9; 18) n = 28	8.5 (5.8; 12) n = 28	8.9 (4.6; 16) n = 23	8.9 (7.7; 10.8) n = 4	8.2 (5.5; 10.5) n = 16	8.3 (5.5; 9.9) n = 16	7.3 (6.3; 12.6) n = 16	8.4 (5.4; 10.3) n = 14	7.8 (6.3; 9.4) n = 10
	% inactivity median (min; max)	93.1 (64.7; 98.7)	93.2 (53.4; 99.8)	93.7 (80.8; 97.9)	95.1 (86.9; 99.7)	93.1 (65.7; 98.1)	94.5 (79.3; 98.2)	92.1 (45.1; 98.2)	95.3 (68.5; 99.1)	90.9 (73.4; 98.6)	96.3 (90.5; 96.9)

None of the patients had psychotic side effects. About half of the patients reported mood disturbance before steroids were started. Only five patients exceeded the cut-off score on the ADS-L for mood disturbance indicating depression before steroids, and four of them improved during therapy. During therapy and in the remission period mood disturbances were significantly less frequent than at baseline. This is also reflected by the improvement of the ADS-L Depression score. Disease inherent mood alteration during relapse activity and reactive mood disorders are possible explanations for this evolution. However, during the remission period mood disturbances were still reported by about 19% of patients. All patients reported fatigue before and during therapy. Sleep quality and fatigue had significantly improved at the follow-up visit in CIS patients as compared to the infusion period. Challenges of dealing with the new situation and diagnosis of "CIS" could be the reason for this observation. At follow up visits MS patients reported fatigue more often (87%) than CIS patients (50%), possibly reflecting disease inherent fatigue. A remarkable proportion of patients missed the follow up visit, therefore a selection bias may account for this observation. Unlike the complaints of sleep disturbances, wrist actigraphy demonstrated high sleep efficiency which is discrepant to the complaints of the patients. However, this could be explained by times when patients lie awake quietly. With the actigraphy we detect inactivity but not insomnia, and this could potentially explain the discrepancy of actigraphy and the subjective feeling of insomnia by many patients. When the patient lies awake quietly he is inactive and sleepless, but actigraphy would indicate sleep.

To summarise, no severe adverse effects were noted in CIS and MS patients during IVMP treatment. From this point of view there is no reason not to change from an inpatient management of IVMP to an outpatient management when patients receive IVMP for the first time. With the small sample analysed rare adverse effects such as psychosis are not likely to be detected. Therefore clinical vigilance is of crucial importance when IVMP is administered in an outpatient setting. Patients with known depression or psychosis should still be admitted to hospital if steroid treatment is required, and should be treated only under special precautions and adoption of psychiatric medication and sedatives.

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Table 5b: Comparison of hours in bed and nocturnal inactivity periods during steroid therapy (day 1–5) and after steroid therapy (day 31–35).

		Median (max,min) Day 1–5	Median (max,min) Day 31–35	p value	Median differences	95% CI median differences
CIS	Hours in bed	8.6 (9.7,6.1)	7.5 (10.6, 6.4)	0.013	1.002083	[0.20000, 1.38125]
	%Inactivity	93.8 (99.7, 77.2)	95.2 (97.9, 49.6)	0.528	0.2104167	[-0.2479167, 1.3333333]
MS	Hours in bed	8.5 (14.0, 6.4)	8.2 (9.8, 6.6)	0.433	-1.5275	[-3.7375, 4.5050]
	%Inactivity	93.3 (98.4, 80.7)	93.2 (98.2, 73.9)	0.105	-2.02	[-5.5000, 0.8875]

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