

ORIGINAL ARTICLE

Methylprednisolone, Valacyclovir, or the Combination for Vestibular Neuritis

Michael Strupp, M.D., Vera Carina Zingler, M.D., Viktor Arbusow, M.D.,
Daniel Niklas, Klaus Peter Maag, M.D., Ph.D., Marianne Dieterich, M.D.,
Sandra Bense, M.D., Diethilde Theil, D.V.M., Klaus Jahn, M.D.,
and Thomas Brandt, M.D.

ABSTRACT

BACKGROUND

Vestibular neuritis is the second most common cause of peripheral vestibular vertigo. Its assumed cause is a reactivation of herpes simplex virus type 1 infection. Therefore, corticosteroids, antiviral agents, or a combination of the two might improve the outcome in patients with vestibular neuritis.

METHODS

We performed a prospective, randomized, double-blind, two-by-two factorial trial in which patients with acute vestibular neuritis were randomly assigned to treatment with placebo, methylprednisolone, valacyclovir, or methylprednisolone plus valacyclovir. Vestibular function was determined by caloric irrigation, with the use of the vestibular paresis formula (to measure the extent of unilateral caloric paresis) within 3 days after the onset of symptoms and 12 months afterward.

RESULTS

Of a total of 141 patients who underwent randomization, 38 received placebo, 35 methylprednisolone, 33 valacyclovir, and 35 methylprednisolone plus valacyclovir. At the onset of symptoms there was no difference among the groups in the severity of vestibular paresis. The mean (\pm SD) improvement in peripheral vestibular function at the 12-month follow-up was 39.6 ± 28.1 percentage points in the placebo group, 62.4 ± 16.9 percentage points in the methylprednisolone group, 36.0 ± 26.7 percentage points in the valacyclovir group, and 59.2 ± 24.1 percentage points in the methylprednisolone-plus-valacyclovir group. Analysis of variance showed a significant effect of methylprednisolone ($P<0.001$) but not of valacyclovir ($P=0.43$). The combination of methylprednisolone and valacyclovir was not superior to corticosteroid monotherapy.

CONCLUSIONS

Methylprednisolone significantly improves the recovery of peripheral vestibular function in patients with vestibular neuritis, whereas valacyclovir does not.

From the Departments of Neurology (M.S., V.C.Z., V.A., D.N., D.T., K.J., T.B.) and Epidemiology and Biometrics (K.P.M.), University of Munich, Munich; and the Department of Neurology, University of Mainz, Mainz (M.D., S.B.) — both in Germany. Address reprint requests to Dr. Strupp at the Department of Neurology, University of Munich, Klinikum Grosshadern, Marchionistr. 15, 81377 Munich, Germany, or at mstrupp@nefo.med.uni-muenchen.de.

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VESTIBULAR NEURITIS IS THE SECOND most common cause of peripheral vestibular vertigo (the first being benign paroxysmal positional vertigo). It accounts for 7 percent of the patients who present at outpatient clinics specializing in the treatment of dizziness¹ and has an incidence of about 3.5 per 100,000 population.² The key signs and symptoms of vestibular neuritis are the acute onset of sustained rotatory vertigo, postural imbalance with Romberg's sign (i.e., falls, with the eyes closed, toward the affected ear), horizontal spontaneous nystagmus (toward the unaffected ear) with a rotational component, and nausea. Caloric testing (irrigation of the ear with warm or cold water) invariably shows ipsilateral hyporesponsiveness or nonresponsiveness.

In the past, either an inflammation of the vestibular nerve³⁻⁵ or labyrinthine ischemia⁶ was proposed as a cause of vestibular neuritis. Currently, a viral cause is favored. The evidence, however, remains circumstantial.^{1,7,8} Postmortem studies have shown atrophy of the vestibular nerve and the vestibular sensory epithelium that is similar to the histopathological findings in known viral disorders, such as herpes zoster oticus.⁹ Herpes simplex virus type 1 (HSV-1) DNA has been detected on autopsy with the use of the polymerase chain reaction in about two of three human vestibular ganglia.^{10,11} This indicates that the vestibular ganglia are latently infected by HSV-1, as are other cranial-nerve ganglia.¹²⁻¹⁴ A similar cause is also assumed for Bell's palsy and is strongly supported by the detection of HSV-1 DNA in the endoneurial fluid of affected persons.¹⁵

Recovery after vestibular neuritis is usually incomplete.^{1,7} In a study of 60 patients, horizontal semicircular canal paresis was found in about 90 percent one month after the onset of symptoms and in 80 percent after six months; the caloric responses normalized in only 42 percent.¹⁶ On the basis of the incidence of this condition,² a substantial and permanent unilateral dynamic deficit of the vestibulo-ocular reflex, which cannot be compensated for by other mechanisms,^{17,18} develops in approximately 4000 people per year in the United States alone. This deficit leads to impaired vision and postural imbalance during walking and especially during head movement toward the affected ear.¹⁹

Despite the assumed viral cause of vestibular neuritis, the effects of corticosteroids, antiviral agents, or the two in combination are uncertain.^{1,8} We conducted a prospective, randomized trial of

these treatments in patients with vestibular neuritis, in whom we assessed vestibular function at baseline and the change after 12 months.

METHODS

PATIENTS

Patients 18 through 80 years of age were recruited from emergency departments in two hospital centers specializing in the diagnosis and treatment of vertigo, at the University of Munich and the University of Mainz, between January 1, 1998, and June 30, 2002. All patients underwent complete neurologic, neuro-ophthalmologic, and neuro-otologic examination as well as electronystagmography (including caloric irrigation), neuro-orthoptic examination (which provides detailed measurement of eye movements), cranial magnetic resonance imaging, laboratory testing, and measurement of blood pressure and heart rate. The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

As in a previous study,²⁰ the diagnosis of vestibular neuritis was based on four criteria. There was a history of the acute or subacute (i.e., within minutes to hours) onset of severe, prolonged rotatory vertigo, nausea, and postural imbalance. On clinical examination, there was a horizontal spontaneous nystagmus with a rotational component toward the unaffected ear (fast phase) without evidence of a central vestibular lesion, and the head-thrust test (performed by turning the head of the patient rapidly to the right and left to provoke compensatory eye movements) showed an ipsilateral deficit of the horizontal semicircular canal.¹⁷ Caloric irrigation showed hyporesponsiveness or lack of responsiveness of the horizontal canal of the affected ear. (The maximal slow-phase velocity during caloric irrigation with water at 30°C and 44°C should be less than three degrees per second on the affected side, and the asymmetry between the two sides should be more than 25 percent as measured with the use of Jongkees's formula for vestibular paresis.^{21,22}) Finally, there was a perceived displacement of verticality and the eyes rotated toward the affected ear without showing vertical divergence of one eye above the other.^{23,24}

Patients were excluded if they had a history of vestibular dysfunction before the acute onset of symptoms or had symptoms that began more than three days before recruitment; if they had additional cochlear symptoms, such as tinnitus or acute

hearing loss before, during, or after the onset of vertigo; if they had central ocular motor dysfunction or central vestibular dysfunction; if they had other signs or symptoms of brain-stem or cerebellar disorders, abnormal findings on magnetic resonance imaging of the brain stem or cerebellum in diffusion-weighted images or of hyperintense lesions in T₂-weighted images in combination with contrast enhancement in T₁-weighted images, a history of psychiatric disorders, glaucoma, ongoing infection, severe diabetes mellitus (a fasting blood glucose level >180 mg per deciliter [10.0 mmol per liter] on admission, despite treatment), or severe hypertension (blood pressure on admission >180 mm Hg systolic or >110 mm Hg diastolic); or if there were contraindications to the use of corticosteroids, such as peptic ulcer disease or known osteoporosis (on the basis of bone-density testing or a history of fracture), or to valacyclovir, such as dysfunction of the liver (i.e., known cirrhosis of the liver or alanine aminotransferase levels two times the upper limit of the normal range or higher) or dysfunction of the kidneys (i.e., creatinine level >2.6 mg per deciliter [230 μmol per liter] in women and >3.5 mg per deciliter [310 μmol per liter] in men), malignant disease, or heart failure.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned (by means of computer-generated block randomization) to one of four treatment groups: the placebo group, the methylprednisolone group, the valacyclovir group, and the methylprednisolone-plus-valacyclovir group. Methylprednisolone (or a matching placebo) was administered daily as a single morning dose of 100 mg on days 1 through 3, 80 mg on days 4 through 6, 60 mg on days 7 through 9, 40 mg on days 10 through 12, 20 mg on days 13 through 15, 10 mg on days 16 through 18, and 10 mg on days 20 and 22. Valacyclovir, an L-valyl ester of acyclovir (or matching placebo), was given as two 500-mg capsules three times daily for seven days. Valacyclovir was used in this study, because the serum concentrations that result from its use are similar to those resulting from intravenous acyclovir²⁵ and because it is given at less frequent intervals than oral acyclovir. The study drugs were first administered to all subjects on the day of admission, which was within three days after the onset of symptoms. Patients also received 150 mg of pirenzepine (a muscarinic M1-receptor antagonist) once a day to reduce the secretion of gastric acid. If necessary,

patients also received antiemetic agents (50 to 150 mg of dimenhydrinate a day) for a maximum of three days.

All patients were admitted to the hospital for at least one day and up to seven days (they were discharged when they were able to walk unassisted with their eyes closed). During the hospital stay, compliance with the assigned regimen was checked by the physicians and nurses by counting the capsules. On discharge from the hospital, all patients were provided with the study drugs for the following days (through day 22) in standardized packages of the daily regimen with written instructions for taking the drugs. Compliance was checked in an interview within one week after treatment was completed.

During hospitalization, the patients' blood pressure was measured three times per day and the blood glucose levels at least once per day (four times per day for patients with known diabetes mellitus). After discharge, patients with known hypertension were instructed to measure their blood pressure at least three times per day, and those with known diabetes to measure their blood glucose level four times per day. Medication was to be adjusted by the patient's physician. All patients received written information about possible adverse effects of methylprednisolone and valacyclovir, as well as a standardized protocol with open questions about adverse effects that might have occurred before the patients were included in the study. They were instructed to inform the investigators about any adverse effects as soon as possible, by telephone, fax, or e-mail. Adverse effects of the medication were assessed three to four weeks after treatment was started; at that time, patients were asked whether they had had any adverse effects, although they were not asked about specific effects.

Treatment was stopped if patients did not want to continue or if they did not comply with the regimen (i.e., did not take the study drug at least twice), if adverse effects developed during treatment, or if signs or symptoms (such as tinnitus or hearing loss) developed during the course of the disease that were not compatible with vestibular neuritis. Patients who did not return for the 12-month follow-up examination were excluded from the final analysis.

EFFICACY ANALYSIS

As a measure of unilateral vestibular loss, the mean peak slow-phase velocity during caloric irrigation with water at 30°C and 44°C was measured and

automatically analyzed with the use of IGOR Pro software (version 3.13, WaveMetrics) on the first or second day of hospitalization and at the 12-month follow-up. Because the nystagmus induced by caloric irrigation may vary considerably among subjects but only to a small extent in a healthy person, Jongkees's vestibular paresis formula^{21,22,26} was used as the primary outcome variable in the efficacy analysis. The extent of unilateral caloric paresis, expressed as a percentage, was calculated with the use of the following formula: $\{[(R30^\circ + R44^\circ) - (L30^\circ + L44^\circ)] \div (R30^\circ + R44^\circ + L30^\circ + L44^\circ)\} \times 100$, where, for example, R30° is the mean peak slow-phase velocity during caloric irrigation of the right labyrinth with water at 30°C (R denotes right, and L left, and 30° or 44° indicates the water temperature). With the use of this formula, a direct comparison can be performed between the function of the horizontal semicircular canals of the right and left labyrinths. The formula is highly reliable in detecting unilateral peripheral vestibular loss.²² A 12-month follow-up was used, because there have been reports of delayed spontaneous recovery of vestibular function.^{16,27}

STATISTICAL ANALYSIS

The sample size was calculated with the use of SampleStat software (SPSS) and was based on a mean (\pm SD) difference between groups (calculated with Jongkees's formula) of 25 ± 26 percent. The calculation yielded a sample size of 30 patients in each treatment group, assuming a t-test for two independent groups, with a two-sided alpha level of 0.01 and a statistical power of 85 percent.

Data are presented as means \pm SD. A two-by-two factorial analysis of variance (in which the factors were methylprednisolone and valacyclovir), used to compare the percentage of vestibular paresis measured at the initial examination of the patient and the percentage measured at follow-up, was performed with the use of Statistica 6 software (StatSoft). All reported P values are two-sided.

An interim analysis was performed (in 2001) after one year of follow-up of a total of 50 patients. There was no significant difference between groups, and the study was continued.

Hoechst Pharma, Germany, supplied the study drugs and placebo but was not involved in the design of the study, the data collection and analysis, the preparation of the manuscript, or the decision to publish the findings.

RESULTS

Of 157 patients who underwent screening, 141 met the criteria for inclusion and were willing to participate. Of those 141 patients, 38 were randomly assigned to the placebo group, 35 to the methylprednisolone group, 33 to the valacyclovir group, and 35 to the methylprednisolone-plus-valacyclovir group. Eight patients in the placebo group, six in the methylprednisolone group, six in the valacyclovir group, and seven in the methylprednisolone-plus-valacyclovir group were excluded (because the patient did not want to continue treatment, was not compliant, had severe adverse effects and treatment was stopped, or was lost to follow-up) (Table 1). Thirty patients in the placebo group, 29 in the methylprednisolone group, 27 in the valacyclovir group, and 28 in the methylprednisolone-plus-valacyclovir group completed the study at 12 months, for a total of 114 patients. The groups did not differ with regard to mean age, sex ratio, and time from the onset of symptoms to the start of treatment (Table 1).

Calculations performed with the use of Jongkees's formula at the initial examination showed no significant differences in the extent of the peripheral vestibular deficits among the groups at baseline (Fig. 1 and Table 2). The mean extent of vestibular paresis was 78.9 ± 24.0 percent in the placebo group, 78.7 ± 15.8 percent in the methylprednisolone group, 78.4 ± 20.0 percent in the valacyclovir group, and 78.6 ± 21.1 percent in the methylprednisolone-plus-valacyclovir group. At the 12-month follow-up, the improvement in vestibular paresis was 39.6 ± 28.1 percentage points among patients in the placebo group, 62.4 ± 16.9 percentage points in the methylprednisolone group, 36.0 ± 26.7 percentage points in the valacyclovir group, and 59.2 ± 24.1 percentage points in the methylprednisolone-plus-valacyclovir group (Fig. 1 and Table 2). Analysis of variance showed a significant effect of methylprednisolone ($P < 0.001$), but not of valacyclovir ($P = 0.43$). Furthermore, there was no interaction between methylprednisolone and valacyclovir ($P = 0.92$), indicating that the addition of valacyclovir did not affect the efficacy of methylprednisolone.

A combined analysis of the two groups that received methylprednisolone showed a change in the percentage of vestibular paresis of 60.9 ± 20.6 percent (95 percent confidence interval, 55.4 to 66.3 percent), as compared with 37.9 ± 27.2 percentage

Table 1. Baseline Characteristics of the 141 Patients.*

Characteristic	Placebo Group (N=38)	Methylprednisolone Group (N=35)	Valacyclovir Group (N=33)	Methylprednisolone-plus-Valacyclovir Group (N=35)
Age (yr)				
Mean	47.0±9.9	45.8±8.9	51.7±11.1	48.5±10.5
Range	18–68	19–66	21–71	19–63
Sex (no.)				
Male	22	16	19	20
Female	16	19	14	15
History of arterial hypertension (no.)	8	6	5	6
History of diabetes mellitus (no.)	4	2	3	2
Patients excluded (no.)	8	6	6	7
Reasons for exclusion (no.)				
Did not want to continue treatment	2	2	1	1
Noncompliance	2	0	1	3
Stopped treatment because of severe adverse effect	0	1	0	0
No follow-up	4	3	4	3
Patients in the final analysis (no.)	30	29	27	28
Time from onset of symptoms to treatment (days)	1.77±1.00	1.83±1.11	1.65±0.97	1.71±1.05

* Plus-minus values are means ±SD.

points (95 percent confidence interval, 30.7 to 45.1 percent) in the two groups who did not receive methylprednisolone. The pooled effect of valacyclovir (change, 47.8±27.8 percentage points; 95 percent confidence interval, 40.3 to 55.3 percent) was not significantly different from the change in the percentage of vestibular paresis without valacyclovir (50.8±25.8 percentage points; 95 percent confidence interval, 44.1 to 57.5 percent).

The treatment groups differed significantly in the number of patients who had a complete or almost complete recovery of peripheral vestibular function (defined as a difference of less than 25 percent between the affected and unaffected labyrinths, as calculated with the use of Jongkees's formula). The number of patients who had complete or partial recovery was 8 of 30 in the placebo group, 22 of 29 in the methylprednisolone group, 10 of 27 in the valacyclovir group, and 22 of 28 in the methylprednisolone-plus-valacyclovir group (placebo vs. methylprednisolone, $P<0.001$; placebo vs. methylprednisolone plus valacyclovir, $P<0.001$).

In the methylprednisolone group, a gastric ulcer with minor bleeding developed in one patient (a

67-year-old man) 10 days after he started therapy (despite the administration of pirenzepine to him and all other subjects). Methylprednisolone was stopped, and the bleeding was halted with a local injection of epinephrine. Three patients reported dyspepsia and five reported mood swings, but all these patients continued treatment. The adverse effects resolved after the patients completed treatment with corticosteroids. In two patients who had normal fasting blood glucose levels on admission, hyperglycemia developed (fasting blood glucose >180 mg per deciliter [10.0 mmol per liter]) during treatment. Both patients started long-term treatment with oral antidiabetic agents, and the blood glucose level normalized. Patients in the placebo and valacyclovir groups reported no other adverse effects that affected treatment.

DISCUSSION

Treatment with methylprednisolone alone significantly improved the long-term outcome of peripheral vestibular function among patients with vestibular neuritis, whereas treatment with the antiviral

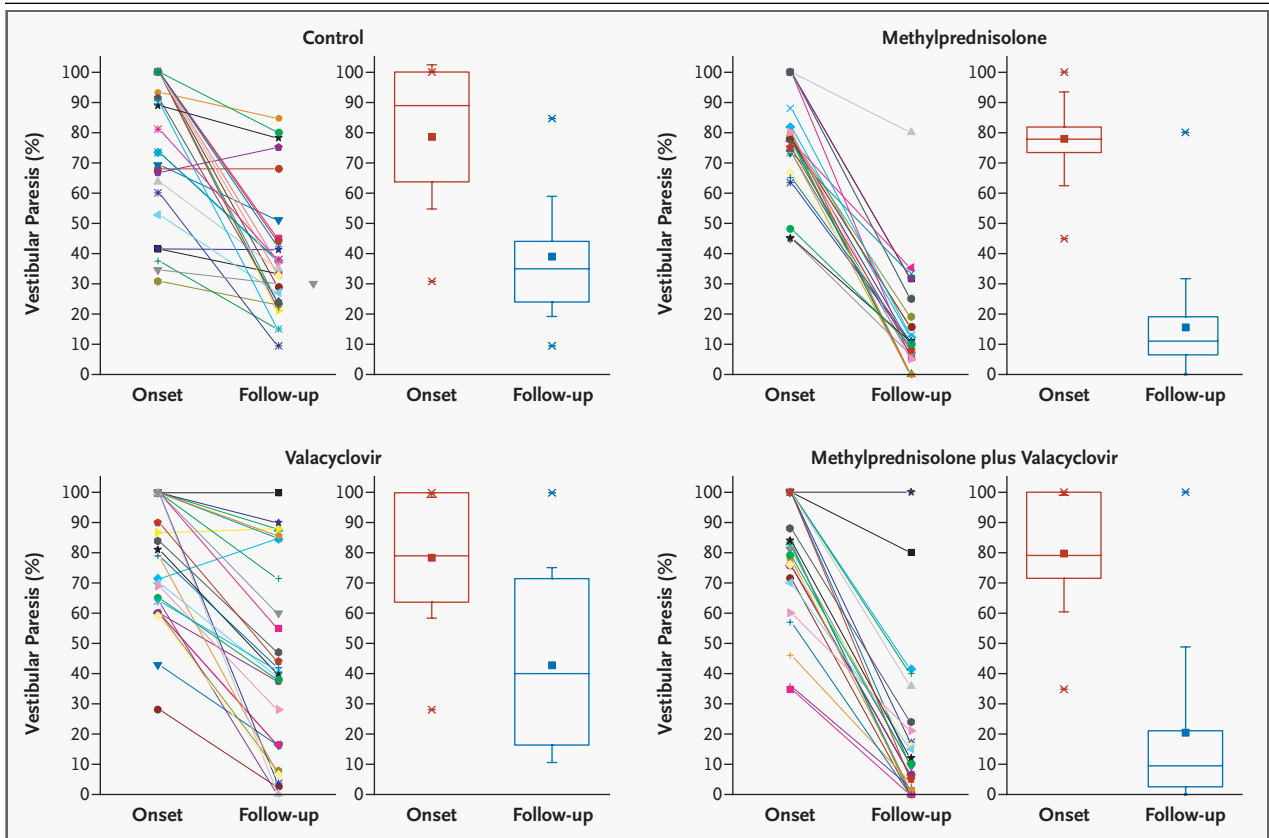


Figure 1. Unilateral Vestibular Loss within Three Days after the Onset of Symptoms and after 12 Months.

Vestibular function was measured for each patient in the four study groups with the use of caloric irrigation and Jongkees's formula for vestibular paresis for a direct comparison of the function of the right and left labyrinths. Clinically relevant vestibular paresis was defined as an asymmetry greater than 25 percent between the right-sided and left-sided responses.²⁶ In the box plot for each treatment group, the solid square indicates the mean, the horizontal lines the 25th, 50th, and 75th percentiles, the error bars above and below the boxes the SDs, and the crosses the 1st and 99th percentiles. Analysis of variance for the comparison of methylprednisolone and methylprednisolone plus valacyclovir with placebo or valacyclovir alone showed significantly more improvement with methylprednisolone. The combination of methylprednisolone and valacyclovir was not superior to corticosteroid monotherapy.

agent valacyclovir did not improve the outcome. The combination of these drugs was no more effective than methylprednisolone alone.

Previous data have supported the hypothesis that corticosteroids have a beneficial effect on the course of acute peripheral vestibular vertigo. One double-blind, prospective, placebo-controlled, crossover study²⁸ included 20 patients who had the opportunity to switch medication within 24 hours of starting treatment; in the final analysis, 16 patients had received corticosteroids (beginning with a dose of 32 mg per day) for eight days, and 4 patients had received placebo. At follow-up at four weeks, electro-nystagmography showed that values returned to normal in all 16 patients who had received corticosteroids but in only 2 of the 4 patients in the control

(placebo) group. Thirteen of the 16 patients who had been treated with corticosteroids had remission of their symptoms within six hours of starting treatment. In another study²⁷ that was neither prospective nor placebo-controlled, 34 patients received corticosteroid therapy for vestibular neuritis and 77 received no treatment. The recovery rate in that study, as measured with the use of Jongkees's formula over a mean follow-up period of seven months, was twice as high among the patients who received corticosteroids as among those who did not, although corticosteroids had no significant effect on the symptoms.

For Bell's palsy, which probably has the same pathogenesis as vestibular neuritis,^{15,29} one trial showed that the combination of acyclovir and cor-

Table 2. Extent of Vestibular Paresis at Baseline and at 12 Months.*

Extent of Vestibular Paresis	Placebo Group (N=30)	Methylprednisolone Group (N=29)	Valacyclovir Group (N=27)	Methylprednisolone-plus-Valacyclovir Group (N=28)
At baseline (%)	78.9±24.0	78.7±15.8	78.4±20.0	78.6±21.1
At 12 mo (%)	39.0±19.9	15.4±16.2	42.7±32.3	20.4±28.4
Improvement (%)	39.6±28.1	62.4±16.9	36.0±26.7	59.2±24.1
P value†	—	<0.001	0.63	0.006
Analysis of variance‡	—	<0.001	0.43	0.92

* Percentages were calculated with the use of Jongkees's formula for vestibular paresis (which indicates the extent of unilateral caloric paresis). Percentages below 25 percent are considered to be normal; higher percentages indicate a greater unilateral peripheral vestibular deficit. At baseline, the mean (\pm SD) percentage of vestibular paresis and the range among patients excluded were 72.1 \pm 35.0 percent (range, 38 to 100 percent) in the placebo group (n=8); 80 \pm 23.8 percent (range, 42 to 100 percent) in the methylprednisolone group (n=6); 75.3 \pm 22.2 percent (range, 41 to 100 percent) in the valacyclovir group (n=6); and 86.2 \pm 38.7 percent (range, 31 to 100 percent) in the methylprednisolone-plus-valacyclovir group (n=7).

† P values are for pairwise comparisons with the placebo group.

‡ P values by analysis of variance showed a significant effect of methylprednisolone but not of valacyclovir. There was no interaction between methylprednisolone and valacyclovir, indicating that the addition of valacyclovir did not affect the efficacy of methylprednisolone.

ticosteroids significantly improved the outcome as compared with corticosteroids alone.³⁰ However, meta-analyses of studies of treatment for Bell's palsy^{29,31} have shown contradictory results with regard to the reported trials, and the authors concluded that corticosteroids are probably effective and that acyclovir (combined with prednisolone) is possibly effective in improving facial function.²⁹

In our study, the antiviral drug did not improve the outcome in patients with vestibular neuritis, despite the assumed viral cause. Replication of HSV-1 in the vestibular ganglia may conceivably have already occurred by the time the antiviral drug was initiated — that is, within three days after the onset of symptoms. The findings in two studies of the treatment of herpes simplex encephalitis may provide some support for this hypothesis. In both studies, the most relevant prognostic factor was early acyclovir therapy — within two days after admission to the hospital.^{32,33} Furthermore, there is good evidence that the major damage in vestibular neuritis is caused by the swelling and mechanical compression of the vestibular nerve within the temporal bone, which is also assumed in Bell's palsy.²⁹ The antiinflammatory effect, which results in reduced swelling, may explain why treatment with corticosteroids results in improvement in both disorders.

Our study has several limitations. We did not assess the duration and severity of symptoms (vertigo and imbalance). In studies in animals, however, corticosteroids have been shown to improve central

vestibular compensation.³⁴ Data on symptoms and on postural imbalance would not allow differentiation between an improvement in peripheral vestibular function and an improvement in central vestibular compensation, and therefore we did not collect these data. The percentage of improvement in vestibular paresis cannot be directly translated into clinical terms; nonetheless, methylprednisolone therapy significantly increased the extent of recovery, and the likelihood of complete recovery, of peripheral vestibular function. We did not measure vestibular function during the period between the start of treatment and the 12-month assessment. Thus, we cannot estimate the effects of the different regimens on the times to improvement. Furthermore, data on the potential adverse effects of methylprednisolone and valacyclovir therapy were not systematically collected. Finally, we do not have follow-up data on patients who did not take at least two doses of the assigned study drug or in whom adverse effects developed that necessitated stopping treatment. However, such patients made up only a small proportion of the total number of patients, and at baseline they appeared similar to patients with complete follow-up. Our results show that methylprednisolone alone significantly improved the extent of recovery of peripheral vestibular function in patients with vestibular neuritis.

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