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A randomized, double-blind, placebo-controlled study of the efficacy and safety of tolperisone in spasticity following cerebral stroke

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To study the efficacy and safety of tolperisone – a centrally acting muscle relaxant with membrane stabilizing activity – in the treatment of stroke-related spasticity. This was a randomized, double-blind, placebo-controlled, multicenter study with parallel groups. Treatment lasted 12 weeks and was started with a titration period of variable length (dose range 300–900 mg tolperisone daily). The degree of spasticity determined on the Ashworth Scale in the most severely affected joint area was defined as primary target parameter. Hundred and twenty patients (43 females, 77 males) in a mean age of 63.3 ± 10.6 years were recruited and received treatment. In the majority of patients both limbs of each side (right: $n = 59$; left: $n = 56$) were affected by the spasticity which on average had been present for 3.3 ± 4.4 years. A 62% of the patients were treated with a daily dose ≥600 mg tolperisone. Tolperisone reduced the mean Ashworth Score by a mean of 1.03 ± 0.71 compared with a mean reduction of 0.47 ± 0.54 in the placebo group ($P < 0.0001$). A 78.3% of the patients on tolperisone versus 45% of the placebo patients experienced a reduction by at least 1 point on the Ashworth Scale ($P < 0.0001$). Functional and overall assessments of efficacy confirmed superior efficacy of tolperisone. Adverse events occurred less often on active treatment ($n = 19$) than on placebo ($n = 26$) and were mostly of mild-to-moderate intensity. No withdrawals caused by adverse events were reported in the tolperisone group. The findings of the present study demonstrate the efficacy and excellent tolerance of tolperisone in the treatment of spastic hypertonia following cerebral stroke. Study data further suggest that an individual dose titration which may exceed the recommended maximum dose of 450 mg daily results in optimized therapeutic benefit.

Introduction

The incidence of stroke-related spasticity has not been well studied. When stroke affects upper motor pathways, subsequent spasticity is common, although spasticity after stroke is neither universal nor immediate. Spasticity develops gradually in the days, weeks and months of recovery, and is not necessarily deleterious. It may be useful, as when a hypertonic extensor synergy helps bodyweight bearing in a weakened leg (O'Brien *et al*., 1996). Although a minority of patients may have a functional benefit from spastic hypertonia in their lower extremities, it is a cumbersome problem for most patients, interfering with elementary movements and the activities of daily living (Bes *et al*., 1988).

Spasticity is defined as a velocity-dependent increase in the resistance of muscles to passive stretch associated with exaggerated tendon jerks (Bohannon and Smith, 1987; Sloan *et al*., 1992; Haas *et al*., 1996). It requires treatment only if it interferes with function, causes discomfort and impairs hygiene (O'Brien *et al*., 1996; Dietz, 2001). Treatment options include non-pharmacological measures, such as physical therapy, pharmacologic, and procedural interventions (e.g. surgery, nerve block; O'Brien *et al*., 1996). Baclofen, benzodiazepines, and tizanidine belong to the most commonly used oral medications for spastic hypertonia of cerebral origin. These agents are non-selective, mimicking the effects of neurotransmitters within the central nervous system utilized in descending, regulatory fiber systems (such as the noradrenergic system) or acting as neurotransmitters in local circuits (such as gamma aminobutyric acid) (Emre, 1993). Therefore, these substances may cause general adverse effects, including sedation, drowsiness, weakness, and changes in mood and cognition (Hulme *et al*., 1985; Stien *et al*., 1987; Bes *et al*., 1988; Wallace, 1994; O'Brien *et al*., 1996; Gracies *et al*., 1997; Groves *et al*., 1998; Meythaler *et al*., 2001) which limit their usefulness in the treatment of central spasticity.

Tolperisone hydrochloride (1-piperidino-2-methyl-3-*p*-tolyl-propanone-3 HCl) is a centrally acting muscle

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relaxant which differs from other muscle relaxants in its mode of action and its spectrum of adverse events. Its chemical structure is similar to that of lidocaine, and similarly to lidocaine tolperisone has membrane-stabilizing effects. It dose-dependently reduces the sodium influx through nerve membranes. Consecutively, amplitude and frequency of action potentials are reduced. In addition, inhibitory effects on voltage-dependent calcium channels have been demonstrated, suggesting that tolperisone might also reduce the transmitter release (Ono *et al.*, 1984, 1986; Farkas and Gere, 1994). In animal studies tolperisone reduced the activity of spinal circuits involved in the mediation of pathologically increased muscle tone (Miskolczi *et al.*, 1987).

Clinical data covering more than 9000 patients demonstrate that tolperisone in doses of up to 450 mg daily reduces or even normalizes muscle spasms as well as spasticity with only little or no side-effects. In contrast to other centrally acting muscle relaxants, tolperisone does not cause sedation and does not impair attention-related brain functions, as has been proven for a dose range of 150–450 mg/day in a double-blind study involving a sensitive and valid psychomotoric test battery (Kohnen *et al.*, 1995; Dulin *et al.*, 1998). This lack of sedative potential makes tolperisone well suited for stroke-related spastic hypertonia because elderly stroke patients are particularly prone to drug-induced central adverse events (Hulme *et al.*, 1985; O'Brien *et al.*, 1996).

Since tolperisone was introduced into clinical practice more than 40 years ago, most of the clinical studies do not meet today's scientific standards. However, in painful reflex muscle spasms caused by diseases of the spinal column or the proximal joints a prospective, randomized, double-blind trial lately confirmed significant superiority of tolperisone over placebo (Pratzel *et al.*, 1996). No such trial has been available until now for the treatment of spastic hypertonia because of illness of the central nervous system and therefore the present study was undertaken.

Methods

This was a double-blind, placebo-controlled, randomized trial with parallel groups. Hundred and twenty patients, aged 18–75 years, with central spasticity following cerebral stroke that had occurred more than 2 months ago were recruited from June 1999 to May 2000 by one center in Bulgaria and two centers in Germany. At inclusion, the degree of spasticity had to be level 2 or more in at least one joint region as rated on the Ashworth Scale. All patients were required to discontinue medication with muscle-relaxant properties 7 days before entry. No concomitant medication with benzodiazepines, other muscle-relaxing agents or any other drug with possible influence on the aim of the study was allowed during the trial. Changes of the current physical therapy also lead to exclusion from the study. Further exclusion criteria were concomitant neurological disease, orthopedic illness or any other disease likely to alter muscle tone, hamper motility, or influence the aim of the trial otherwise; hypersensitivity to tolperisone or lidocaine; women in reproductive age without safe contraception; pregnancy or lactation period; known or suspected alcohol or drug abuse; treatment with any investigational drug within the last 3 months; legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope, and possible consequences of the study or to cooperate, and evidence of an uncooperative attitude.

Target parameters and assessment scales

Different scales were used to assess spasticity and its functional consequences at entry and during the study. The degree of spasticity was determined on the Ashworth Scale and was defined to be the primary target parameter. The Ashworth Scale is a five-point ordinal scale for grading the resistance encountered during passive muscle stretching as follows: 0, no increase in muscle tone; 1, slight increase in muscle tone giving a 'catch' when limb is moved; 2, more marked increase in muscle tone, but limb is easily flexed; 3, considerable increase in muscle tone, passive movement difficult; and 4, limb rigid in flexion or extension (abduction/adduction) (Haas *et al.*, 1996). The Ashworth Scale is an internationally accepted and validated instrument (Bohannon and Smith, 1987; Sloan *et al.*, 1992; The United Kingdom Tizanidine Trial Group, 1994; Haas *et al.*, 1996) and is as such suitable to document and monitor the clinical course of spasticity under treatment. Still, the interrater reliability especially for the lower limbs has been questioned (Katz *et al.*, 1992; Haas *et al.*, 1996). Hence in the present study, the degree of spasticity in the most severely affected joint region (target joint) was determined at the initial visit and was assessed at all subsequent visits *by the same investigator* 2 h after the morning dose when peak plasma concentrations would have been reached in all patients (t_{max}: 0.80 ± 0.24 to 1.13 ± 0.45 h; effective elimination half-life: 6–8 h; unpublished data).

Secondary target parameters included the capacity to perform routine activities, walking endurance for 2 min, quantification of spastic hypertonia using a spring balance, and the overall assessments of efficacy. The capacity to perform routine activities was rated at

each visit on a five-point ordinal scale (1, activities performed perfectly without assistance; 2, activities performed nearly perfect without assistance; 3, activities performed slowly without assistance; 4, activities could be performed with assistance; 5, activities are totally impossible). Additionally, in patients with lower limb spasticity walking endurance on a horizontal smooth surface for 2 min was determined after performance of the Ashworth Test. The maximum distance reached was recorded at each visit. In patients in whom only upper limb spasticity was present, the spring balance test as described by Ogawa *et al.* (1992) was performed instead. For this test, the patient was placed on a bed in supine position and told to relax completely. A spring balance was then attached with a string to the wrist of the patient's spastic arm. The force measured in grams needed for extending the elbow joint from flexion to an angle of 90° was recorded. Furthermore, overall assessments of efficacy by patients and physicians were considered a secondary target parameter and were recorded using a four-point ordinal scale (1, inefficient; 2, slight; 3, moderate; 4, excellent).

The modified Barthel Index as described by Shah *et al.* (1989) was recorded as an additional parameter. The Modified Barthel Index measures the patient's functional ability to perform eleven routine activities of self-care. The sum score of this index covers a range from 0 to 100 points, with the maximum score of 100 representing the patient's full independence.

Safety was monitored by: (i) physical examination and vital signs, (ii) laboratory screening (hematology, biochemistry and urine analysis), (iii) ECG tests, and (iv) reporting of adverse events. Additionally, both the investigators and the patients were asked to assess the tolerability of the study medication on a six-point ordinal scale (1, increased well-being; 2, no change of well-being; 3, slight disturbance in well-being; 4, moderate disturbance in well-being; 5, severe disturbance in well-being; 6, study discontinued because of poor tolerability).

Conduct of the study

This study was performed according to the requirements of Good Clinical Practice including the Declaration of Helsinki in its latest version and with ethical approval from the appropriate local committees. Written informed consent was obtained from all patients prior to entry into the study.

Patients fulfilling the inclusion criteria entered a dose titration period lasting between 4 and 20 days. Starting dose in all patients was 3×2 film coated tablets daily which contained according to randomization either 50 mg of tolperisone hydrochloride (Mydocalm®; Strathmann AG & Co., Hamburg, Germany) or placebo. Thereafter, the dose of the trial medication could be increased to 3×3, 3×4 or 3×6 film coated tablets daily at 4–5 days intervals until the patient's optimum response or until intolerable side-effects appeared. Thus, a dose range of 300–900 mg tolperisone daily was investigated. If no optimal response was reached and no adverse reactions occurred, therapy was continued with the highest dose (900 mg/day). In case of adverse drug reactions, the daily dose could be reduced to the previous level or therapy discontinued. The patients were instructed to take the daily dose in three equal portions immediately after a meal. Total duration of study treatment (including the variable titration period) was defined to be 12 weeks.

The evaluating physicians saw the patients at entry, at 4–5 days intervals during the titration period, after 4 weeks of therapy with the individual optimal dose, and for a final assessment at week 12 after the beginning of therapy. Each clinical assessment scale was applied at each visit. Furthermore, adverse events and concomitant medications were registered at each visit. Additionally, a clinical examination including registration of general state, nutritional state, vital signs, body temperature and pathological findings according to body system, an ECG recording and a laboratory examination (hematology, biochemistry, and urine analysis) was performed at entry and at study end. Tolerability of the trial medication was assessed at the end of the titration period, after 4 weeks on the individual optimal dose and at study end.

Statistical methods

The statistical analysis used the Statistical Analysis System for Windows 3.1 in the last available version. Two-sided tests were performed, and a 5% α level was regarded as statistically significant. The intention-to-treat (ITT) and the safety analysis included all patients who were started on treatment with one of the study medications. The per protocol (PP) analysis covered all patients who had participated in the study according to protocol.

The difference between baseline values and the intensity of spasticity (Ashworth Score) in the most severely affected joint region after 4 weeks of treatment with the individual optimal dose was defined as primary target parameter (analysis in ITT population). The hypothesis H_0: 'Tolperisone is not superior to placebo in reducing spasticity' was tested against the alternative hypothesis of tolperisone being superior to placebo. A Wilcoxon rank sums test was performed for the comparison of the primary target parameter in both groups. In case of missing data, the last recorded value was carried forward.

The single primary target parameter (Ashworth Scale) was set at the beginning of the study. Secondary analyses were carried out to put changes in the muscle tone in the context of changes in functional or overall disability. These secondary target parameters were analyzed using descriptive, and if appropriate, also comparative statistics. The secondary and safety parameters were subjected either to the chi-squared test (for discrete variables), *t*-test or Wilcoxon-test (for continuous variables) depending on the type of distribution.

Sample size calculations were based on an anticipated difference of one point in the reduction of the Ashworth Score between patients treated with tolperisone or placebo with an expected reduction of 1.2 points in the placebo group. Accordingly, 60 patients were needed per treatment group ($\alpha = 0.05$, 1-$\beta = 80\%$).

Results

Recruitment

A total of 43 female and 77 males patients suffering from stroke-related spasticity were randomized and enrolled in the study. The ITT population consisted of these 120 patients ($n = 60$ in each group) of which two patients dropped out in the tolperisone group ($n = 1$ on own request, $n = 1$ lost to follow-up). Seven patients withdrew from placebo ($n = 2$ adverse events; $n = 2$ lack of efficacy; $n = 2$ lost to follow-up; $n = 1$ on own request). Additionally, seven patients in each group were excluded from the PP analysis because of protocol violations. Thus, the PP population consisted of 97 patients ($n = 51$ on tolperisone, $n = 46$ on placebo; 37 female and 60 male patients).

Characteristics of the patients

The baseline characteristics of the patients are given in Table 1. Patients had a mean age of 63.3 ± 10.6 years (range: 20–78 years). On average, cerebral stroke had occurred 3.3 ± 4.4 years (range: 0.2–30.5 years) before study entry. In 15 patients of the placebo group and nine patients of the tolperisone group < 6 months had passed between stroke and study start. Overall, treatment groups and study populations (i.e. ITT and PP population) did not differ in demographic measures, baseline features, and anamnestic data relevant to study results. Only the distribution of gender (more female patients on tolperisone) varied between treatment groups. However, this difference was considered not relevant as the treatment groups were well-balanced in all other baseline characteristics. In addition, there was no scientific basis for assuming gender to be a confounding factor for the type and course of spastic hypertonia.

At the beginning of the study, the presence of spasticity was verified in all patients with the mean Ashworth Score being 3.0 ± 0.6 in the ITT population. Most often both limbs of one side ($n = 56$ on tolperisone, $n = 59$ on placebo) were affected. Fifty-two patients each in both treatment groups reported at least one concomitant disease (tolperisone: $n = 88$ concomitant diseases, placebo: $n = 91$ concomitant diseases). Most often were diseases of the circulatory system (tolperisone: $n = 51$, placebo: $n = 54$), followed by diseases of the digestive system (tolperisone: $n = 14$, placebo: $n = 10$), and endocrine, nutritional and metabolic diseases (tolperisone: $n = 12$, placebo: $n = 9$). Physical therapy was applied to only some patients (ITT population: tolperisone: $n = 11$ placebo: $n = 17$).

Study medication

At the end of the titration period, four patients on tolperisone were titrated to a dose of 3×2 tablets (300 mg), 17 patients to a dose of 3×3 tablets (450 mg), 27 patients to a dose of 3×4 tablets (600 mg), one patient to a dose of 3×5 tablets (750 mg), and nine patients to a dose of 3×6 tablets (900 mg). Two tolperisone patients dropped out during the titration period. Correspondingly, 600 mg tolperisone daily was the most common dose whilst 15% of the patients were treated even with 900 mg/day. Correlation analyses failed to establish clear relationships between the dose of study medication and the achieved response, and the dose of study medication and the baseline intensity of symptoms. Furthermore, there was no difference in the mean number of tablets taken between both treatment groups.

Patients were treated for an average of 88.3 ± 17.1 days with tolperisone and 88.1 ± 16.4 days with placebo. The duration of the titration period was 14.6 ± 4.4 and 14.2 ± 4.5 days respectively.

Primary target parameter: muscle tone

The primary target parameter proved tolperisone to be significantly superior to placebo in alleviating central spasticity following cerebral stroke – both in the ITT and the PP population ($P < 0.0001$). As shown in Table 2, 47 patients on tolperisone (78.3%) experienced a reduction of the degree of spasticity by at least 1 point. This was the case in 27 placebo patients (45.0%). The treatment effect was sustained during continued therapy and at study end, two patients in the tolperisone group (3.3%) had a reduction of the Ashworth Score by 3 points, 15 patients (25.0%) by 2 points, 30 patients (50.0%) by one point, and 13 patients (21.7%) experienced no change. Corresponding

Table 1 Baseline characteristics of patients stratified according to treatment group and population of analysis (mean values ± SD)

	ITT population		PP population	
	Tolperisone ($n = 60$)	Placebo ($n = 60$)	Tolperisone ($n = 51$)	Placebo ($n = 46$)
Gender	27 F, 33 M	16 F, 44 M	25 F, 26 M	12 F, 34 M
Age (years)	64.2 ± 10.9	62.3 ± 10.2	65.5 ± 9.1	62.9 ± 10.5
Time interval between stroke and study start (years)	3.0 ± 3.7	3.6 ± 5.0	3.2 ± 3.7	3.2 ± 4.8
Spasticity[a] present in				
left upper limbs	3	0	3	0
right upper limbs	1	0	0	0
both right limbs	27	32	23	25
both left limbs	29	27	25	20
all limbs	0	1	0	1
Ashworth Score	3.0 ± 0.6	3.0 ± 0.52	3.0 ± 0.59	3.0 ± 0.49
Walking endurance (m)[b]	38.5 ± 26.7	30.9 ± 18.7	37.7 ± 26.5	28.4 ± 15.6
Measured force in upper limb spastic hypertonia (kg)[c]	2.2 ± 1.7	1.6 ± 0.8	1.6 ± 0.5	1.5 ± 0.9
Modified Barthel Index	82.9 ± 16.0	83.7 ± 14.8	82.5 ± 2.3	83.9 ± 1.8

F, females; M, males.
[a]Absolute numbers.
[b]Number of available patients: ITT: tolperisone: $n = 43$; placebo: $n = 51$; PP: tolperisone: $n = 39$; placebo: $n = 38$.
[c]Number of available patients: ITT: tolperisone: $n = 16$; placebo: $n = 10$; PP: tolperisone: $n = 12$; placebo: $n = 8$.

Table 2 Improvement of primary target parameter, i.e. Ashworth Score in the ITT population after 4 weeks on the individual optimal dose

Change of intensity of spasticity	Treatment group	
	Tolperisone, *n* (%)	Placebo n (%)
−3	1 (1.7)	0 (0)
−2	13 (21.7)	1 (1.7)
−1	33 (55.0)	26 (43.3)
0	13 (21.7)	33 (55.0)
Total	60 (100.0)	60 (100.0)

figures in the placebo group were 0 (0%), two (3.3%), 27 (45.0%), and 31 (51.7%). Likewise, the mean Ashworth Score was reduced by 1.03 ± 0.71 in the tolperisone group compared with 0.47 ± 0.54 in the placebo group after 4 weeks on the individual optimal dose ($P < 0.0001$). Group differences became significant after 4–5 days on treatment (−0.80 ± 0.61 vs. −0.45 ± 0.50; $P = 0.0017$) and still favored tolperisone over placebo at 12 weeks (−1.10 ± 0.77 vs. 0.52 ± 0.57; $P < 0.0001$).

Secondary target parameters and Modified Barthel Index

The secondary target parameters also show a uniform tendency towards a superior efficacy of tolperisone compared with placebo and thus demonstrate a clinically meaningful impact of tolperisone on the patient's every day life: There was a clear trend ($P = 0.053$) towards a better capacity to perform routine activities whilst treated with tolperisone for 4 weeks with the individual optimal dose which became even more prominent until study end (Table 3). The walking endurance on a smooth horizontal surface for 2 min was also considerably longer at study end compared with placebo (Fig. 1). Correspondingly, the force needed for the extension of the elbow joint increased (week 4 − baseline: $P = 0.08$), and differences between tolperisone and placebo became even more obvious with continued treatment. At study end, the Modified Barthel Index with mean differences to baseline of 5.3 on tolperisone and 1.7 on placebo also tended to favor tolperisone over placebo. In consequence, the overall assessments of efficacy by patients and investigators confirmed the superiority of tolperisone over placebo ($P < 0.001$; Fig. 2).

Safety and adverse events

A total number of 45 adverse events were observed in 22 of 120 enrolled patients with more adverse events being recorded on placebo ($n = 26$) than on tolperisone ($n = 19$). Of these, only one was a serious adverse event that occurred on placebo and was assessed to be 'unlikely' related to study treatment: The patient was suffering from stomach ache, nausea and dyspnea, and was admitted to hospital for proper treatment of a later diagnosed bleeding ulcer. This patient had also received acetylsalicylic acid for prophylaxis of thrombosis.

Table 3 Pre-post differences in the capacity to perform routine activities on tolperisone vs. placebo in the ITT population

	Tolperisone		Placebo	
	At study start, *n* (%)	At study end, *n* (%)	At study start, *n* (%)	At study end, *n* (%)
Activities performed perfectly without assistance		6 (10.00)		1 (1.67)
Activities performed nearly perfect without assistance	4 (6.67)	11 (18.33)	1 (1.67)	3 (5.00)
Activities performed slowly without assistance	13 (21.67)	17 (28.00)	21 (35.00)	22 (36.67)
Activities could be performed with assistance	42 (70.00)	23 (38.33)	36 (60.00)	27 (45.00)
Activities totally impossible	1 (1.67)	1 (1.67)	2 (3.33)	1 (1.67)
No entry		2 (3.33)		6 (10.00)
Total	60 (100.00)	60 (100.00)	60 (100.00)	60 (100.00)

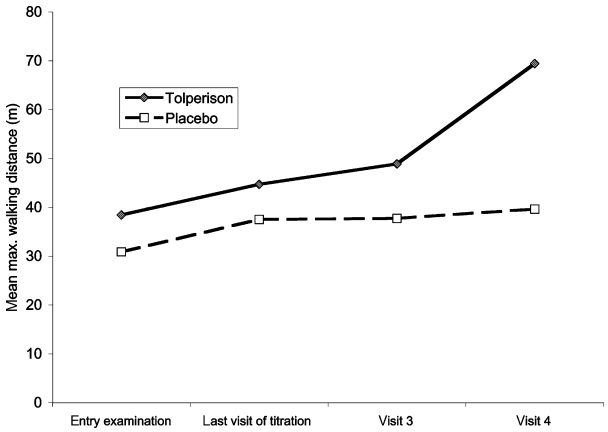

Figure 1 Course of walking endurance on a smooth horizontal surface for 2 min in the ITT population (tolperisone: $n = 43$; placebo: $n = 51$).

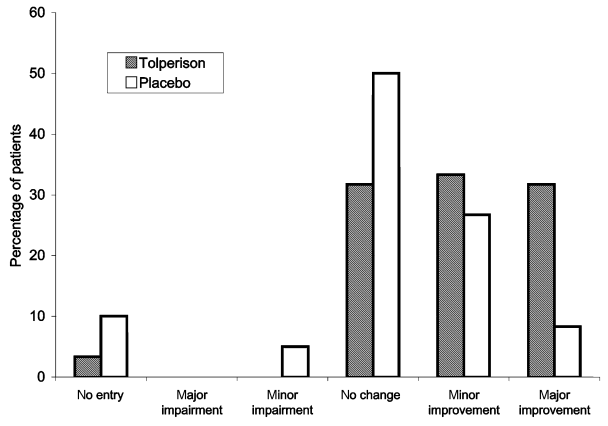

Figure 2 Overall assessment of efficacy by the investigators after 4 weeks on the individual optimal dose in the ITT population (tolperisone: $n = 60$; placebo: $n = 60$).

Other than that, no further serious adverse events or deaths occurred.

There was no difference in nature (Table 4), severity or causality assessment of adverse events in both groups. Thirteen adverse events on tolperisone (stomach ache/abdominal pain: $n = 5$, nausea: $n = 3$, dizziness: $n = 2$, distension: $n = 1$, diarrhea: $n = 1$, vomiting: $n = 1$), and nine adverse events on placebo (stomach ache: $n = 4$, nausea: $n = 3$, headache: $n = 1$, rash: $n = 1$) were assessed to be in some causal relationship to the study drug. Most adverse events were mild (tolperisone: $n = 7$; placebo: $n = 16$), or moderate in intensity (tolperisone: $n = 11$; placebo: $n = 9$). Two

Table 4 Nature of adverse events stratified according to treatment group and irrespective of causality

Nature of adverse event	Tolperisone	Placebo
Stomach ache/abdominal pain	5	6
Nausea	3	4
Dizziness	3	
Common cold/Influenza	2	1
High cholesterol		1
Headache	1	2
Chest discomfort	1	
Distension	1	
Diarrhea	1	1
Vomiting	1	1
Stenocardia	1	
Hypertonia		2
Bone fracture		1
Muscle cramps		1
Rash		1
Insomnia		1
Anxiety		1
Dyspnea		1
Cystitis		1
Podagra		1
Total	19	26

patients on placebo were discontinued because of adverse events. This was not the case in any patient on tolperisone.

The evaluation of laboratory results gave no hints on any medication-related clinically relevant changes. Only in one patient of the tolperisone group (450 mg) transaminases rose to 77.1 IU/l for AST and 45.1 IU/l for ALT. These out of range values were not considered an adverse event and were not followed by the investigator as the magnitude of change did not suggest any severe pathological change. In addition, the data on body temperature, heart rate, blood pressure, and pathologic findings in the ECG did no suggest any medication-related pathology. This was also the case with the data on changes in concomitant diseases and medications.

As shown in Fig. 3, final assessments of tolerability by the patients and the investigators clearly favored tolperisone over placebo [$P = 0.015$ (patients) and $P = 0.026$ (investigators)].

Discussion

The results of the present study demonstrate the efficacy of tolperisone hydrochloride in decreasing spasticity following cerebral stroke. Significant and clinically relevant superiority of tolperisone over placebo was found in both the ITT and the PP population.

In general, quantification of spasticity remains a difficult and largely unresolved problem. Functional assessment scales of activities of daily living appear inappropriate as they only make indirect reference to this physiologic phenomenon and may not measure spastic hypertonia at all (Haas *et al*., 1996). Therefore, the Ashworth Scale – which irrespective of any criticism (Hinderer *et al*., 1990) – is the best validated rating scale for spasticity at present (Katz *et al*., 1992; The United Kingdom Tizanidine Trial Group, 1994; Haas *et al*., 1996) was chosen as the primary target parameter and functional assessment scales as secondary target parameters in the study reported here. The Ashworth Scale has been used in many drug trials of other antispastic agents and in the present study proved tolperisone to be superior to placebo in alleviating increased muscle tone: More than three-fourth of the patients on tolperisone experienced a reduction of the degree of spasticity by at least one point on the five-point Ashworth Scale.

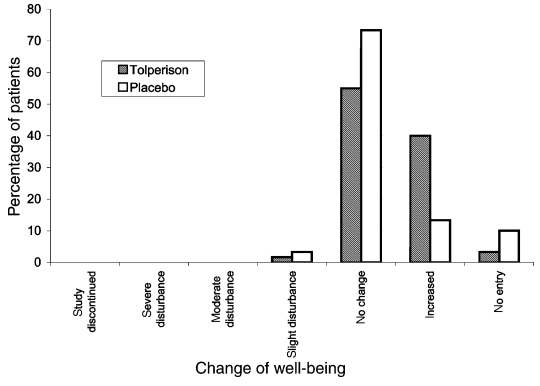

Figure 3 Investigator's assessment of tolerance 12 weeks after start of therapy in the ITT population (tolperisone: $n = 60$; placebo: $n = 60$).

This effect is of clinical relevance as the course of the secondary target parameters related to the patients every day life also favored tolperisone over placebo. This is in contrast to most other antispastic agents including botulinum toxin which also effectively reduces muscle tone but failed to show any meaningful influence on activities of daily living (Stien *et al*., 1987; Bass *et al*., 1988; Medici *et al*., 1989; Milanov, 1992; Lataste *et al*., 1994; Gracies *et al*., 1997; Bakheit *et al*., 2000; Wissel *et al*., 2000; Meythaler *et al*., 2001). Unlike other muscle relaxants such as baclofen or dantrolene (Gracies *et al*., 1997), muscle weakness was not encountered by tolperisone in this study. Consequently the walking endurance on a flat surface was also increased on tolperisone.

Tolerability of tolperisone was again excellent. Adverse events occurred less often on active treatment than on placebo and were mostly of mild-to-moderate intensity. As a result, no withdrawals because of adverse events were reported in the tolperisone group. With respect to the overall assessments of tolerability it should be noted, that the rating scale used was not specific to tolerability alone but rather gave mixed information on tolerability and efficacy. Therefore, it cannot be concluded that the tolerability of tolperisone is superior to that of placebo as the category 'increased well-being' rather reflects the superior efficacy of the test drug.

Overall, the results of our study may have important implications for the drug management of central spasticity as tolperisone not only reduces spastic hypertonia but also enables the patient to perform routine activities of daily living more easily and provides greater independence in self-care. Its good tolerability with minimum contraindications makes tolperisone suitable for a broad range of patients including elderly patients with concomitant diseases.

The data of the present study are in accordance with earlier results from controlled studies comparing tolperisone with placebo which also demonstrated the efficacy of tolperisone in spastic hypertonia (Haque *et al*., 1994; Melka and Haimanot, 1995). Advantages of tolperisone were found in a controlled study on

48 hemiplegic patients with spastic hypertonia because of trauma or illness of the central nervous system who were randomized to either receive 150 mg tolperisone or 25 mg baclofen three times daily for 6 weeks. Patients in both treatment groups improved but tolperisone was significantly superior to baclofen with respect to improvement of mobility and self-reliance (Fehér *et al*., 1985).

Different from these earlier studies, a dose titration design allowing doses between 300 and 900 mg of tolperisone daily was chosen in the present trial. This decision was based on high interindividual kinetic differences which where found in a recent study. This study showed the pharmacokinetics of tolperisone to be highly variable. An approximately 20-fold difference between the highest and the lowest C_{max} value was registered in 24 healthy volunteers after oral intake of 150 mg as a single dose (unpublished data). These pharmacokinetic data together with the long-term experience suggested that an individual dose titration might improve the efficacy of tolperisone without undue risks for the patients.

The results of the present trial entirely confirm this assumption, as we found a clear-cut superiority of tolperisone over placebo and none of the parameters related to safety (e.g. adverse events, safety laboratory, ECG findings, physical examination) demonstrated any significant difference between the two treatment groups. This is of special relevance as in our study 62% of all patients in the tolperisone group were treated with a dose higher than the dose currently recommended, i.e. 450 mg tolperisone daily. However, only 15% of all patients were titrated up to the maximum dose of 900 mg daily. The precise reasons for termination of dose titration where not recorded in the case report forms. In two tolperisone patients and three placebo patients further dose increases were most likely waived because of adverse events and consequently a dose reduction was performed as stipulated in the protocol. In the other patients dose titration was either stopped because the individual optimal response was considered reached by the investigator, or in other cases because patients did not want to take up to 18 tablets daily (i.e. 900 mg). Hence, it may well be that the optimal dose of tolperisone in spastic hypertonia may be even higher than the doses studied here as the large number of tablets required to reach an effective dosage represented significant psychological and practical limitations. This further indicates that a different strength of tablets with for instance 150 mg tolperisone might be more suitable for patients requiring higher doses for individual optimal response.

In conclusion, the results of this clinical study confirm the antispastic efficacy of tolperisone in patients with spastic hypertonia following cerebral stroke. The reduction of spasticity was sufficient to allow a better performance in the activities of daily living and of self-care. Tolerability was excellent, and analysis of the titration regimen indicates that an individual dose titration which may exceed the recommended maximum dose of 450 mg daily results in optimized therapeutic benefit.

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