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Efficacy and tolerance of repeated oral doses of tolperisone hydrochloride in the treatment of painful reflex muscle spasm: results of a prospective placebo-controlled double-blind trial

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Summary The efficacy and safety of oral tolperisone hydrochloride (Mydocalm®) in the treatment of painful reflex muscle spasm was assessed in a prospective, randomized, double-blind, placebo-controlled trial. A total of 138 patients, aged between 20 and 75 years, with painful reflex muscle spasm associated with diseases of the spinal column or proximal joints were enrolled in eight rehabilitation centers. Patients were randomized to receive either 300 mg tolperisone hydrochloride or placebo for a period of 21 days. Both treatment groups recovered during the 3 weeks rehabilitation program. However, tolperisone hydrochloride proved to be significantly superior to placebo: the change score of the pressure pain threshold as the primary target parameter significantly increased during therapy with tolperisone hydrochloride ($P = 0.03$, valid-case-analysis) compared to the results obtained on placebo treatment. The overall assessment of efficacy by the patient also demonstrated significant differences in favor of tolperisone hydrochloride. Best results were seen in patients aged between 40 and 60 years with a history of complaints shorter than 1 year and with concomitant physical therapy. The evaluation of safety data, i.e. adverse events, biochemical and hematological laboratory parameters, demonstrated no differences between tolperisone hydrochloride and placebo. As a conclusion tolperisone hydrochloride represents an effective and safe treatment of painful reflex muscle spasm without the typical side effects of centrally active muscle relaxants.

Key words: Reflex muscle spasm; Tolperisone hydrochloride; Placebo-controlled trial

Introduction

Myofascial pain syndromes including muscle spasm are characterized by a high prevalence in the general population (Drewes and Jennum 1995). Muscle spasm usually accompanies degenerative or inflammatory diseases of the musculoskeletal system and is defined as a sustained involuntary contraction which is usually painful and cannot be relieved completely by voluntary effort (Fisher and Chang 1985). Hence muscle spasm is one of the most important indications for the use of myotonolytic agents. However, most of the centrally active muscle relaxants have considerable side effects such as sedation, dizziness, impairment of co-ordination, mental confusion, weakness, withdrawal phenomena or anticholinergic adverse events (Mutschler 1986; Jurna and Motsch 1993; Kuschinsky et al. 1993; Reynolds 1993). These common side effects often impair the cooperation of the patients with physical therapy and their ability to work.

Tolperisone hydrochloride differs from other myotonolytic agents in its pharmacological properties which mediate muscle relaxation without concomitant sedation or withdrawal phenomena. Contributing to its related chemical structure, the tertiary aryl amine tolperisone hydrochloride has a lidocaine-like-activity and stabilizes nerve membranes as shown in experiments on isolated nervus ischiadicus (Ono et al. 1984). Tolperisone hydrochloride blocks in a dose-dependent manner mono- and polysynaptic reflexes at the spinal level (Fukuda et al. 1970; Ito et al. 1985; Morikawa et al. 1987). It is also effective in alleviating experimental gamma-rigor of reticular origin (Ochiai and Ishida 1981; Morikawa et al. 1987).

In several clinical studies tolperisone hydrochloride has been shown to relieve painful muscle spasm associated with diseases of the spinal column or proximal joints

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(reviewed by Kohnen 1995). Tolperisone hydrochloride demonstrated superiority over placebo and additional therapeutic benefit when given concomitantly with standard treatment: In an open controlled sequential study with a 1-week placebo-run-in-period followed by a 3-weeks period of active drug treatment, 300 mg tolperisone hydrochloride lessened paravertebral muscle spasms in 19 out of 21 patients compared with only five responders on placebo (Ammer 1980). In a three-arm open controlled study in 74 patients with rheumatoid arthritis, tolperisone hydrochloride was able to reduce the consumption of non-steroidal anti-inflammatory agents (NSAID) (Porkolab 1978). This result was confirmed 2 years later by Galos (1980) in a similar designed study in 57 patients with rheumatoid diseases and secondary muscle spasm. In a further open controlled trial in 53 patients with rheumatic diseases standard NSAID therapy was able to effectively relieve rheumatic symptoms, with the exception of morning stiffness and muscular hypertension. These symptoms were alleviated significantly in 53 patients on concomitant tolperisone hydrochloride treatment (Udvardi 1987). In an open comparative study in 94 patients with paravertebral muscle spasm, tolperisone hydrochloride given in addition to physiotherapy proved to shorten the time period until relief of pain and muscle spasm was achieved when compared with physiotherapy alone (Kiss and Martos 1993). The ability of tolperisone hydrochloride to increase the efficacy of physiotherapy had previously been reported by Bobko (1970) who performed a four-arm unblinded placebo-controlled study with 314 patients.

However, efficacy had until now been evaluated primarily by subjective measures, and investigators were not blinded with regard to the trial medication. A double-blind placebo-controlled clinical trial using a pressure tolerance meter as an objective measurement was therefore conducted to prove the efficacy and safety of tolperisone hydrochloride in painful reflex muscle spasm.

Methods

The study was conducted as a prospective, double-blind, randomized, placebo-controlled investigation. A total of 138 patients aged between 18 and 75 years were enrolled in eight rehabilitation centers. Patients eligible for this trial were to have painful reflex muscle spasm associated with diseases of the spinal column or proximal joints. The presence of muscle spasm was verified by means of manual palpation both by the investigator and by a physiotherapist. As basic features of muscle spasm involuntary muscle contraction and local tenderness on palpation had to be present. The pressure pain threshold as a quantitative parameter for muscle tenderness had to be ≤ 2 kg/cm^2 in the point of maximal pain associated with increased muscle tension and ≤ 4 kg/cm^2 as a mean of 16 myofascial standard pressure points (Pratzel 1992). Every patient had to give informed written consent before the start of the study.

Patients with acute inflammatory diseases that required specific drug therapy, with ankylosis, with myasthenia gravis, or severe physical or mental concomitant diseases that might impair trial performance according to protocol were to be excluded. Further exclusion criteria were hypersensitivity to tolperisone hydrochloride or lidocaine, diabetic neuropathy, concomitant medication with glucocorticoids, benzodiazepines, or other muscle relaxing agents or other drugs possibly influencing the aim of the trial. NSAID were allowed, provided that no changes had occurred within the last 4 weeks before or during the trial. Women in reproductive age without secure contraception or who were pregnant or lactating, were also excluded from the study.

Patients were randomized to receive either 3 × 2 tablets, i.e. 3 × 100 mg tolperisone hydrochloride (Mydocalm®, Strathmann AG & Co., Hamburg, Germany) per day, or a corresponding number of placebo tablets identical in shape, smell and color for 21 days. Additional physiotherapy was allowed. An attempt was made to minimize, and as far as possible standardize physiotherapy during the first 10 days of the trial in each patient. Any concomitant medication or physiotherapy had to be recorded in the case record form. Treatment compliance was to be ensured and medication dosage checked by pill counting.

The change score of the pressure pain threshold measured by means of the Pressure Tolerance Meter (Pain Diagnostics & Thermography, GB) scaled to a maximum of 11 kg/cm^2 as described by Pratzel et al. (1992) during the first 10 days of treatment was defined to be the primary target parameter. This method has been proven to be useful in clinical practice for quantification of deep muscle tenderness as a key feature of muscle spasm (Fischer 1987) and shows distinct advantages over manual palpation. Manual palpation, although capable of detecting muscle spasm, suffers from poor repeatability (List 1989; Levoska 1993). Although the pressure pain threshold shows a significant correlation with manual palpation scores, this method exhibits a considerably better reliability ($r = 0.79$–0.94; List 1989). The pressure pain threshold proved to have a high inter-rater reliability of $r = 0.8$–0.9 as well as a high intra-rater reliability of $r = 0.8$–0.91 indicating its suitability for diagnosis and monitoring of myofascial pain syndromes such as muscle spasm (Delaney and McKee 1993).

Muscle spasm can, especially if present for some time, involve neighboring muscles and also affect muscles farther away which have the same segmental or multisegmental innervation or that are a pathophysiological part within the dynamical system formed by the spinal column or proximal joints (Tilscher and Eder 1986). To provide a reliable basis for the assessment of efficacy of a systemically acting muscle relaxant, several potential sites for pathophysiological changes should therefore be evaluated and we decided to investigate a total number of 16 symmetrical standard myofascial pressure points (Fig. 1) according to the method of Pratzel et al. (1992). These had to be checked by the investigator at each visit in addition to the pressure pain threshold in the point of maximal pain as a result of muscle spasm. For evaluation of efficacy the values of the pressure pain threshold during the first 10 days of therapy were calculated to give a change score considering all measurements and corresponding time points by means of the following formula:

$$S = \tfrac{1}{2}[(D_4 - D_1) + (D_7 - D_1) + (D_{10} - D_1)] + \tfrac{1}{2}[(P_4 - P_1) + (P_7 - P_1) + (P_{10} - P_1)]$$

$D_{1,4,7,10}$ and $P_{1,4,7,10}$ denote the mean pressure pain threshold of all 16 standard points (D) and the pressure pain threshold in the point of maximal pain (P) on days 1 (before therapy), 4, 7 and 10, respectively. The total score is an integrative value that describes the dynamics of changes in the mean pressure pain threshold and of the pressure pain threshold in the point with maximal pain. This change score allows for a very comprehensive evaluation of treatment effects since it considers the time-effect-profile as well as changes in the primarily affected region and in pathophysiologically dependent areas in a standardized parameter. Since the point with maximal pain is most bothersome for the patient, changes in the pressure pain threshold in this point are defined to be more important than in any of the other 16 points measured and therefore contribute to 50% of the score value. Irrespectively, due to the given lower pressure pain threshold in the point with maximal pain at the beginning of the study muscle relaxation and in this alleviation of muscle tenderness has to be proportionally more pronounced in this point in order to equally affect the change score.

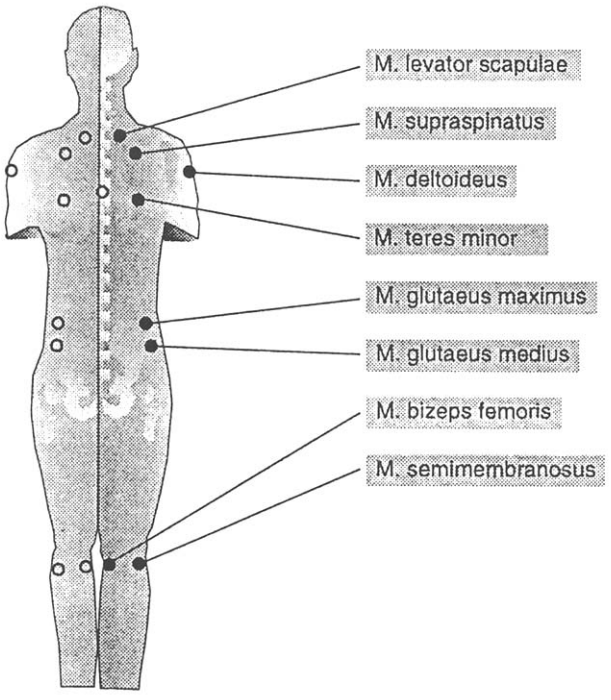

Fig. 1. Distribution pattern of 16 standard myofascial pressure points that were to be measured for determination of the pressure pain threshold. Additionally, the pressure pain threshold was to be measured in the point of maximal pain.

The pressure pain thresholds and a number of secondary target parameters (Clinical Global Impressions Scale [CGI], subjective judgment of symptoms, reduction of mobility, judgment of manual palpation findings in the region affected by muscle spasm and the underlying pathological process) were evaluated before and after 4, 7, 10 and 21 days of therapy. The CGI consists of three items, i.e. severity of illness, healing process and efficacy index, that are evaluated by the investigator in a standardized questionnaire (Collegium Internationale Psychiatriae Scalarum 1996).

For the subjective judgment of symptoms, the patients had to record the intensity of pain, restriction of mobility and muscle tension daily according to a four-point scale (no, slight, moderate, severe). At each visit the physiotherapist measured the joint mobility in the affected area in degrees of motion. Furthermore, restriction of mobility as well as muscle tension in the worst affected area were rated by the investigator according to a four-point scale (no, slight, moderate, severe). At the end of the trial, patient and investigator had to give an overall assessment of the efficacy and tolerability of the study medication. The investigator was not blind to the measurements of the pressure pain thresholds and therefore was able to take these into account of his assessment of efficacy. Due to the quantity of single measurements, however, the values of pressure pain threshold were not able to primarily influence the assessment but rather the overall impression of the patient's status was likely to be the key feature for the evaluation of efficacy by the physician. Adverse events had to be recorded continuously during the course of the trial.

Complete clinical and laboratory examinations were performed before the beginning and after 21 days of therapy. The standard clinical screening included medical history, a clinical examination, the determination of body weight, height, a standard ECG (12 lead), measurements of blood pressure and heart rate after 5 min of supine rest. The standard laboratory screening covered 15 biochemical and hematological blood parameters (creatinine, uric acid, urea, glucose, total bilirubin, AST, ALT, γ-GT, alkaline phosphatase, prothrombin time, hemoglobin, hematocrit, erythrocyte, leukocyte, and platelet count) as well as a semiquantitative determination of nine parameters in urine (Combur 9) and evaluation of urine sediment.

The biostatistical evaluation was carried out by means of the statistical software package SAS for Windows 3.1, version 6.10 (Statistical Analysis System SAS-Institute, Cary NC, USA). The statistical analysis was conducted both for valid cases (VC), i.e. all patients that had participated in the trial according to protocol, and for the intention-to-treat-population (ITT), i.e. all patients having received the study medication at least once. For the intention-to-treat-analysis the last value registered for each parameter in drop-outs had to be 'carried forward'. This procedure was chosen to ensure that drop-outs tended against efficacy.

Previous studies with tolperisone hydrochloride indicate that maximal effects in respect of responder rates and extent of efficacy can be expected from the 10th day of treatment onwards (Kokemohr 1995). On account of the data of Kiss and Martos (1991) maximal effects of a rehabilitation program shall be achieved on the 15th day of treatment. In order to allow the registration of drug effects and avoid blurring by the concomitantly permitted long-term physiotherapy day 10 was chosen as primary endpoint for the comparison of target parameters. The period between the 10th and 21st day of the trial was defined as a double-blind follow-up period. The level of significance was defined as $P = 0.05$.

The Mann–Whitney–Wilcoxon U-test was performed for the evaluation of the primary efficacy parameter. Subgroup analyses were performed to investigate the influence of concomitant physiotherapy, duration of present complaints, concomitant intake of NSAID, localization of disease and treatment in different centers. The secondary efficacy target parameters in the above given hierarchical sequence as well as the overall assessments were compared by means of Pearson's χ^2 test.

The study was reviewed and approved by the responsible local Ethics Committees.

Results

Patient populations

A total number of 138 patients took part in the study. One patient dropped out at baseline examination, but this was before treatment was initiated. The intention-to-treat-population therefore consisted of 137 patients. Fig. 2 gives the time point and reason leading to exclusion from the valid-case-analysis in 25 patients. With respect to the intention-to-treat-population, the flow-chart also shows the last visit of which the values were carried forward. In one center randomization was not followed. The center was therefore excluded from the valid-case-analysis.

Demographic and baseline characteristics of the valid-case- and intention-to-treat-population are given in Table I. Patients of both populations as well as of both treatment groups did not differ in demographic measures, baseline features or anamnestic data. All patients complained about painful muscle spasm, which was verified both by the investigator and the physiotherapist during the initial clinical examination. With respect to the given possibility of multiple localizations, spasms of the paravertebral muscles were documented 149 times: 63 patients of the intention-to-treat-population had muscle spasms at the cervical, 54 at the upper lumbar and 32 at the lumbar sciatic spine. Twenty-four patients complained of muscle spasms in the shoulder region. Muscle spasm was primarily considered to be a result of spondylarthrosis or spondylosis ($n = 74$). Other

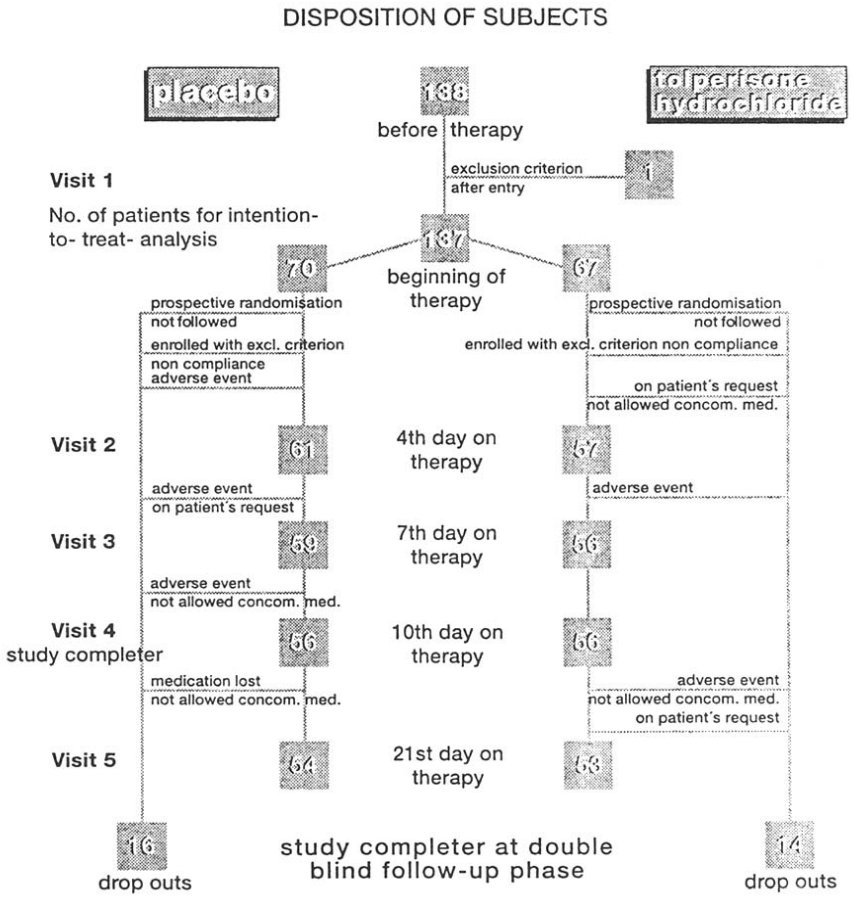

Fig. 2. Absolute frequencies of drop-outs and protocol deviations leading to exclusion from the intention-to-treat- or the valid-case-analysis. Intention-to-treat-population, $n = 137$; valid-case-population, $n = 112$.

causes of muscle spasm were arthromuscular dysfunction ($n = 11$), protrusion or prolapse of intervertebral disc ($n = 9$), trauma ($n = 7$) and lumbalgia statica ($n = 5$). In 21 cases the causes of muscle spasms could not be elucidated. No considerable differences were present with respect to different centers, treatment groups and populations of the statistical analysis (i.e. VC and ITT).

As the study was conducted in rehabilitation centers the patients had a long standing history of muscle spasm and were characterized by their relative resistance to previous therapeutic measures. In both treatment groups patients with a disease duration of more than 2 years were predominant (tolperisone hydrochloride, $n = 22$; placebo, $n = 27$; Table II). No differences between the two groups were observed with respect to previous physiotherapeutic or drug treatment. Sixty-two percent ($n = 86$) had already been treated by other forms of therapy with 68% having no or moderate improvement before entering the trial.

TABLE I

DEMOGRAPHIC AND BASELINE FEATURES (MEAN ± SD) OF THE INTENTION-TO-TREAT- AND VALID-CASE-POPULATION, STRATIFIED WITH RESPECT TO TREATMENT WITH TOLPERISONE HYDROCHLORIDE OR PLACEBO

Group	*n*	Age (years)	Sex		Height (cm)	Weight (kg)	Pressure pain threshold	
			M	F			Maximum pain point	Mean of all points
Intention to treat								
Tolperisone hydrochloride	67	50.2 ± 11.5	20	47	167.2 ± 8.9	74.9 ± 13.3	1.56 ± 0.29	2.55 ± 0.60
Placebo	70	48.5 ± 13.2	18	52	167.8 ± 8.0	77.0 ± 18.1	1.58 ± 0.26	2.63 ± 0.61
Valid cases per protocol								
Tolperisone hydrochloride	56	50.8 ± 10.3	17	39	167.7 ± 7.8	76.0 ± 13.2	1.58 ± 0.29	2.56 ± 0.57
Placebo	56	47.8 ± 13.1	14	42	168.5 ± 8.0	77.6 ± 19.1	1.58 ± 0.28	2.70 ± 0.64

TABLE II

HISTORY OF PAINFUL REFLEX MUSCLE SPASM (INTENTION-TO-TREAT-POPULATION, $n = 137$; MISSING DATA, 27)

Muscle spasm	Treatment group		Total
	Tolperisone hydrochloride	Placebo	
Up to 3 months	13	12	25
Since 3–6 months	5	3	8
Since 6–12 months	7	9	16
Since 1–2 years	7	5	12
Since 2–5 years	6	15	21
More than 5 years	16	12	28
Total	54	56	110

No relevant difference in concomitant diseases or medication could be observed. A total number of 10 patients in the tolperisone hydrochloride and nine patients in the placebo group received continuously NSAID during the trial. Absolute frequencies and types of physical therapy applied in the course of the trial are given in Table III.

Compliance with treatment was excellent. In the intention-to-treat-population a mean of 117 ± 28 tablets out of 126 tablets planned were taken by patients in the active drug treatment group and 115 ± 27 tablets by patients in the placebo group. In the valid-case-analysis both patients on tolperisone hydrochloride and on placebo took 125 ± 4 tablets, respectively.

Efficacy

Tolperisone hydrochloride proved to be significantly superior to placebo as judged by the primary target parameter both after 10 and 21 days of treatment. The change score of the pressure pain threshold during treatment with tolperisone hydrochloride increased to values significantly (intention-to-treat: $P = 0.05$ at day 10, $P = 0.04$ at day 21; valid-case-analysis: $P = 0.03$ at day 10, $P = 0.02$ at day 21; Mann–Whitney–Wilcoxon U-test) above those observed in therapy with placebo (Fig. 3). Stratification with respect to concomitant physiotherapy showed tolperisone hydrochloride to be more effective compared to placebo when given in combination with physiotherapeutic measures ($P < 0.05$, Mann–Whitney–Wilcoxon U-test; Fig. 4). Patients with a duration of complaints of less than 1 year responded considerably better to therapy with tolperisone hydrochloride than those with a longer standing history ($P < 0.05$, Mann–Whitney–Wilcoxon U-test; Fig. 5). Best results were achieved in patients aged 40–60 years ($P < 0.05$, Mann–Whitney–Wilcoxon U-test).

No center-related differences were noted, as tolperisone hydrochloride was superior to placebo in all centers. Furthermore, no particular difference between tolperisone hydrochloride and placebo was observed in patients with concomitant NSAID therapy. Almost identical efficacy was documented in respect to the localization of the muscle spasms with some tendency for a better effect in the group of patients with main localization in the upper lumbar region.

The CGI, the hierarchically most important secondary target parameter, demonstrated a trend similar to that of the primary target parameter although no statistical significance between treatment groups was reached ($P > 0.05$, Pearson's χ^2 test, Fig. 6). The manually palpated muscle tone also improved considerably during treatment with tolperisone hydrochloride although no significant difference was observed compared with placebo: With respect to the valid-case-population, after 21 days of therapy 15 pa-

TABLE III

ABSOLUTE FREQUENCIES OF PHYSIOTHERAPEUTIC MEASURES IN THE COURSE OF THE TRIAL: EQUAL DISTRIBUTION BETWEEN THE TOLPERISONE HYDROCHLORIDE AND THE PLACEBO GROUP (INTENTION-TO-TREAT-POPULATION, $n = 137$)

Type of physiotherapy	Total number on tolperisone hydrochloride	Total number on placebo
Gymnastics	128	140
Bath	108	91
Sport therapy	76	70
Massage	65	66
Electrotherapy	60	50
Fango compress	49	36
Mobilization	50	33
Water massage	37	41
Water gymnastics	28	40
Traction	31	35
Pelose	25	35
Others	117	123
Total	774	760

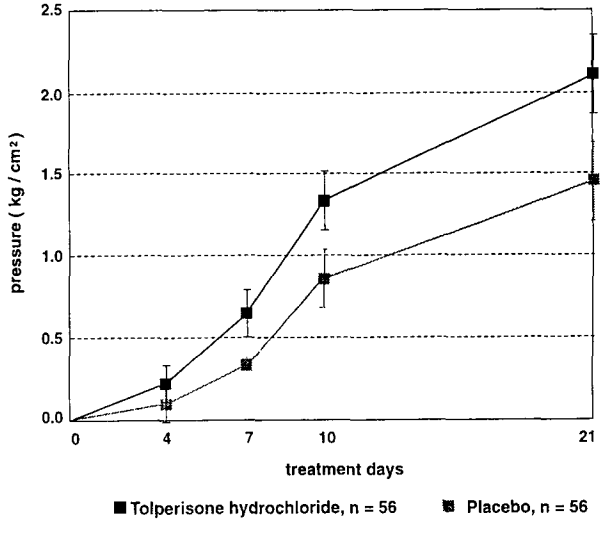

Fig. 3. Course of cumulative differences of the change score of the pressure pain threshold (for details see under Methods). Significant superiority of tolperisone hydrochloride over placebo (valid-case-population, $n = 112$; $P < 0.05$; mean ± SEM).

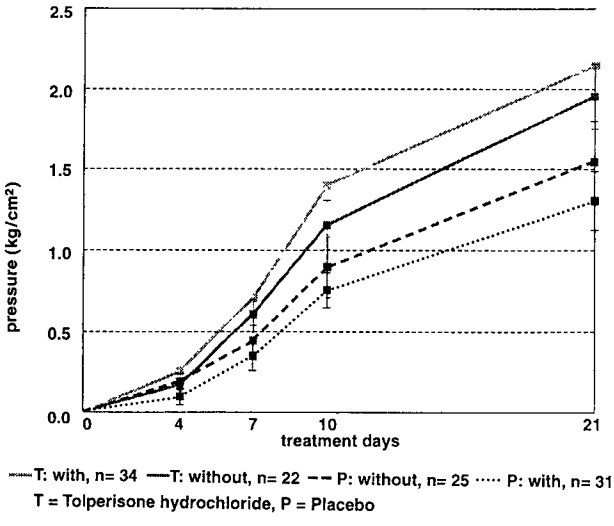

Fig. 4. Course of cumulative differences of the change score of the pressure pain threshold stratified with respect to patients with, and patients without additional physiotherapy. Better results are achieved in patients receiving additional physiotherapy comparing tolperisone hydrochloride and placebo ($P < 0.05$; valid-case-population, n = 112; mean ± SEM).

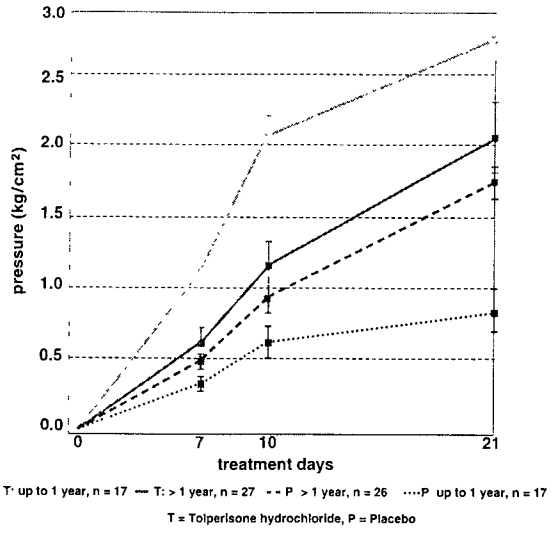

Fig. 5. Course of cumulative differences of the change score of the pressure pain threshold stratified with respect to duration of muscle spasm. Better results are achieved in patients with a disease history ≤1 year comparing tolperisone hydrochloride and placebo ($P < 0.05$; valid-case-population, $n = 112$; mean ± SD).

tients in the tolperisone hydrochloride group had normal, 28 mild and 11 moderately increased muscle tone. Corresponding figures on placebo were 9, 34 and 10. Two patients on placebo were judged to still have severely increased muscle tone. The effects of tolperisone hydrochloride on mobility showed no significant difference to placebo either, with 20 patients being able to move normally, 28 having mild and 7 moderate restrictions of mobility after 21 days of treatment (valid-case-population). In the placebo-group 15 patients had no, 31 mild and 9 patients moderately restricted mobility, respectively. Subjective ratings of single symptoms by the patient were insignificant (Pearson's χ^2 test) in differentiating between tolperisone hydrochloride and placebo as most patients of both groups had no or only mild pain (tolperisone hydrochloride, $n = 43$; placebo, $n = 39$), restriction of mobility (tolperisone hydrochloride, $n = 43$; placebo, $n = 41$), or increased muscle tone at the end of the study period (tolperisone hydrochloride, $n = 43$; placebo, $n = 39$; out of 56 patients in each treatment group).

According to the overall assessment of the physicians at the end of the trial 89.6% of the intention-to-treat-population ($n = 60$ out of 67 patients) and 94.6% of the valid-case-population ($n = 53$ out of 56 patients) responded to the treatment with tolperisone hydrochloride. Physicians favored tolperisone hydrochloride in the overall evaluation with 16 very good and 18 good, 19 moderate and 3 ineffective ratings compared with placebo being very good in 7, good in 17, moderate in 25 and ineffective in 7 cases in the valid-case-analysis ($P = 0.06$, Pearson's χ^2 test, one-tailed). The corresponding data in the intention-to-treat-analysis are 18 very good, 22 good, 20 moderate and 6

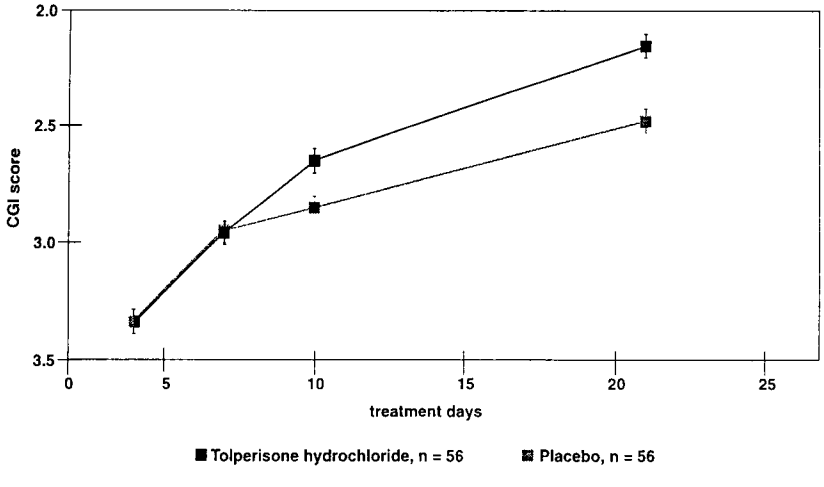

Fig. 6. Course of the hierarchically most important secondary target parameter: the Clinical Global Impression of Efficacy (valid-case-population, $n = 112$; mean ± SEM; 1 = very good, 2 = good, 3 = slight, 4 = ineffective).

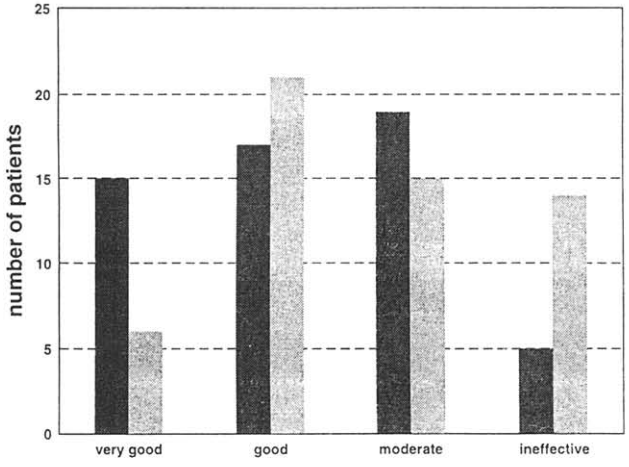

Fig. 7. Overall assessment of efficacy by the patients (absolute numbers) after 21 days of treatment. Significant superiority of tolperisone hydrochloride (dark grey bars) compared to placebo (light grey bars) ($P < 0.05$; valid-case-population, $n = 112$).

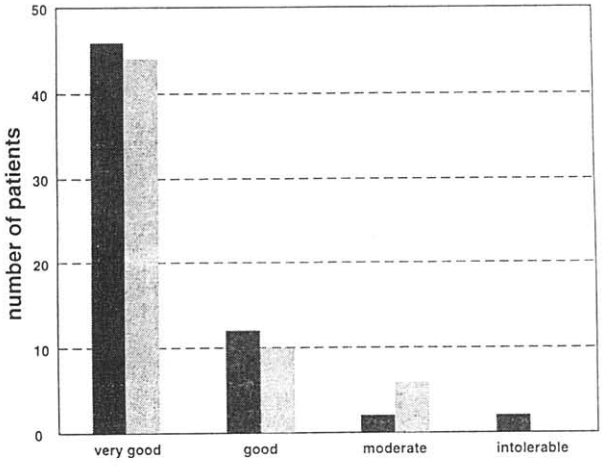

Fig. 8. Overall assessment of tolerability by the patients (absolute numbers) after 21 days of treatment. No difference between tolperisone hydrochloride (dark grey bars) and placebo (light grey bars) ($P > 0.05$; valid-case-population, $n = 112$).

ineffective assessments on tolperisone hydrochloride versus 9 very good, 19 good ratings, 29 moderate and 11 ineffective ratings on placebo ($P = 0.05$, Pearson's χ^2 test, one-tailed). With respect to the patients' overall assessment of efficacy tolperisone hydrochloride proved to be superior over placebo in the valid-case-analysis with $P = 0.02$ (Pearson's χ^2 test, one-tailed, Fig. 7; ITT, $P = 0.03$).

Safety

The number of patients who reported adverse events did not differ in both treatment groups. A total number of 70 adverse events in 44 patients was observed during the trial (34 in the tolperisone hydrochloride group, 36 in the placebo group; Table IV). Twenty-three adverse events (67.6%) in the tolperisone hydrochloride group and 16 adverse events (44.4%) in the placebo group were attributed to the drug given, with three events being probably, 14 possibly and six improbably related to tolperisone hydrochloride.

TABLE IV

NATURE AND INCIDENCE OF ADVERSE EVENTS (AE) IN THE COURSE OF THE TRIAL: NO DIFFERENCE IN ABSOLUTE FREQUENCIES OF ADVERSE EVENTS ON TREATMENT WITH TOLPERISONE HYDROCHLORIDE AND PLACEBO (INTENTION-TO-TREAT-POPULATION: $n = 137$)

Type of adverse events (AE)	Absolute number on tolperisone hydrochloride	Absolute number on placebo
Deterioration of main disease	0	2
Muscle weakness, tiredness	2	2
Muscle pain	3	9
Headache	7	6
Dizziness	2	2
Sleepiness, sleep disturbance	1	1
AE of respiratory system	4	3
AE of cardiovascular system	1	1
Thirst, dry mouth, bitter taste	2	1
Gastric complaints	6	2
Diarrhea, constipation	2	1
AE of genito-urinary tract	1	1
AE of Skin, allergy	3	3
Total	21 patients with 34 AE	23 patients with 36 AE

Four adverse events in the placebo group and three in the tolperisone hydrochloride group led to withdrawal. Two serious adverse events were reported during the trial (one case of asthma bronchiale and one hospitalization due to a broken arm), both being in the placebo group and not related to treatment. Concerning the laboratory parameters no difference was noted between the initial values and values after treatment for any parameter. Comparisons of blood pressure and heart rate demonstrated no influence of tolperisone hydrochloride on any of these parameters.

The overall assessments of tolerability demonstrated no differences between both treatments. Physicians judged tolperisone hydrochloride in 96.4% as very well or well tolerated compared to 92.8% corresponding assessments in the placebo group. The overall assessment of tolerability by the patient is given in Fig. 8.

Discussion

Tolperisone hydrochloride demonstrated significant superiority over placebo in increasing the change score of the pressure pain threshold reflecting alleviated painful reflex muscle spasm associated with diseases of the spinal column or proximal joints. Efficacy seemed to be most pronounced in patients with a duration of complaints of less than 1 year and those receiving concomitant physiotherapy.

Patient populations investigated in the present study were comparable with respect to all relevant demographic and baseline features. Drop-outs and patients excluded from the valid-case-analysis had no effect on the comparability of tolperisone hydrochloride and placebo treatment, as can be seen by the similar results in the valid-case- and intention-to-treat-population.

In scientific investigations comparisons with placebo are often considered necessary to assess the effect of a test drug and to reliably differentiate pharmacological actions from suggestive effects. Chronic pain syndromes are known to show a marked placebo response of up to 66% or even more (Bodem 1994). Despite the high placebo effect in the patient population studied tolperisone hydrochloride proved to be superior.

The pressure pain threshold as cumulated intra-individual difference between values during therapy and baseline values, was validated as a measure to monitor treatment effects in myofascial pain syndromes in previous trials and demonstrated high inter- and intra-rater reliability (Delaney and McKee 1993). Since myofascial pain can be widespread (Gerwin 1995), 16 standard pressure points were measured in addition to the point with maximal pain as a result of muscle spasm to provide a broad reliable basis for the evaluation of efficacy. On treatment with tolperisone hydrochloride the change score of the pressure pain threshold as a quantitative measure for tenderness due to muscle hypertension significantly increased when compared with placebo. And to that extent, the unexpected outcome was the definite and very pronounced long-term profit of therapy with tolperisone hydrochloride. Day 10 was chosen as endpoint for the confirmative comparison of the primary target parameter since the concomitantly permitted long-term physiotherapy was expected to blur drug mediated differences between treatment groups. The results of the present trial do not support this hypothesis. On the contrary, it was demonstrated that in spite of concomitant physiotherapy which was equally distributed in both groups, the differences between tolperisone hydrochloride and placebo became significant at day 10 and became even greater between days 10 and 21.

No particular differences between tolperisone hydrochloride and placebo concerning the primary target parameter were observed in patients with concomitant NSAID therapy, but this may be a result of the longer history of present complaints in tolperisone hydrochloride patients with concomitant NSAID intake. On account of there being only 19 patients involved in this comparison, results have to be interpreted with care.

The more subjectively based secondary target parameters were, although showing some trends in favor of tolperisone hydrochloride, apparently less sensitive in differentiating between treatment groups. This was expected, since at least for manual palpation scores poor repeatability and poor differentiating capacities had been previously documented (List 1989; Levoska 1993). Furthermore, it seems that the change score of the pressure pain threshold is the most discriminating parameter corresponding also with the results of the overall assessment of efficacy despite the effects of basic physiotherapy in both treatment groups.

Of pertinent importance for the interpretation of the trial results seems to be the long standing history of painful reflex muscle spasms in the studied population as well as the fact that 62% of the patients had been treated by other forms of therapy before entering the trial, with 68% showing no or moderate improvement. Tolperisone hydrochloride proved to be effective and significantly superior to placebo in a population previously resistant to therapeutic intervention. The superiority of tolperisone hydrochloride in the treatment of patients with painful reflex muscle spasm associated with diseases of the spinal column or proximal joints was further confirmed by the overall assessments in the physicians' judgment, and patients also clearly favored treatment with tolperisone hydrochloride.

Tolperisone hydrochloride was generally well tolerated. Although no difference between treatment groups could be noted in the quantity of adverse events, the comparison of the overall pattern of adverse events in both treatment groups indirectly supports the benefit of tolperisone hydrochloride: None of the patients on tolperisone hydrochloride reported deterioration of the main disease compared to two patients in the placebo group. Only three patients on tolperisone hydrochloride reported pain or other complaints in the extremities and muscles compared to nine cases in the placebo group.

Furthermore, the nature of adverse events confirms the experience that treatment with tolperisone hydrochloride does not result in sedation. Only one case of drowsiness and sleep disturbance, respectively, was noted in both treatment groups. Comparison of adverse event patterns revealed that investigators more readily attributed unspecific symptoms such as headaches and gastric discomfort to the application of tolperisone hydrochloride. No serious adverse events were noticed on treatment with tolperisone hydrochloride lending further evidence that this muscle relaxing agent is a well tolerated substance. This was also confirmed by the overall assessments of tolerability by the physicians and patients involved in the study.

In the overall conclusion, results of the present trial prove that tolperisone hydrochloride is an efficient and safe medication in the treatment of muscle spasms associated with diseases of the spinal column or proximal joints.

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