Muscle spasms are characterized by a high prevalence in the general population. Muscle spasm usually accompanies degenerative or inflammatory disease of the musculoskeletal system and is defined as a sustained involuntary contraction which is usually painful and cannot be completely relieved by voluntary effort.

1 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 coordination, mental confusion, weakness, withdrawal phenomenon or anti-cholinergic adverse events.

These common side effects often impair the cooperation of the patients with physical therapy and their ability to work.

Tolperisone is a centrally acting muscle relaxant which differs from other myotonolytic agents in its pharmacological properties that 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.

Tolperisone hydrochloride blocks the mono and polysynaptic reflexes at its spinal level in a dose dependent manner. In several clinical studies tolperisone hydrochloride has been shown to relieve muscle spasms associated with painful muscle spasm who are intolerant to NSAIDs or in whom NSAIDs are contraindicated. Tolperisone was well tolerated with no sedation reported by any patient during study period. The incidence of common adverse effects like nausea, gastric irritation was less than 2%.

Conclusions: Tolperisone is a safe, effective and non sedative alternative in management of acute painful spasm conditions associated with degenerative or inflammatory diseases of the musculoskeletal system.

Key Messages: Tolperisone is a skeletal muscle relaxant without concomitant sedation or withdrawal phenomena. In this open-labelled, non-comparative, prospective study tolperisone was proved to be a safe & effective alternative to skeletal muscle relaxants in the management of acute painful spasm conditions associated with degenerative or inflammatory diseases of the musculoskeletal system.
Methods and Procedures

Study Design

This was a prospective, open-labelled, non-comparative, multi-centre phase IV observational study conducted at 174 participating orthopaedic care centres across India.

Study subjects

Nine hundred & twenty adult patients between 18 to 70 years of age having painful muscle spasm associated with degenerative or inflammatory conditions were enrolled after obtaining informed consent.

Patients with known hypersensitivity to tolperisone, lidocaine and Non-Steroidal Anti-Inflammatory drugs (NSAIDs) were excluded from the study. Those with myasthenia gravis or severe physical or concomitant diseases that might impair trial performances, those with corrective surgery to or contracture of the measurable hip, knee, or ankle joints were also excluded. Patients with clinically significant hepatic disease, any recent history of illness or any condition that in the opinion of study investigator would prohibit study participation or affect outcome were also excluded from the study. Patients receiving glucocorticosteroids, benzodiazepines or methocarbamol, and pregnant and lactating females were not enrolled in the study.

Interventions

All enrolled patients were administered tablet tolperisone 150 mg thrice daily orally for a period of 7 days. During the study, antacids, H₃ blockers or proton pump inhibitors, analgesics, antihypertensive & antidiabetics were permitted but however oral or injectable corticosteroids were not permitted.

Assessments

Primary efficacy assessment variable was the muscle spasm (tone) assessed on a 0-3 Likert scale where 0 implies no spasm and 3 implies severe muscle spasm. Change in the mean baseline score for muscle spasm was assessed on day 3 and day 7.

Secondary efficacy variables were the mobility of affected area assessed on a 0-3 Likert scale where 0 implies complete mobility and 3 implies severe immobility, and pain at the affected area assessed on a 0-10 visual analogue scale (VAS) where 0 implies no pain and 10 implies severe intolerable pain. Change in scores for mobility and pain were assessed on day 3 and day 7.

Global assessment for efficacy and tolerability was assessed separately by the clinician and patient at end of therapy on day 7 on a 4-point scale of excellent, good, satisfactory, poor & very poor.

Safety assessment was made based upon the adverse events reported by the patients.

Statistical Analysis

Measurement data is expressed as Mean & Standard deviation (S.D.) and discrete data expressed as numbers (No.) & percentages (%). Efficacy and safety analysis was done on intention-to-treat (ITT) population. Expecting concomitant use of NSAID’s in such patients, a subgroup analysis was done. Change from baseline in the mean scores for joint pain, joint swelling & joint tenderness were analyzed using Friedman test with post-hoc tests (Wilcoxon Sign Rank test) for individual visits. Chi-Square test was used for the global assessments at end of therapy. For all statistical tests, the significance level was at 95% C.I. with $\alpha=0.05$.

Results

All patients completed the study period of 7 days. Of the 920 patients, 507 (55.1%) were male and 413 (44.9%) were female. All patients had painful spasm on enrolment and the mean (SD) age of the patients was 42.25 (12.2) years. Concomitant medications received by the patients were NSAIDs (45.7%), anti-secretary (13.5%), calcium & vitamins (7.7%), anti-arthritic (2.2%), and others (3.0%).

Efficacy Outcomes

Figure 1 (A,B,C) shows the mean scores for muscle tone, mobility & pain at baseline and on days 3 & 7. Significant improvements ($p<0.0001$) in the scores for muscle tone, mobility & pain were seen on days 3 & 7. The mean muscle tone score reduced from 2.53 at baseline to 1.46 on day 3 and to 0.38 on...
Fig. 2: Mean percentage fall from baseline in the muscle tone, mobility and pain in both groups. Group 1: NSAID. Group 2: non NSAID group.

**Global tolerability by Doctor**
- Excellent, 59.4
- Satisfactory, 3.38
- Good, 36.82
- Poor, 0.34

**Global efficacy by doctor**
- Excellent, 58.66
- Satisfactory, 4.02
- Good, 36.65
- Poor, 0.67

**Global efficacy by patient**
- Excellent, 54.36
- Satisfactory, 4.95
- Good, 39.75
- Poor, 0.9

Fig. 3: Global Tolerability rating as per Clinician and Patient

Fig. 4: shows the global efficacy rating as per the clinician and the patient.
day 7. The mean mobility scores reduced from 2.62 at baseline to 1.64 on day 3 and to 0.52 on day 7. The mean VAS score for pain reduced from 7.74 at baseline to 4.39 on day 3 to 1.14 on day 7. These reductions in scores indicate good muscle relaxation.

Table 1 shows the reduction (mean reduction & % reduction) from baseline in the mean scores for muscle tone, mobility & pain on days 3 & 7. The improvements in the scores from baseline for muscle tone, mobility & pain with the VAS score were 42%, 37% and 43% respectively on day 3 and 85%, 80% and 85% respectively on day 7.

Of the 920 patients, 420 patients received NSAIDs whereas 500 patients did not receive NSAIDs along with tolperisone. Other concomitant medications received by the patients were anti-arthritis 18 (2.0%), anti-diabetics 6 (0.65%), anti-hypertensive 7 (0.76%), topical steroids 14 (1.5%) and multivitamin preparations 71 (7.72%). Results were analyzed for two subgroups, the one which received NSAID with tolperisone (NSAID group) and the other who were on tolperisone alone (non NSAID group).

Figure 2 shows a subgroup analysis of the improvement (% change from baseline) on day 3 and day 7 in the scores for pain (43.28%, NSAID group & 43.31% non-NSAID group on day 7; 86.77%, NSAID group & 83.96% non-NSAID group on day 7), mobility (37.14%, NSAID group & 37.69% non-NSAID group; 80.41%, NSAID group & 80.22% non-NSAID group) & muscle tension (41.49%, NSAID group & 43.11% non-NSAID group; 86.81%, NSAID group & 83.67% non-NSAID group) was similar in patients receiving NSAID & those not receiving NSAID along with tolperisone.

Figure 3 shows the Global efficacy assessment by clinicians which shows that the therapy was rated as excellent-good for 95.3% patients, satisfactory for 4.0% patients and poor in 0.2% patients. Similarly, efficacy assessment by patients (n=888) shows that the therapy was rated as excellent by 483 (54.4%) patients, good by 353 (39.8%), and satisfactory by 44 (4.9%) patients. Therapy was rated as poor only by 8 (0.9%) patients.

Figure 4 shows the Global tolerability assessment by clinicians (n=888) shows that the therapy was rated as excellent for 528 (59.5%) patients, good for 327 (36.8%), and satisfactory for 30 (3.4%) patients. Therapy was rated as poor only in 3 (0.3%) patients. Similarly, tolerability assessment by patients (n=880) shows that the therapy was rated as excellent by 488 (55.5%) patients, good by 342 (38.9%), and satisfactory by 46 (5.2%) patients. Therapy was rated as poor only by 4 (0.4%) patients.

Adverse Events

A total of 35 adverse events were reported by 31 (3.4%) patients, during the study period of 7 days. All events were mild to moderate in intensity and none of them resulted in discontinuation of the therapy. Most common adverse event reported was gastric irritation by 12 (1.3%) patients, followed by dizziness by 10 (1.1%) patients. Nausea was reported by 5 (0.5%) patients, whereas one patient each reported other events like facial swelling, diarrhea, arthritic pain, dryness of mouth, sweating, constipation, pedal edema & itching. Because of concomitant medication in addition to tolperisone, the causality of these AE’s cannot be associated with tolperisone treatment only.

Discussion

This observational post marketing study was aimed at generating some real world Indian clinical data on the safety and efficacy of tolperisone in patients having painful skeletal muscle spasm. Tolperisone hydrochloride in this study has shown significant improvements in the scores for muscle tone, mobility & pain on days 3 & 7. Improvement seems to begin early from day 3 & increases by day 7. Subgroup analysis showed that the improvement in the scores for pain, mobility & muscle tension was similar in patients receiving NSAID & those not receiving NSAID along with tolperisone. Tolperisone alone could therefore be a useful alternative in patients who are intolerant to or have a contraindication for NSAIDs.

The efficacy of tolperisone as demonstrated in this study is also consistent with several international controlled studies that support the efficacy of tolperisone in management of acute painful conditions.11,12

In the study by Pratzel H.G. et al (1996), the efficacy and safety of oral tolperisone hydrochloride in the treatment of painful reflex muscle spasm was assessed in a prospective, randomized, double-blind, placebo-controlled trial in a total of 138 patients 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, however, tolperisone hydrochloride proved to be significantly superior to placebo treatment (p=0.03). It was concluded that tolperisone hydrochloride is an effective and safe treatment of painful reflex muscle spasm without the typical side effects of centrally active muscle relaxants.

In the present study tolperisone was well tolerated with no sedation reported by any patient during the study period. The incidence of common adverse effects like nausea, gastric irritation, dizziness was less than 2%.

Literature suggest that by the virtue of the mechanism by which centrally acting muscle relaxants act, their beneficial effects are also associated with the central nervous system side effect like drowsiness and dizziness. These effects are seen with conventional centrally acting skeletal muscle relaxants like carisoprodol, chlorzoxazone & tizanidine. Tolperisone is documented to be devoid of sedation. The lack of sedative side effects in the present study also correlate well with the results of a randomized double-blind placebo- controlled trial that evaluates the sedative effects of Tolperisone 150 mg in 72 healthy young adults. The psychometric test battery used in the trial revealed that tolperisone hydrochloride does not have any sedative effects and does not impair attention- related brain function. Tolperisone hydrochloride though being a centrally active muscle relaxant does not cause any sedation and does not impair reaction time.13

The present study however is limited by the fact that it was open label, non comparative and observational, observations of this study therefore need to be strengthened by randomized controlled interventional trials in the indication assessed.

In conclusion, the real world clinical data generated in the present study suggests that tolperisone is effective, safe and well tolerated in the short term treatment of degenerative and inflammatory musculoskeletal spasm and pain in the Indian population.

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