Original Article

Pharmacology Section

A Post-Marketing Surveillance Study of Tolperisone [MYOTOP-150]: It's Use in the General Clinical Practice in India

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ABSTRACT

Background and Objective: Tolperisone hydrochloride is a centrally acting muscle relaxant that has been used for the symptomatic treatment of spasticity and muscle spasm. The present observational study was undertaken to assess the safety and efficacy of Tolperisone (Myotop-150) in Indian patients.

Settings and Design: An observational study involving 92 physicians across the various states of India, who prescribed Tolperisone (Myotop-150) to their patients.

Methods and Material: The demographic exposure and outcome data of the patients who were prescribed Myotop-150 (Tolperisone hydrochloride) were obtained from the completed case record forms which were received from the physicians. Adverse events which were observed during the therapy were recorded. Symptom severity was given a scoring on a 7-point Likert scale before and after the therapy.

Results: Data was collected for 165 patients, with a mean age of 43.88 ± (SD) 11.27 years [Range: 15 to 72 years]. At the baseline, the mean ± SD of the score on the 7-point Likert scale was 4.96 ± 1.01. After treatment with tolperisone, the mean score was 1.87 ± 0.91, with a significant reduction of 3.08 ± 1.14; $p < 0.0001$. After therapy, 42.04% of the patients reported "no problem". In 88.02% of the patients who were treated, the physicians rated the treatment with tolperisone as excellent, very good or good. Side-effects were observed in 7.88% of the patients.

Conclusions: The present observational study demonstrates that the therapy with tolperisone is an effective and well-tolerated strategy in patients with diseases or conditions which are associated with spasticity or muscle spasm.

Key Words: Muscle spasm, Muscle relaxant, Tolperisone, Spasticity, Muscle sprain

KEY MESSAGE

- Tolperisone hydrochloride is a muscle relaxant that has been used for the symptomatic treatment of spasticity and muscle spasm.
- The treatment with tolperisone is effective and it improves the patient's ability to perform routine activities.
- It can be used safely in a wide range of patients, including the elderly and patients with co-morbid diseases.

INTRODUCTION

Tolperisone is a centrally-acting muscle relaxant that has been in therapeutic use for more than three decades for the symptomatic treatment of spasticity and muscle spasm [1, 2]. This compound was first developed in Hungary and is available today in Europe, Africa and Asia [3]. It was recently launched in India for acute and chronic back pain and for spasticity of neurological origin [4].

Tolperisone hydrochloride differs from other myotonolytic agents in its pharmacological properties, which mediate muscle relaxation without concomitant sedation or withdrawal phenomena [5]. Tolperisone blocks mono and polysynaptic reflexes in a dose-dependent manner at the spinal level via a combined action on voltage-gated sodium and calcium channels [3, 5]. Besides being an effective antispastic agent, tolperisone also has analgesic activity in rodents and humans by the inhibition of the action potential propagation on both the A- and C-fibers [6].

Tolperisone is an adrenergic α-receptor blocking agent and its site of action is within the vasculature. The blocking action was found to be rapid in onset, short-lived, and in addition competitive, thus resulting in a selective femoral vasodilatation [7]. This action is noteworthy, since a muscle contracture may compress the small blood vessels and induce an ischaemia, thus leading to the release of pain stimulating compounds [4].

First study reports about the clinical use of tolperisone appeared in the early seventies describing the effect of the substance on spastic muscle, myotonia, and in peripheral arterial disease. Most papers describe the clinical applications of the drug in different clinical settings and diseases [1], which include low back pain [8], post cerebral stroke spasticity [9], spinal pain, neuropathic diabetic foot syndrome, tension headaches, neurosensory hypoacusis, climacteric complaints, lockjaw and neurolatyrism [1, 10, 11, 12, 13, 14].

The present study was an observational, post marketing surveillance study on Tolperisone [Myotop-150] to assess the safety and efficacy of the drug in Indian patients.

METHODS

This current study was an observational, post marketing assessment which was carried out among the doctors all over India. This observational study was initiated in July 2009 and all therapeutic decisions were determined solely by the attending physician.

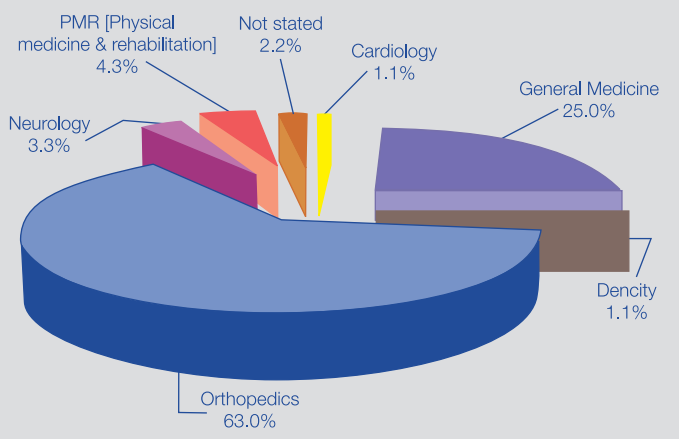
At the initial visit, the patients demographic data, the dosage and the administration of tolperisone, the severity of the symptoms and the presenting complaint were entered in a case record form (CRF). The severity of the symptoms was graded on a 7 point Likert scale and the scoring was done as follows:

1: No problem; 2: Minimal (the symptom can be easily ignored without effort); **3: Mild** (the symptom can be ignored with effort); **4: Moderate** (the symptom cannot be ignored, but it does not influence the daily activities); **5: Moderately severe** (the symptoms cannot be ignored and they occasionally limit the daily activities); **6: Severe** (the symptoms cannot be ignored and they often limit the concentration on the daily activities); **7: Very severe** (the symptoms cannot be ignored, they markedly limit the daily activities and the patient often requires rest). An assessment was made before initiating the therapy and at the end of the therapy. Based on the outcome of the treatment for each patient, the physicians rated the therapy as excellent, very good, good, satisfactory or poor. Each practitioner had to complete the case report forms which pertained to the individual patient's therapy outcome and record the adverse events which were observed during the therapy.

The data which was collected during the study was analyzed descriptively and it was described as the percentage and the total number of observations or the mean and standard deviation. The safety was estimated by measuring the proportion of patients who reported any adverse event. The efficacy was estimated by measuring the change in the severity of the symptoms before and after the treatment. The change in the severity of the individual symptoms between the visits was assessed by using the Wilcoxon signed-rank test. P values which were < 0.05 were considered to be statistically significant.

RESULTS

The study was conducted during the period from July 2009 to April 2010, wherein 92 healthcare practitioners across the various states of India provided the data of the patients who were prescribed Tolperisone [Myotop-150] for the management of various conditions which were associated with spasm and spasticity. [Table/Fig-1] shows the distribution of the healthcare practitioners based on the speciality of their practice. The data from the 165 patients was received out of which 157 were evaluable for symptom severity and efficacy, while the safety assessment was evaluable in all the 165.



[Table/Fig-1]: Distribution of healthcare practitioners based on their specialty of practice

Patient Characteristics

The mean age of the study population was 43.88 ± (SD) 11.27 years [Range: 15 to 72 years]. The demographic data of the study population is shown in [Table/Fig-2]. The minimum duration of the therapy was 3 days while the maximum duration was 90 days.

Reduction in the Symptom Severity Score

Before the start of the therapy, the mean score for symptom severity on the 7 point Likert scale was 4.96 ± 1.01 [Range 2 to7], which became 1.87 ± 0.91 [Range: 1 to 6] after the completion of the therapy. The duration of the therapy varied amongst the patients. The mean score reduction at the end of the therapy was 3.08 ± 1.14. The reduction in the score at the end of the therapy versus the baseline score was found to be statistically significant ($p < 0.0001$). The distribution of the patients based on the severity of the symptoms before and after the therapy, is shown in [Table/Fig-3] and [Table/Fig-4] respectively. At the end of the treatment period, 3.82% (6) patients had a reduction on the Likert scale score by 1 point, 24.2%

Variable	Catagory	% [n] of patients [N = 165]
Age (Years)	< 20 years	1.21% [2]
	21–40 years	39.39% [65]
	41–60 years	48.48% [80]
	> 60 years	8.48% [14]
	Not stated	2.42% [4]
Gender	Male	66.06% [109]
	Female	31.52% [52]
	Not stated	2.42% [4]
Dosage	300 mg/day	7.27% [12]
	450 mg/day	88.48% [146]
	900 mg/day	0.61% [1]
	Not stated	3.64% [6]
Duration of therapy	Up to 1 week	58.18% [96]
	Up to 2 weeks	21.82% [36]
	Up to 3 weeks	6.67% [11]
	Up to 4 weeks and above	4.24% [7]
	Not stated	9.09% [15]
Diagnosis	Cervical spasm	0.61% [1]
	Ankylosis Spondilitis	0.61% [1]
	Spondylosis (Cervical/ Lumbar)	4.24% [7]
	Low back pain	5.45% [9]
	Muscle Sprain	44.24% [73]
	Osteoarthritis	0.61% [1]
	Post stroke spasticity	6.06% [10]
	Backache associated with spasm due to prolapsed IV disc	35.15% [58]
	Chicken guinea	0.61% [1]
	Fractures	0.61% [1]
	Not stated	1.82% [3]

[Table/Fig-2]: Patient Demographic Data

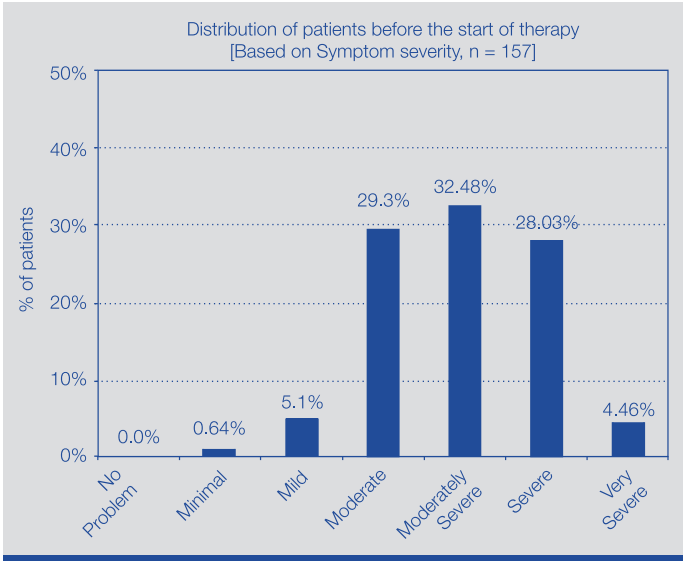
(38) patients had reduction by 2 points, 36.94% (58) patients had reduction by 3 points, 21.66% (34) patients had reduction by 4 points, 10.19% (16) patients had reduction by 5 points and 1.27% (2) patients had reduction by 6 points. Three patients did not experience any change in their symptom score, while none reported any deterioration in their condition.

The physician's opinions about the therapy

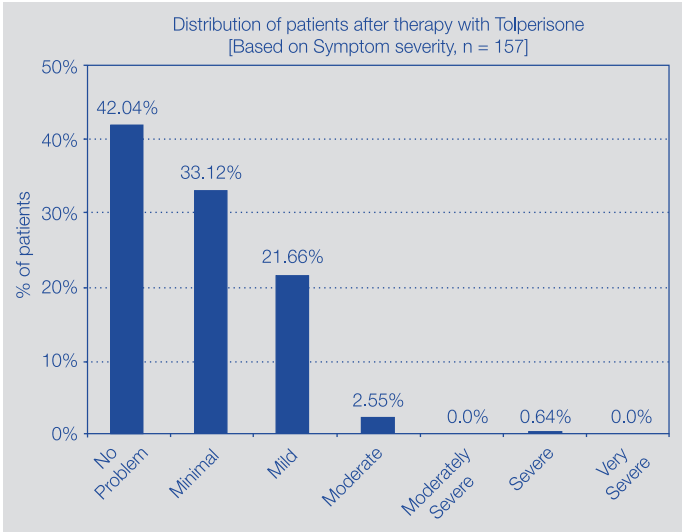
In 88.02% of the patients who were treated, the physicians rated the treatment with tolperisone as excellent, very good or good. The distribution of the rating of the therapy by the physicians in patients who received tolperisone is shown in [Table/Fig-5].

Safety Assessment

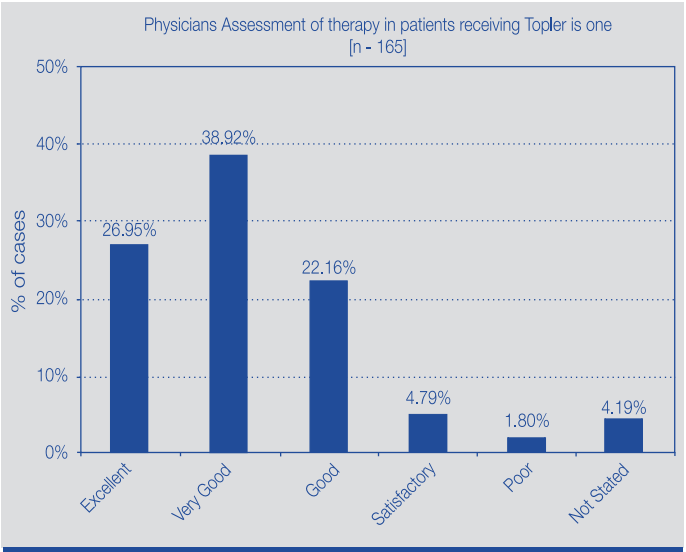
The safety assessment included all the 165 patients who's CRFs were collected during the study. The adverse events which were reported during the treatment with tolperisone are tabulated in [Table/Fig-6]. In the total study population, 92.12% of the patients did not report any adverse event following the treatment with tolperisone.



[Table/Fig-3]: Distribution of patients based on symptom severity before therapy



[Table/Fig-4]: Distribution of patients based on symptom severity after therapy with tolperisone



[Table/Fig-5]: Physicians assessment of therapy in patients receiving tolperisone

Adverse event	% [n] of patients [N= 165]
Sedation/Drowsiness	3.03% [5]
Dizziness/Vertigo	3.03% [5]
Nausea	1.21% [2]
Dryness of mouth	0.61% [1]

[Table/Fig-6]: Adverse events reported during therapy with tolperisone

DISCUSSION

Tolperisone, which has been assigned to the group of centrally acting muscle relaxants has been in clinical use now for decades. The publications on tolperisone describe the clinical application of the drug in different clinical settings and diseases [1]. A similar trend was observed in the present study, which involved physicians of different specialties [Table/Fig-1] and varied causes of muscle spasm or spasticity [Table/Fig-1].

In this study, it was observed that at the time of initiating the therapy, 64.97% of the patients had moderately severe to very severe symptoms, that is, their daily activities were affected because of the disease condition. Following the treatment with tolperisone, the severity of the complaints were significantly moderated in response to the treatment, wherein 42.04% of the patients had "no problem", that is, were free from the symptoms that affected their daily activities, while 57.32% had minimal to moderate symptoms, that is, they had symptoms that did not affect their daily activities. These results demonstrated a clear trend towards a better ability to perform routine activities and a clinically meaningful impact of tolperisone on the patients everyday quality of life.

A general recommendation of the optimal dosage of tolperisone in clinical practice is difficult. There are clinical reports on a wide range of dosages which are used (150–900 mg/day) [1]. The recommended dosage of tolperisone is 150 mg, three times daily (450mg/day) [2]. It has also been reported that a dosage as high as 900 mg/day improves the efficacy of tolperisone without undue risk for the patients [9]. In this study, a majority (~90%) of the patients received the recommended dose of tolperisone as 450 mg daily. One patient was prescribed a dose of 900 mg daily as well.

In this observational study, tolperisone hydrochloride was generally well tolerated with overall adverse events being reported in only 7.88% of the patients. The most commonly encountered problem

regarding muscle relaxant usage in the general clinical practice was sedation, varying from 20% to 67% [15, 16, 17, 18]. In this study, sedation or drowsiness was observed only in 3.03% of the patients. In the study which was conducted by Dulin J et al. [19], single and repeated doses of 50 mg and 150 mg of tolperisone did not cause any sedation and did not impair the reaction time. The current reporting of sedation/ drowsiness in this post marketing study represents the actual reflection of the drug tolerability in practical settings.

In conclusion, the results of the present observational study demonstrate that tolperisone hydrochloride is an efficient and safe medication in the treatment of muscle spasms and spasticity.

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