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Efficacy and tolerability of tapentadol prolonged release in the elderly and fragile patient: an observational study

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Abstract. – OBJECTIVE: The incidence of chronic pain increases with age and comorbidities, a particularly relevant issue in the elderly over the age of 80 years. Thus, the choice of the best analgesic treatment is difficult to make. The therapeutic priority in elderly patients is to favor the least invasive route of administration, and the minimum effective dose, with a gradual and slow up-titration, if needed. Tapentadol with its dual mechanism of action, combining synergistically a reduced load (<40% that of strong opioids) of μ-opioid receptor agonism (MOR) with noradrenaline reuptake inhibition (NRI), can be an interesting analgesic option for geriatric patients, because of its easy manageability, the lower rate of adverse effects, the good level of analgesia, and the ability of improving the overall quality of life of elderly patients.

PATIENTS AND METHODS: A total of 49 elderly patients (>80 years) with chronic pain from different etiologies received tapentadol PR daily over 8 weeks.

RESULTS: At the end of the study, responders to treatment were 43% (n=17 patients). Compared with baseline, pain intensity both at rest and during loading, decreased by 60% and by 55%, respectively ($p<0.000$). Tolerability was high throughout the study period, with 92% of patients grading it either good or excellent during follow-up. In total, 16 episodes of adverse effects were reported, with five considered severe and leading to therapy discontinuation (in case of therapy discontinuation occurred, most of them (five patients, 10%) due to the ineffectiveness of analgesic treatment.

CONCLUSIONS: Tapentadol PR, adequately titrated according to patients' need, are safe and effective to control pain in most elderly patients.

Key Words:
Chronic musculoskeletal pain, Elderly, Opioid therapy, Tapentadol.

Introduction

The incidence and frequency of chronic pain increase with age and with the number of comorbidities, as well as the number of medications[1-3]. This is particularly relevant in the elderly over the age of 80 years, leading problems in choosing the best analgesic treatment for pain control in this subpopulation[3]. In the elderly, chronic pain is mainly determined by chronic diseases, such as degenerative diseases of the joints, arthritis, osteoporosis, and peripheral or diabetic vasculopathies[2,3]. In most cases, pain is mainly of neuropathic or mixed origin. Notably, common analgesics are rarely effective on these types of pain.

The therapeutic priority in elderly patients is to favor the least invasive route of administration, and to start therapy at the minimum effective dose, with a gradual and slow up-titration[3].

Tapentadol may represent an effective therapeutic opportunity for the management of chronic pain in the elderly: it has a dual mechanism of action, combining synergistically a reduced load (<40% that of strong opioids) of μ-opioid receptor agonism (MOR) with noradrenaline reuptake inhibition (NRI)[4]. Its efficacy is the same in children, adults, and elderly patients. Moreover, tapentadol can also be administered in patients with stabilized cardiovascular diseases, with mild to moderate renal insufficiency and with mild hepatic insufficiency, which are very frequent conditions in the elderly[5,6].

Tolerability of tapentadol prolonged release (PR) is increased compared to that of classical opioids, with similar levels of analgesia[4,6,7]. Furthermore, tapentadol PR can be an interesting analgesic option for geriatric patients, because of its easy manageability, the lower rate of adverse effects, the good level of analgesia, and the ability of improving the overall quality of life of elderly patients. A dose adjustment is usually not required, with the low-dose formulation (25 mg) being more suitable for frail elderly patients. However, further evidence on the efficacy and safety

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of tapentadol PR in the treatment of chronic pain in the elderly is necessary.

The aim of this study was to evaluate the analgesic efficacy and tolerability of tapentadol PR in reducing pain intensity during loading in a sample of elderly fragile subjects (over 80 years) with chronic pain of different etiologies afferent to the pain therapy clinic of the Department of Anesthesia and Resuscitation of the Azienda Ospedaliero Universitaria Federico II in Naples.

Patients and Methods

All patients of either gender aged ≥80 years, with chronic pain of whichever etiology were eligible to this study.

All patients received tapentadol PR at a starting dose of 25 mg twice daily, which could be gradually increased according to clinical needs up to a maximum dose of 300 mg/day. In case of insufficient pain control, other medications could be added if needed. Existing concomitant medications were maintained throughout the study.

The baseline assessment (V0) was followed by three visits, at 1 (V1), 4 (V2), and 8 weeks after enrollment.

The primary endpoint was the proportion of responder patients, defined as patients with a reduction in pain intensity during loading by 4 on the Numeric Rating Scale (NRS) compared with baseline. Secondary endpoints were pain at rest on the NRS; the quality of sleep assessed on a subjective verbal scale with 4 points where 0 = very disturbed sleep, frequent awakenings, 2 = good sleep, 3 = restful sleep; the variation in mobility, physical well-being reported by the patient, neuropathic symptoms, extension of the painful area and joint function compared with baseline; the overall efficacy of the analgesic therapy: on a 4-point verbal scale (0 = ineffective, 1 = not very effective, 2 = effective, 3 = very effective); patient's Global Impression of Change (PGIC): the assessment of the change in his/her own clinical condition and health state expressed by the patient on a 7-point verbal scale (significantly improved, very improved, minimally improved, no change, minimally worsened, very worsened, very much deteriorated), compared with baseline; tolerability of the analgesic therapy (0 = very poor, 1 = poor, 2 = good, 3 = excellent); safety of tapentadol PR treatment according to presence, duration, severity of side effects and actions to control them (e.g., dose reduction, therapy discontinuation, etc).

Statistical Analysis

Statistical analysis was performed with Statistical Analysis System (SAS) 9.4 statistical software (SAS Institute, Cary, NC, USA). Data were analyzed by descriptive statistics; statistical comparisons were performed by the Student's *t*-test, the ANOVA test or the χ^2-test, as appropriate. A *p*-value of <0.05 was considered statistically significant.

Results

The study population consisted of patients (19 males, 38.8%; mean age: 85 years, age range: 80-91 years). Pain etiology is reported in Table I. Table II lists all comorbidities with respective frequencies. A total of 52 concomitant medications were ongoing for comorbidities before the beginning of the study and were maintained throughout the study period. One patient (2%) reported pain in the last 3 months; five patients (10.2%) suffered from pain during the previous 3-6 months; 43 patients (87.8%) experienced pain for longer than 6 months. Pain characterization was nociceptive in

Table I. Pain etiology.

Causes of chronic pain	n	%
Vertebral column diseases	18	36.7
Arthrosis:	23	46.9
Hip	1	2.0
Sacrum-iliac joint	1	2.0
Neck	1	2.0
Vertebral column	2	4.1
Knee	4	8.2
Multiple locations	11	22.4
Shoulder	1	2.0
Unspecified	2	4.1
Neuropathy	31	63.3
Rheumatic disease	1	2.0
Other	12	24.5
Fall and injury to the foot	1	2.0
Rib fracture	1	2.0
Gout	1	2.0
Polymyalgia	1	2.0
Bone tumor	1	2.0
Leg ulcer	1	2.0
Vasculopathy	6	12.2

Table II. Main existing comorbidities according to presence/absence of specific treatment.

Comorbidities	Under treatment		Not treated		Total	
	n	%	n	%	n.	%
Respiratory	3	6.1	2	4.1	5	10.2
Endocrinology	12	24.5	1	2.0	13	26.5
Neurologic	7	14.3	1	2.0	8	16.3
Liver	0	0.0	0	0.0	0	0.0
Renal	2	4.0	0	0.0	2	4.0
Cardiovascular	37	75.5	0	0.0		
Other:	8	16.3	0	0.0	8	
Psoriatic arthritis	1	2.0	0	0.0	1	2.
Rheumatoid arthritis	1	2.0	0	0.0		2.
Hypercholesterolemia	1	2.0	0	0.0		
Hyperlipidemia, gout and prostatic hypertrophy	1	2.0	0		1	
Prostatic hypertrophy	1	2.0	0		1	2.0
Chronic linfatic leukemia	1	2.0	0		1	2.0
Homocisteinemia	1	2.0	0			2.0
Osteoporosis	1	2.0		0.0	1	2.0

five patients (10.2%), neuropathic in 20 patients (40.8%) and mixed in 24 patients (49%); pain was present both at rest (100%) and during loading (96%, 47 patients). Before the study, analgesia was achieved with a combination of drugs: paracetamol and its associations (41 cases, 83 NSAIDs (30 cases, 61.2%), COXIB (six ca 12.2%), opioids (ten cases, 20.4%) or other ad vants (20 cases, 20.8%). Only two ients (4% did not use medications to contro ore enrollment in the study. Notewo , prev s analgesia was considered eithe i cti tients, 4.3%) or poor (44 ents,), whereas its tolerability was gr poorly t patients (23.4%) and good b p ts (74.5%

The average d ge of tap dol PR increased from 55 mg/d at V0 to 85 day at V1, 115 mg/day at V and 1 mg/day at V3. Additional analgesic t y uired for pain control during tapent l PR ment shown in Table III.

S data issing throughout assment e to pa ts who dropped out or incplet g, and only 36 patients comple e study. Efficacy was evaluated in 47 patie whereas safety and tolerability were evaluate n 49 patients. At V3, the responders to treatment were 43% (20 patients out of 47). In 13 cases, treatment was discontinued (six dropouts, three treatment inefficacy, three side effects, one patient request). Data regarding pain intensity during loading were recorded at all evaluations in 34 patients. Compared to V0, pain intensity at loading decreased by 23% at V1, from an average NRS of 8.7 to an aver-

ag ; at V2, th duction of pain intensity v 39% (average NRS = 5.3); at V3, the overa eduction ain intensity was 55% (average N = 3.9). p-values were statistically signifi 001). Regarding pain intensity at rest, data were available for 35 patients in all uations. A similar decrease in the average N by 60% from V0 to V3 was noted (NRS = 7.9 at V0; 5.8 at V1; 4.4 at V2; 3.2 at V3; all $p<0.0001$; Table IV). Sleep quality improved in a statistically significant way ($p<0.01$; Figure 1). Mobility, physical well-being, neuropathic symptom, the extent of the painful area, and joint function improved in more than 60% of

Table III. Analgesic treatments associated to tapentadol for pain control.

Drug	n	%
Acetilcarnitine	1	2.0
Buprenorfine	3	6.1
Celecoxib	1	2.0
Clonazepam	1	2.0
Deflazacort	1	2.0
Dexamethasone	2	4.1
Fentanil	1	2.0
Gabapentin	14	28.6
Lamotrigine	5	10.2
Lidocaine	4	8.2
Palmitoiletanolamide	1	2.0
Paracetamol	27	55.1
Paracetamol + Codeine	1	2.0
Pregabalin	13	26.5
Tizanidine	3	6.1
Tramadol	2	4.1

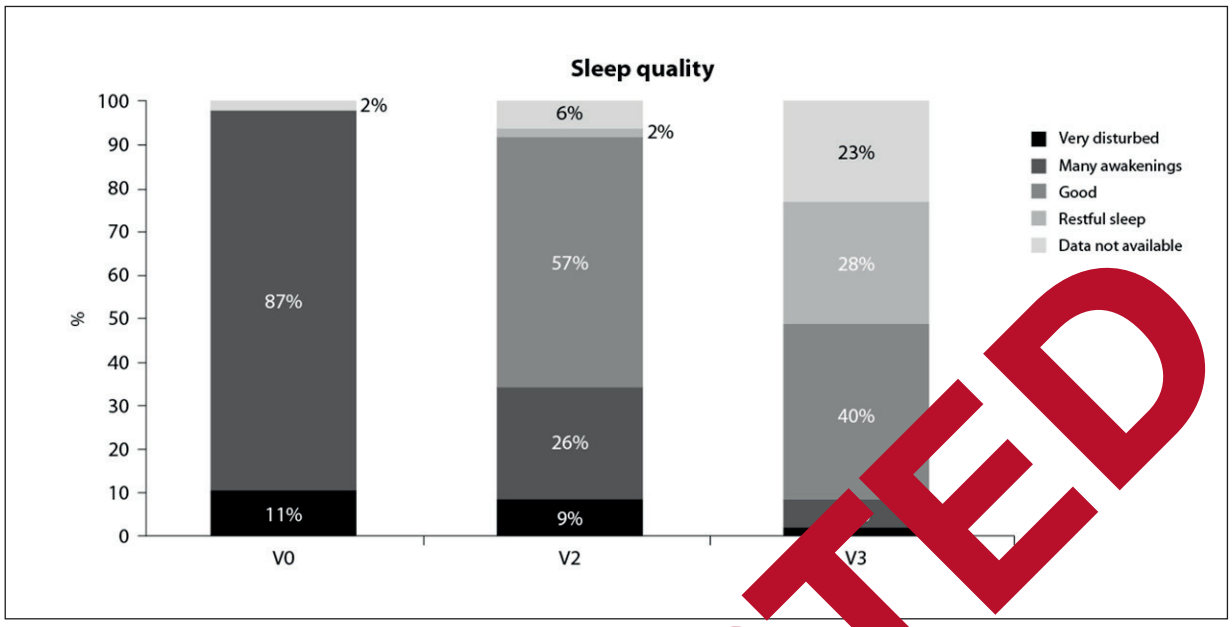

Figure 1. Sleep quality assesse[illegible]rbal scale.

patients, although not all baseline assessment were recorded. In total, 2% of patients reported pain exacerbation at V2, but not at V3.

Tapentadol PR treatment was considered effe[illegible]e or very effective for pain control by 66% of patie[illegible] at V3. Moreover, self-assessment of th[illegible]atients r[illegible] vealed satisfaction for the treatmen[illegible]related to general health condition, wh[illegible] was c[illegible]sidered improved or very much impr[illegible]ve[illegible] 64[illegible] V3. Conversely, only 7% [illegible]atient[illegible]dered their health condition minim[illegible]vorsened.

Tolerability was [illegible]h t[illegible]ghout th[illegible]udy period, with 92% [illegible]atients g[illegible]ng it either good or excellent at [illegible] and V2, *vs.* [illegible]t V3.

A total of [illegible]ide ef[illegible]s in 12 patients (24%) were reported; th[illegible]st [illegible]quent side effect was drowsiness (si[illegible]ven[illegible]ed to [illegible] patients, 10%). In five cas[illegible]ses o[illegible], one headache, one heartb[illegible] and [illegible] drows[illegible]s), the event was considered [illegible], b[illegible] therapy discontinuation; in one cas[illegible]ntadol PR dose reduction was sufficient to contro[illegible]mptoms, whereas in two cases of constipation a [illegible]ific treatment was added.

At each study visit, continuation of the analgesic treatment with tapentadol PR was evaluated. In case of treatment discontinuation, the reasons for therapy interruption were recorded. A total of 10 suspensions (20% of patients) were needed; most cases of discontinuation (five patients, 10%) were due to ineffectiveness of analgesic treatment; three patients (6%) discontinued treatment d[illegible]o advers[illegible]ffects, and two patients (4%) discon[illegible]ment due to complete resolution of pain. Eight out of ten discontinuations occurred [illegible] at least 4 weeks of treatment with tapentadol (a[illegible]V2).

Discussion

The aim of this study was to test whether tapentadol PR, an innovative and potent centrally acting MOR-NRI analgesic drug, could be a valuable alternative option for fragile geriatric patients suffering from chronic pain of different etiologies.

Tapentadol partially shares the mechanism of action of strong opioids, but the μ-load of tapentadol is <40% that of strong opioids[4,6], with a better tolerability profile. Moreover, tapentadol PR can be started at very low doses (e.g., the 25 mg tablet is the lowest formulation available) and up-titrat-

Table IV. Pain intensity at rest and during loading over the study period, with mean and standard deviation.

NRS score	V0	V1	V2	V3
Rest	7.9±1.2	5.8*±1.7	4.4*±1.9	3.2*±1.8
Loading	8.7±0.9	6.7*±1.7	5.3*±1.8	3.9*±2.0

*p<0.0001 *vs.* V0.

ed gradually according to patients' needs. In fact, in the elderly patients, it is a priority to preserve the least invasive route of administration, and the minimum effective dose. Thus, tapentadol PR is a good alternative to currently available analgesics. Notably, tapentadol PR can also be administered in patients with stabilized cardiovascular diseases, with mild to moderate renal insufficiency and with mild hepatic insufficiency, which are very frequent conditions in the elderlies.

Noteworthy, chronic pain increases with age and comorbidities, and in the elderly, it is mainly determined by chronic diseases, such as joint degeneration, arthritis, osteoporosis, and peripheral or diabetic vasculopathies[2,3]. Approximately 50% of elderly patients experience fastidious pain for at least 30 days. In our study, 87.8% of patients experienced pain for more than 6 months.

Moreover, drug interaction is a relevant issue in elderly patients, usually suffering from a high number of comorbidities, as also shown in our experience: we recorded 52 concomitant therapies in our population. Drug interaction may be even more detrimental in case of NSAIDs and opioids. These medications, although contraindicated in the elderly[8-10], are still over-used, and they several important side effects[11].

In our study, only 43% of patients were c sidered responders at the end of f -up, r porting a reduction in pain inten at ding t levels lower than NRS 4. Ho er, th verage NRS decreased significantl i bas end of the study, both at and g loading, corresponding to a 60 d a 55% ction, respectively, compare it eline. T educed tolerability may pend on high number of concomitant p cations that h ave interfered one-anothe d wit pentadol, despite the low potential fo g ag int actions of this molecule, a ting overal erability of the treatme l sid ff occurred, with therapy ontinu on nee in five cases. The overall abil ntadol PR treatment was good, and quality improved, as well as mobility, physi ell-being, neuropathic symptoms, the extent o e painful area, and joint function with more than 60% of patients satisfied from therapy. Only <7% of patients considered their health condition minimally worsened. These results suggest that analgesic therapy should be carefully tailored on individual needs, in order to balance efficacy and tolerability, as already reported by similar experiences in comparable populations of elderly patients treated with tapentadol[12].

Conclusions

Our study focused on the management of chronic pain in a population of elderly and fragile patients, with several comorbidities, who are at increased risk of therapy intoxication, side effects, and drug interactions. Patients were treated with several analgesics before enrollment in the study, with poor tolerability and fficacy of previous treatments. Converse s of our study show that tapenta PR, adeq ly titrated according to patients d, are saf nd effective to control pain most ly pa ts. However, the reporte e of resp only 43% in our popula of v elder atients. Of note, in our st se to t atment was defined as pa inten durin ading lower than 4 on RS afte s of treatment. This wa ub tial goal patients >80 years, and it is importa underline that the average NR , indeed, t the end of the study. S p quality was also improved with tapentadol with a eral improvement in physical w being of e patients.

S e effects were reported, few of which needed dose adjustment or therapy discontinuation, but the overall satisfaction for the analgesic treatment with tapentadol PR was high.

Key Points

- Tapentadol has a dual synergistic mechanism of action combining reduced μ-opioid receptor agonism (<40%) with norepinephrine reuptake inhibition, with similar efficacy and improved tolerability compared to opioids.
- Tapentadol PR was effective to control pain in a high percentage of our elderly patients with chronic pain from different etiologies, although the rate of responders was only 43%.
- In our study, the reduction in pain intensity with tapentadol PR, both at rest and during load, was statistically significant at each visit compared with baseline (p<0.01).
- Several side effects were reported, but the overall tolerability and satisfaction for treatment were good.

Conflict of interest

The authors declare that they have no conflict of interest.

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