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Original article

Tapentadol in cancer pain management: a prospective open-label study

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Abstract

Objectives:
The aim of this prospective, open-label study was to evaluate the efficacy and tolerability of tapentadol (TP) in the management of cancer pain.

Methods:
A 4 weeks' prospective study was carried out in 50 opioid-naive cancer patients with moderate–severe pain. Each patient initially received twice-daily doses of slow-release TP 50 mg. Doses were then managed to maintain adequate relief or dose-limiting toxicity, on the basis of the clinical response. The following parameters were recorded at weekly intervals for 4 weeks: pain and opioid-related adverse effects, quality of life measured with the Spitzer score, TP escalation index percent (TPEI%) and TP escalation index in mg (TPEImg), calculated at the end of the study, pain mechanisms, and PainDETECT at baseline.

Results:
Of 50 patients, 39 completed the entire study and 11 discontinued the treatment for different reasons. Pain intensity significantly decreased from baseline to all the week intervals ($p < 0.0005$), and adverse effects did not changed significantly, while quality of life improved. TP escalation indexes were low and no relationship was found with age, gender, and pain mechanisms.

Conclusion:
Tapentalol started in doses of 100 mg/day was well-tolerated and effective in opioid-naive patients with cancer pain, regardless of the pain mechanism. It can be considered as a flexible drug to be used in patients with moderate–severe pain.

Limitations:
This was an open-label study for exploratory purposes. Data should be confirmed in controlled studies with a larger number of patients.

Introduction

Cancer pain management is based on a sequential approach of drugs, as suggested by the WHO, through steps corresponding to drugs with different potencies. Application of the WHO three-step analgesic ladder has been reported to provide satisfactory pain relief in up to 90% of patients with cancer pain[1]. This approach has had an impact of paramount importance in terms of clinical outcome and educational perspective, although evidence is lacking, particularly with regard to possible alternatives, because of the paucity of controlled studies in this field. More recently, studies have examined the role of opioid analgesics and confirmed that more data are necessary[2]. It is anticipated that new drugs will be evaluated in the near future.

Tapentadol (TP) is a novel, centrally acting analgesic agent with two mechanisms of action: as a mu opioid receptor agonist and by norepinephrine reuptake inhibition. TP has been developed for the management of moderate–severe chronic pain. The moderate affinity at the mu receptor and the opioid-sparing effect of inhibition of norepinephrine reuptake suggest that TP should produce fewer opioid-related adverse effects than typical mu agonists[3]. TP has been shown to be effective in a variety of pain models. In these models the development of tolerance was considerably delayed with TP compared to morphine[4–6]. In humans, efficacy and safety of TP have been demonstrated in comparative studies with placebo and oxycodone in several non-malignant conditions[7–10], but have never been assessed in patients with cancer pain. This class of patients, in contrast to non-cancer patients with pain, may require high doses of opioids, owing to disease-related factors, pain characteristics, as well as prolonged use. Thus, it is of paramount importance to gather information about the use of this new drug with its unusual pharmacologic characteristics in this context.

TP is available as controlled-release tablets to be administered twice daily. The aim of this prospective, open-label study was to evaluate the efficacy and tolerability of TP in the management of cancer pain. The secondary outcome was to evaluate the tendency to increase the dose in the medium-term.

Patients and methods

A prospective study was carried out on a sample of 50 consecutive advanced cancer patients with moderate–severe pain. Informed consent and institutional approval from the University of Palermo were obtained. Inclusion criteria were: moderate–severe cancer pain (more than 4 on a numerical scale from 0 to 10, see below), unresponsive to step one analgesic ladder drugs (non-opioid drugs), or occasional use of opioids for moderate pain, and a Karnofsky status of 50 or more. Exclusion criteria were: poor renal or hepatic function, history of drug abuse, cognitive failure, brain metastases or brain damage, and short expected survival.

Each patient initially received twice-daily doses of slow-release TP 50 mg, and oral morphine as rescue medication (5 mg initially). Doses were then managed to maintain adequate relief or dose-limiting toxicity, on the basis of the clinical response. If patients were receiving non-opioid analgesics, these were continued, if tolerated by patients. Adjuvant-symptomatic drugs were used according to clinical need and departmental policy. Patients were visited or contacted at least once weekly to change therapy, according to the clinical status. The following parameters were recorded before starting the study (T0), 1 week after (W1) and at weekly interval for 4 weeks (W2,W3, and W4):

- Pain intensity monitored using a numerical scale from 0 to 10.
- Symptoms associated with opioid therapy or which are commonly present in advanced cancer patients, such as nausea and vomiting, drowsiness, confusion, and dry-mouth were rated using a scale from 0 to 3 (not at all, slight, a lot, severe). Constipation was assessed as follows: 0 = stool in the previous 24 hours; 1 = 2 days before; 2 = 3 days before; 3 = 4 or more days before, or need for clyster.
- Quality of life measured with the Spitzer score (5 items including activity, daily living, health, support, outlook, from 0 to 2, for a maximum score 10), which is considered a well-validated system[11].
- The TP escalation index percent (TPEI%) was calculated at W4. This score expresses the mean percentage increase of opioid dosage from opioid starting dose (TPSD), according the following formula: [(TPMD–TPSD)/TPSD]/days × 100, where TPMD is the maximal dose of TP. The TP escalation index in mg (TPEImg) was calculated as the mean increase of TP dosage in mg using the following formula: (TPMD–TPSD)/days[12].
- The pain mechanisms were considered on the basis of clinical history, anatomical site of primary tumor and distant metastases, physical examination, investigations such as CT-scan, MNR and so on, when necessary. The PainDETECT questionnaire was used to determine the prevalence of neuropathic pain components[13].

Statistical analysis

Frequency analysis was performed with the chi-square test and Fisher's exact test, as needed. The paired Wilcoxon signed-rank test was used to compare pain intensity scores and symptom intensity scores in the four weekly periods. The paired samples Student *t*-test was used to compare opioid mean dose in the four weekly periods. The one-way analysis of variance (ANOVA) and the Kruskal–Wallis statistic test were used to evaluate the differences in TPEI% and TPEImg for parametric and nonparametric variables, respectively. All *p*-values were two-sided and *p*-values less than 0.05 were considered to indicate statistical significance. Data were analyzed by Epi Info software, version 3.2.2, (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) and Systat Software 8.0 version (SPSS, Inc.).

Results

Of 50 patients recruited for the study, 30 were female, and the mean age was 66.3 years (SD 13.9). The mean

Table 1. Pain, symptom intensity and Spitzer score at time intervals: T0 = baseline, W1 = 1st week, W2 = 2nd week, W3 = 3rd week, W4 = 4th week.

	T0	W1	W2	W3	W4
No. patients	50	49	45	40	38
Pain	5.88 (1.5)	2.79 (1.8)	2.33 (1.4)	2.05 (1.5)	1.71 (1.1)
Nausea	0.20 (0.4)	0.16 (0.4)	0.11 (0.3)	0.15 (0.4)	0.13 (0.3)
Drowsiness	0.14 (0.3)	0.26 (0.5)	0.24 (0.5)	0.12 (0.3)	0.08 (0.2)
Confusion	0.04 (0.2)	0.08 (0.2)	0	0.10 (0.3)	0
Dry mouth	0.60 (0.7)	0.49 (0.6)	0.71 (0.7)	0.70 (0.6)	0.65 (0.6)
Constipation	0.36 (0.7)	0.42 (0.6)	0.53 (0.7)	0.52 (0.7)	0.55 (0.5)
Spitzer	6.54 (1.8)	7.06 (1.7)	7.24 (2.2)	7.40 (1.9)	7.97 (1.4)

Data are expressed as mean (SD).

Table 2. Doses of tapentadol (mean, SD) and frequency of use (%) of adjuvants at time intervals T0 = baseline, W1 = 1st week, W2 = 2nd week, W3 = 3rd week, W$ = 4th week.

	T0	W1	W2	W3	W4
Tapentadol dose, mg, mean (SD)	146 (86)	173 (96)	180 (107)	190 (114)	
Antiemetics *n* (%)	14 (28)	18 (36)	18 (40)	19 (47)	13 (34)
Laxatives *n* (%)	12 (24)	15 (30)	14 (31)	13 (32)	11 (29)
Corticosteroids *n* (%)	11 (22)	12 (24)	10 (22)	10 (25)	8 (21)
Antidepressants *n* (%)	5 (10)	5 (10)	4 (9)	4 (10)	3 (8)
Anticonvulsants *n* (%)	7 (14)	5 (10)	7 (15)	7 (17)	8 (21)
Neuroleptics *n* (%)	2 (4)	3 (6)	3 (6)	2 (5)	1 (2)
Benzodiazepines *n* (%)	7 (14)	5 (10)	3 (6)	4 (10)	4 (10)
NSAIDs – paracetamol *n* (%)	7 (14)	2 (4)	3 (6)	2 (5)	4 (10)

Karnofsky status was 67 (SD 11.2). Primary tumors were in a rank order: breast ($n = 13$), urogenital ($n = 10$), gastrointestinal ($n = 9$), lung ($n = 7$), pancreas ($n = 5$), others ($n = 6$). Eleven patients did not conclude the study or discontinued TP for different reasons: three patients died during the study period, three patients had adverse effects requiring to a switch to other opioid analgesics, four patients manifested poor compliance to the treatment, and one patient was lost to follow-up.

Data regarding pain and symptoms at the different time intervals are presented in Table 1. Pain intensity significantly decreased from baseline to all the week intervals ($p < 0.0005$).

Some symptoms varied in intensity during the study period. Drowsiness significantly increased at W1 ($p = 0.034$), and decreased at W4 ($p = 0.030$). Dry mouth increased from W1 to W3 ($p = 0.018$), and decreased from W1 to W4 ($p = 0.026$). No significant changes were observed in intensity of confusion, nausea, and constipation. The Spitzer score significantly increased at W1 ($p = 0.014$), W2 ($p = 0.028$), W3 ($p = 0.006$), and W4 ($p = 0.001$).

From clinical evaluation, ten patients had somatic pain, six patients had visceral pain, and one patient had neuropathic pain. Mixed syndromes were more frequent: 19 patients had somatic-neuropathic pain, 11 patients had somatic and visceral pain, two patients had visceral-neuropathic pain, and one patient had somatic-visceral and neuropathic pain. PainDETECT mean value was 5.4 (SD 6). The values were negative, positive, and uncertain in 23, 19, and eight patients, respectively. No difference in the use of adjuvants was observed during the study period (Table 2).

TPEI% and TPEImg were 1.78 (SD 2.5) and 2.26 (SD 3.3), respectively. No relationship between TPEI indexes and primary tumor (TPEI%, $p = 0.829$, TPEImg, $p = 0.868$), pain mechanism (TPEI%, $p = 0.488$, TPEImg $p = 0.353$), painDETECT (TPEI%, $p = 0.516$, TPEI%, $p = 0.777$), age (TPEI%, $p = 0.079$, TPEImg $p = 0.183$), or gender were found (TPEI%, $p = 0.105$, TPEImg $p = 0.217$).

Discussion

The present study evaluated TP with starting doses of 100 mg/day in opioid-naive patients with moderate–severe cancer pain. Pain intensity significantly decreased to acceptable levels during the study period. The dose of TP, given according to the patients' clinical response, slowly increased over 4 weeks, with low escalation indexes. TPEI calculated in this study was even lower than that observed in previous studies with a similar design in

opioid-naive patients with oral morphine[14], transdermal buprenorphine[15], and transdermal fentanyl[16]. The reduced tendency to increase the dose, already observed in animal models[5,6], may reflect a less toleragen effect of TP, possibly due to its pharmacological characteristics with a dual analgesic mechanism[3].

TP seems to be particularly appropriate for patients with neuropathic pain[17,18]. TP was equally effective, regardless of the mechanisms assessed by clinical judgment, as well as tools commonly used for assessing predominantly neuropathic pain, such as PainDETECT. While there is good evidence that screening tools may provide a common language among researchers and a guidance for further diagnostic evaluation, they should not replace clinical judgment[19]. However, the relatively low number of patients participating in this preliminary trial does not provide conclusive information, and trials with a larger number of patients could identify subclasses of patients who could benefit from TP.

TP was well-tolerated, as only 7% of patients discontinued TP for alternative treatments or poor compliance with TP therapy. This rate was considered acceptable, given the reported need to switch to other opioids from morphine because of unfavorable responses in the cancer population[20]. The percentage of patients who discontinued TP (7%) seems to be even less than patients treated with oral morphine (13%), transdermal buprenorphine (15%), and transdermal fentanyl (about 14%) reported in previous studies with a similar design and duration[14–16]. In studies of non-cancer pain, TP was associated with a lower rate of discontinuation in comparison with oxycodone[7,8,10]. The occurrence of expected opioid-related adverse effects was low and these effects resolved over time. Finally, the quality-of-life score was improved after initiation of TP therapy.

The use of adjuvant drugs administered prior to entering the study or symptomatic drugs did not change during the study period, confirming the efficacy and tolerability of the drug, particularly regarding gastrointestinal adverse effects which are frequently associated with opioid therapy[21].

This study was the first performed in cancer patients, and the findings require confirmation in controlled studies with a larger number of patients. Like most studies in patients with cancer pain, it was limited by its open-label, uncontrolled design, the number of patients lost in follow-up, and discontinuation of the treatment for various reasons. However, a low drop-out rate was found, suggesting that TP may be of particular benefit to opioid-naive patients or, for example, in the elderly. More data on different kinds of cancer population are needed, for example patients with a lower performance status. Moreover, an interesting issue to be explored is the question of the dose, as the manufacturer recommends a maximum dose of 400–500 mg/day, which would be the dose range for many cancer patients with pain. Data regarding the effect on the inhibition of norepinephrine reuptake at such high doses are unknown. As mentioned above, specific cancer population may benefit from TP treatment. Finally, as it is frequently the case in clinical practice, a change of opioid is required for a variety of reasons, and it would be of interest to explore the conversion ratio existing between TP and other opioids, although it has been suggested that an equianalgesic ratio with oral morphine would be 1:2.5[22].

Conclusion

TP started in doses of 100 mg/day was well-tolerated and effective in opioid-naive patients with cancer pain and could be considered as a flexible drug to be used for the management of moderate–severe cancer pain. Four weeks after starting TP, responsive patients were receiving a mean dose of less than 200 mg/day, suggesting a slow development of tolerance.

Transparency

Declaration of funding
This study was not sponsored and no role of sponsors in the preparation of the article exists.

Declaration of financial relationship
S.M. acts as a paid consultant or speaker for Janssen, Molteni, TEVA, Grunenthal, and Prostrakan. The other authors declare no conflicts of interest.

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