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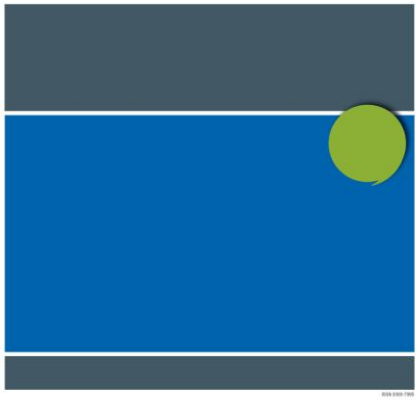

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Opioid switching from and to tapentadol extended release in cancer patients: conversion ratio with other opioids

Sebastiano Mercadante, MD, Giampiero Porzio, MD, Federica Aielli, MD, Claudio Adile, MD, Lucilla Verna, MD, Corrado Ficorella, MD, Antonello Giarratano MD, Alessandra Casuccio, BS.

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Abstract

Objectives: The aim of this exploratory study was to assess the conversion ratios between tapentadol and other opioids in patients requiring an opioid switching.

Methods: A prospective study was carried out in a convenience sample of consecutive patients admitted to an acute palliative care unit and a home care unit for a period of one year. Patients who were switched from/to tapentadol were selected. The initial ratio between tapentadol and other opioids, expressed as oral morphine equivalents was 1:3.3. The subsequent doses were flexible and were changed timely to fit the patients' needs. Pain intensity and distress score were recorded until opioid doses were stable. 37 patients were examined. 24 and 13 patients were switched from and to tapentadol, respectively.

Results: The most frequent sequences were tapentadol-morphine (18 patients) in one direction, and morphine-tapentadol (8 patients) on the other direction. In the sequence tapentadol-morphine and morphine-tapentadol, the mean final tapentadol-morphine ratio were 3.9:1 (SD 2.3), and 1:4.5 (SD 3.2), respectively, which did not significantly differ from the initial established conversion ratio. A minority of patients were switched from/to tapentado to/from other opioids. Globally, the initial ratio did not change after switching took place.

Conclusion: Data suggest that a conversion ratio between tapentadol and other opioids, expressed in oral morphine equivalents could be 1:3.3 in both direction, particularly in patients who are switched in conditions of equianalgesia. The limited number of patients cannot allow to draw definitive conclusion, and data should be interpreted with caution, given the exploratory nature of the study and the low number of patients, and should be replied in future studies with a larger number of patients.

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ABSTRACT

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Key-words: cancer pain, tapentadol, opioid switching, conversion ratio.

INTRODUCTION

Cancer pain management is based on a sequential approach of drugs, suggested by WHO through steps corresponding to drugs with different potencies. The application the WHO three-step analgesic ladder has been reported to provide satisfactory pain relief in up to 90% of patients with cancer pain (1). **However, despite these WHO-guidelines, the prevalence of cancer pain remains high and several authors call for a revision of the WHO stepladder approach (2) .** This approach has had an impact of paramount importance in terms of clinical outcome and educational perspective, although it lacks evidence particularly regarding the possible alternatives, due to the paucity of controlled studies in this field. More recently guidelines examined the role of opioid analgesics and confirmed that more data are necessary (3). Tapentadol is a novel, centrally analgesic agent acting with two mechanisms of action: mu-opioid receptor agonism and norepinephrine reuptake inhibition. Tapentadol has been developed for the management of moderate to severe chronic pain. The moderate affinity at mu receptor and the opioid-sparing effect of inhibition of norepinephrine reuptake suggest that tapentadol should

produce fewer opioid-related adverse effects than typical mu-agonists (4). Tapentadol has been shown to be effective in different pain models (5-7), and in humans, efficacy and safety of tapentadol have been shown in comparative studies with placebo and oxycodone in several non-malignant conditions (8-12). A recent overview of tapentadol trials clearly shows that for certain domains less adverse effects are reported (13). However, information regarding the efficacy and tolerability in cancer pain management are lacking. In only existing study, tapentadol has been found to be effective and well tolerated in the management of opioid-naive patients with cancer pain in an open-label clinical trial (14).

Cancer patients with pain often require changes in the opioid therapy during the course of disease, due to disease-factors, pain characteristics, as well as prolonged use of opioids. The practice of opioid switching has been invariably used successfully (15), although the scientific evidence remains poor due to lack of controlled studies (16). The biological mechanisms are not fully understood and should be based on the variation in each individual in their sensitivity to each of the opioids, due to pharmacokinetics and pharmacokinetics, and genetic polymorphisms which produce an asymmetric tolerance among opioids (17). The anti-hyperalgesic effects of tapentadol (14) could be potentially helpful in states of hyperexitation such in those observed in patients who have received multiple trials of opioids, unsuccessfully. However, data on conversion ratio between tapentadol and other opioids are lacking. As opioid switching is more frequently used in these last years to improve the balance between analgesia and adverse effects, and tapentadol is increasingly used in cancer patients, it is of paramount importance to gather information about the ratios to be used when substituting an opioid with tapentadol and viceversa. Recent recommendations did not include this new drug, because it was made

available after their development (3,18). The aim of this exploratory study was to assess the conversion ratios between tapentadol and other opioids in patients requiring an opioid switching.

PATIENTS AND METHODS

A prospective study was carried out in a convenience sample of consecutive patients admitted to an acute palliative care unit and a home care unit for a period of one year. Informed consent (from relatives in case of cognitive failure) and institutional approval were obtained. Patients who were switched from/to tapentadol were selected. Advanced cancer patients who required to switch opioid therapy were included in four categories (18):

a) Patients presenting relevant adverse effects despite good pain control: to be switched patients had to present at least one relevant symptom, such as drowsiness, confusion, or myoclonus with an intensity = 2 on a scale from 0 to 3 (see below), or other symptoms (constipation, dry mouth) rated as severe (3) (patients AE).

b) Patients with a poor analgesic response despite having their dose doubled in one week (patients P)

c) Patients with both poor pain control and prevalent adverse effects (patients PAE).

d) Some patients, considered as volunteers, were switched for patient's preference and/or convenience, because they had adequate pain control and acceptable adverse effects (patients C).

According to an initial experience with tapentadol, the ratio between tapentadol and other opioids, expressed as oral morphine equivalents was 1:3.3. **Doses were rounded according to existent dose tablets.** The subsequent doses were flexible and were changed timely to fit the patients' needs in an attempt to find the best balance between pain and opioid-related symptoms, according to the amount of drugs consumed as rescue doses in the previous day and the clinical judgement. Oral morphine was offered as a breakthrough pain medication.

Adjuvant drugs, previously administered to control symptoms due to illness or treatment, were continued at the same doses during the switching, or were administered to assist opioid switching in case of need. Non-opioid analgesics were also continued if previously administered, at the same doses. No patient received anticancer therapy during the course of the study. The following data were recorded:

- Age, gender, primary cancer, and performance status.

- Symptoms associated with opioid therapy or commonly present in advanced cancer patients, such as nausea and vomiting, drowsiness, confusion, constipation, dry-mouth, myoclonus, sweating, using a scale from 0 to 3, corresponding to a verbal scale (not at all, slight, a lot, awful), were recorded. A distress score was also calculated as a sum of symptom intensity. Although never validated, this score has been previously used in different studies for determining the "weight" of adverse effects. The aim of using a sum of intensities is justified by the high variability of symptom intensity requiring opioid substitution in individual patients. This score is able to determine a general improvement of symptoms. The evaluation of the changes in intensity of a single symptom, different for

each patient, make a global evaluation, and statistics for a group of patients, practically impossible. Moreover, it is not rare to switch a patient for more than one symptom. Changes in distress score have been already used to assess outcomes of switching (18). On the other hand an important decrease of the principal symptom which required the switching is another parameter to take into consideration. Thus, these parameters were used to define a successful switching (see above). Symptoms were assessed by the patient, whenever possible. However, in patients who had severe cognitive failure, and switched for adverse effects, a proxy evaluation was taken into account.

- The following parameters and intervals were recorded: daily opioid doses, pain intensity measured using the patient's self report on a numerical 0-10 scale, and distress before switching (T0), at 24 hour intervals for three days, and at time of stabilization, which is the time to reach a stable daily dose considered as the first of two consecutive days requiring no more than two rescue doses (T-end).

Statistical analysis

All continuous data are expressed as a mean ± standard deviation of the mean. Statistical analysis of quantitative data, included descriptive statistics, was performed for all the items. The paired samples Student's t-test and the paired Wilcoxon signed-rank test were used to compare parametric and nonparametric variables, respectively, at the different intervals. Data were analyzed by the Epi Info software, version 3.2.2, (Centers for Disease

Control and Prevention) and by SPSS Software 14.0 version (SPSS, Inc., Chicago, Ill, US). All P-values were two sided, and P values less than 0.05 were considered statistically significant.

RESULTS

From a sample of 732 consecutive patients (inpatients and home care) assessed in one year, thirty-seven patients (5%) were switched from or to tapentadol in a period of one year. 24 and 13 patients were switched from and to tapentadol, respectively. 17 were females, and the mean age was 65.9 years (SD 13.4). The mean Karnofsky status was 60.9 (SD 13.6). Primary tumors were in a rank order: breast (n. 8), gastrointestinal (n. 7), urogenital (n. 5), lung (n. 3), pancreas (n. 4), others (n. 10). 19 patients were switched for convenience (C), 5 patients for poor pain control (P), 1 patients for adverse effects (AE), and 12 patients for both poor pain control and adverse effects (PAE). Time to achieve stabilization in patients who were switched successfully, was 3.2 days (SD 2).

The most frequent sequences of **opioid switching** were tapentadol-morphine (18 patients) in one direction, and morphine-tapentadol (8 patients) on the other direction. In the first sequence, the mean final tapentadol-morphine ratio was 3.9:1 (SD 2.3), which did not significantly differ from the initial established conversion ratio (p=0.647). The distress score significantly changed at T1 and T2, principally due to nausea and vomiting. Metoclopramide was used in four of these patients. Pain intensity significantly decreased

at T2, T3 and T-end (see table 1). In patients C, the mean initial and final ratio were practically identical, 3.28:1 (SD 0.03)and 3.34:1 (SD 0.52) , respectively.

With the inverse sequence of opioid **switching** morphine-tapentadol, the mean final morphine-tapentadol conversion ratio was 1:4.5 (SD 3.2), which did not significantly differ from the initial established conversion ratio (p=0.211). Pain intensity and distress score decreased, although they did not attain significance. In patients C, the initial and final ratio were the same and no changes in doses were done.

Three patients did not complete the study. One patient C who was switched from 200 mg/day of tapentadol to 60 mg/day of oral morphine, discontinued the treatment due to severe confusion and was switched to other opioids. In one patient, who was switched from 200 mg/day of tapentadol to 60 mg/day of oral morphine, data were incomplete as the patient died. One patient PAE who was switched from 60 mg/day of oral morphine to tapentadol 150 mg/day, was switched back to high doses of intravenous morphine due to uncontrolled pain (90mg/day, correspondent to 270 mg of oral morphine) .

A minority of patients were switched from/to tapentadol to/from other opioids. Three patients PAE were switched from oxycodone to tapentadol. One patient was receiving oxycodone 160 mg/day and was switched to 300 mg/day of tapentadol, successfully. Doses of tapentadol did not change. One patient was switched from oxycodone 20 mg/day to tapentadol 100 mg/day. At time of stabilization the dose of tapentadol was 200 mg/day . A third patient, was switched from oxycodone 40 mg/day to tapentadol 100 mg/day. The final dose of tapentadol was 300 mg/day.

One patient P was switched from hydromorphone24 mg/day to 500 mg/day of tapentadol. At time of stabilization the dose of tapentadol decreased (200 mg/day). One patient PAE was switched from 400 mg of tapentadol to 24 mg of hydromorphone, successfully. Doses did not change at time of stabilization. One patient PAE was switched from 300 mg of tapentadol to 16 mg of hydromorphone, unsuccessfully, and then further opioids were administered.

One patient PAE was switched from 400 mg/day of tapentadol to transdermal fentanyl 1.2 mg/day. The dose did not change at time of stabilization. Similarly, one patient was switched with the inverse sequence from transdermal fentanyl 0.6 mg/day to tapentadol 200 mg/day and the dose remained stable. One patient PAE was switched from 500 mg/day of tapentadol to 1.2 mg/day of transdermal buprenorphine. Doses of buprenorphine did not change. One patient was switched from 150 mg/day of tapentadol to an initial dose of 32 mg/day of methadone. The dose was almost halved at time of stabilization (18 mg/day). One patient PAE was switched from tramadol 200 mg/day to an initial dose of tapentadol 150 mg/day. The final dose at time of stabilization was doubled (300 mg).

DISCUSSION

Tapentadol produces potent analgesia through its dual mechanism of action. The two mechanisms are complementary (9). Tapentadol has a weak affinity for opioid μ-receptors. Despite having 50 times less affinity than morphine, tapentadol provides an analgesic effect

which is equivalent to one third that observed with equivalent doses of morphine. A relevant contribution to the analgesic effect of tapentadol is possibly due to the high selectivity for the norepinephrine transporter protein that blocks reuptake of norepinephrine at the terminal endings of interneurones and descending inhibitory fibers. Norepineprhine inhibits transmission of noxious impulses by activating α- adrenergic receptors located on noxious nerve fibers in the spinal cord and central nervous system. The increase of norepineprine may further suppress pain transmission at receptor endings. This mechanism would be expected to delay the development of opioid-tolerance, other than providing additive analgesia in conditions of neuropathic pain (5,7,14). The noradrenergic component can produce an opioid-sparing effect, such as a moderate opioid-receptor activity is sufficient to produce potent analgesia, thus reducing opioid-induced adverse effects (14,20). Thus, when switching from and to tapentadol, the equianalgesic ratio could be difficult to determine, due to the noradrenergic component which is difficult to predict. Data from experimental studies in animals have suggested an equianalgesic ratio with oral morphine of 1:2.5 (21).

In some countries tapentadol is available as an immediate release formulation. However, information about the use of tapentadol for breakthrough pain is absent, and morphine was chosen for its familiarity and typical mu-receptor activity.

Data on tapentadol in cancer patients are poor. In the only existing study in patients with cancer pain, tapentadol at starting doses of 100 mg/day in opioid-naïve patients with moderate-severe cancer pain produced significant decrease in pain intensity with low dose escalation indexes (12). The reduced tendency to increase the doses, already observed in

animal models (6,7) may reflect a less toleragen effect of tapentadol, possibly due to its pharmacological characteristics with a dual analgesic mechanism (4). Similarly, data on tapentadol switching are almost inexistent. In a case report tapentadol provided excellent analgesia in a patients who was difficult to manage with methadone. A patient with vertebral metastases was receiving 60 mg/day of methadone and was reporting severe pain intensity at rest and a very limited activity to prevent incident bone pain. Moreover, she was complaining dizziness. At the end of switching, with doses of tapentadol of 250 mg/day, the clinical condition improved as well as physical activity (22). In this study, the initial conversion ratio with oral morphine equivalents was 1:3.3. In patients C, this ratio was maintained in time in most patient on both direction. Interestingly. A patient who was switched for poor pain control (P), required to doubling the dose of tapentadol.

Of interest while patients switched from morphine to tapentadol did not show relevant changes in distress score, patients who were switched from tapentadol to morphine exhibit more adverse effects as evidenced by the need of antiemetic drugs and the temporary increase in distress score, principally due to nausea and vomiting. This score has never been validated, but was successfully used in most studies of opioid switching to define express the weight of the principal opioid-related symptoms (19).

Data regarding the other opioids are limited by the low number of patients. However, the indirect starting ratio calculated with oral morphine seemed to work, although changes in doses may occur on individual basis, as observed with other opioid switching sequences

Cancer pain patients can need much higher doses of opioids. Data regarding the use of higher doses of tapentadol are lacking and this information should be assessed in future studies.

Conclusion

In conclusion tapentadol may offer new opportunities among opioids for the atypical mechanism of action. Data suggest that an acceptable conversion ratio could be 1:3.3 in both direction, particularly in patients who are switched in conditions of equianalgesia, when pain and symptoms are controlled. As observed with other opioids, individual variation may be important. This study has expected limitation, given its exploratory nature. The limited number of patients cannot allow to draw definitive conclusion, and data should be interpreted with caution. More experience with a larger number of patient, possibly replied in different setting, is necessary to apply this initial information, which however provide some suggestion on research agenda of this new drug. For the same reasons, the low number of subgroup patients did not allow an analysis of pain mechanisms in influencing the conversion ratio between tapentadol and other opioids.

Transparency

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	T0	T1	T2	T3	T end
	n=18	n=17	n=17	n=17	n=16
Tapentadol	280.5 (164)				
Morphine	80.8 (54)	84 (55)	80.3 (50)	80.3 (50)	85.6 (55)
Pain intensity	2.7 (1.3)	2 (1.8)	1.7 (1.8) *§	1.7 (1.8)*§	1.3 (1.7)*§
Distress score	1.9 (1.6)	2.8 (1.7)*	2.8(1.1)*	2.6(1.4)	2.2 (1.4)

Table 1. Data of patients who were switched from tapentadol to morphine **(expressed as mg, mean (SD) at the different intervals considered. Values of pain intensity are expressed a mean (SD).** * p<0.05 vs T0; § p<0.05 vs T1; ^ p<0.05 vs T2 and T3.

	T0	T1	T2	T3	T end
	n=8	n=8	n=8	n=8	n=7
Morphine	81.4 (57)				
Tapentadol	228 (173)	250 (171)	278 (177)	307 (179	300 (181)
Pain intensity	4.1 (2.2)	2.6 (1.3)	3.9 (1.5)	2.3 (1.2)	3 (2.2)
Distress score	2 (1.4)	1.4 (1)	0.9 (0.9)	1.1 (1.2)	1 (1.1)

Table 2. **Data of patients who were switched from morphine to tapentadol (expressed as mg, mean and SD) at the different intervals considered. Values of pain intensity are expressed a mean(SD).**