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ORIGINAL ARTICLE

Opioid switching and variability in response in pain cancer patients

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Abstract

Introduction Opioid switching is a possible strategy for inadequate analgesia or unmanageable side effects. Its effectiveness ranges from 50 to 90% and is still debated.

Purpose We analyzed the impact of opioid switching in a cancer pain population treated with strong opioids for pain.

Methods This is a post hoc analysis from a multicenter, randomized, four-arm, controlled, phase IV clinical trial. Outcome variables included the percentages of switches, the reasons for the switch, the dose changes before and after the switch, depending on the starting opioid, the response in case of inadequate analgesia, and unmanageable toxicity, and the variability of response among and within patients.

Results We analyzed 498 patients. The opioid was switched in 79 patients (15.9%) 87 times, mainly for uncontrolled pain (52.3%), adverse opioid reactions (22.1%), both of these (4.8%), and dysphagia (20.8%). The reasons for switching varied depending on the starting opioid. Pain reduction was good after 51.45% of switches and control of opioid side effects was good after 43.5%. The relief of opioid-induced toxicity varied among adverse events and within each patient. The daily doses were higher after switching oral opioids and lower after transdermal drugs.

Conclusions Half of the patients who underwent switching experienced improved relief of pain or amelioration of opioid toxicity. The switch can help in the management of some cases but with many limits and uncertainties.

Keywords Cancer pain · Opioid switching · Pain relief · Toxicity relief

Introduction

Opioids do not always relieve cancer pain. About 20–25% of patients receiving opioids for chronic pain do not achieve ≥ 30% pain reduction [1–3], thus fixing a cutoff for satisfactory pain reduction [4, 5].

For this reason, opioid treatment often requires strategic changes and the substitution of the opioid in use (opioid switch, also known as opioid rotation) is a recurring choice. The poor response can reflect the onset of tolerance or, sometimes, the presence of some forms of cancer pain not well responsive to opioids, as myofascial and neuropathic pain. Independently from the cause, the uncontrolled pain can initially request an adjustment of the administered dose to overcome the loss of sensitivity to the drug, but the increase of dose could increase the toxicity as well. Furthermore, although a higher dose may be necessary to restore analgesia, this effect lasts a variable time, and repeated attempts at ensuring analgesia by increasing the dose often vanish.

The balance between the control of pain and the level of adverse reactions is essential and when it turns negative, the more appropriate choice can be to switch the opioid.

After this decision, results are not always positive and the satisfactory pain control has been reported in 50–90% of patients [6–8]. In other cases, the clinical concern is the burden of toxic reactions to opioids that not only limits their use [9–11] but are not always easily controlled with symptomatic therapies [12].

Loss of analgesia and unmanageable adverse reactions are therefore important limits to the effective and safe use of opioids. In this study, we considered pain as uncontrolled when intensity does not achieve a reduction of at least 30% with

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respect to the basal score [4]. At the same time, the opioid-induced toxicity was considered uncontrolled when it was so high and unmanageable that continuing the treatment became unacceptable for the patients.

To deal with these negative consequences, the opioid switch can nevertheless help achieve a satisfactory clinical balance between analgesia and adverse effects.

Despite its consolidated use over more than 20 years, the effectiveness of the switch is still debated [6, 13–16]. To contribute to this topic, we assessed the impact of the switches on the decrease of pain intensity and/or opioid-induced toxicity in a population of cancer patients treated with World Health Organization (WHO) step III opioids. We focused particularly on the differences of response among and within the patients.

Methods

This is a secondary post hoc analysis that is based on a multicenter, randomized, open-label, longitudinal, active-controlled, four-arm, superiority, phase IV clinical trial previously performed [2]. Patients with advanced/metastatic solid tumors were randomized (1:1:1:1 ratio) to receive either oral morphine (active comparator) or transdermal buprenorphine or oral oxycodone or transdermal fentanyl. Eligibility criteria included persistent moderate to severe cancer pain [average pain intensity (API) in the last 24 h $\geq$ 4 points measured on a 0 to 10 Numerical Rating Scale (NRS) ranging from no pain to the worst imaginable pain] and the prescription of WHO step III strong opioids never previously given. Patients with concurrent radiotherapy, ongoing first-line chemotherapy, non-pharmacological analgesic treatment, and pre-existing renal failure were excluded. Further details of the recruitment criteria and results are available in the original study [2]. Observation lasted 28 days and included six visits, at baseline and on days 3, 7, 14, 21, and 28.

Pain intensity (PI) was assessed by measuring the API and the worst pain intensity (WPI) experienced by the patients in the 24 h before the visits, using the 0–10 NRS. We recorded the presence of neuropathic pain, using the "Douleur neuropathic 4" (DN4) questionnaire [17], and of breakthrough pain, according to the Davies algorithm [18]. The measures of PI were repeated during the six scheduled visits, and adverse drug reactions (ADRs) were assessed with the Therapy Impact Questionnaire (TIQ) [19]. The TIQ is self-reported and patients rate both the presence and the intensity of the symptoms on a 4-point verbal rating scale, where 0 means "not present" and 3 means "severe." The starting dose of background opioids was suggested according to the European Association of Palliative Care recommendations [20]. The doses were reported as "oral morphine equivalent daily dose" (OMEDD). During the follow-up, any change in the pain therapy (type of drug, doses, and switches), freely determined by the physicians to manage pain better, was recorded.

In this analysis, we investigated the switches made throughout the follow-up period. Importantly, in this study, the decision of switching was entirely entrusted to the physicians' evaluation. This decision included whether to make the switch, the reason and the moment of the change, the new chosen opioid, and the conversion of doses between opioids. We recorded the number of switches, the reasons for each switch, the changes of background daily doses of opioid before and after the switch, and the response in case of inadequate analgesia and uncontrolled toxicity.

The response to the switch because of previous analgesic inefficacy was analyzed based on the difference of API between the pre- and post-switch visits. Patients whose API decreased by at least 30% were considered responders (R), those whose API decreased from 1 to 29% were classified as poor responders (PR), and those with an unchanged or worse API were considered non-responders (NR).

For the switches due to opioid toxicity, we focused on the most severe ADRs (i.e., rated 2 to 3 in the TIQ) before the switch. The response was evaluated by comparing the difference in the intensity of each ADR before and after the switch. Patients whose ADR disappeared or decreased at least 2 points in intensity were classified as responders (R), those with a decrease of 1 point as poor responders (PR), and patients with an unchanged or worse intensity as non-responders (NR). Finally, the responses were analyzed for any adverse event in the whole population (variability among patients) and for each patient presenting multiple ADRs (variability within patients).

Statistical analysis

All the patients randomized in the original trial, with no major violations of the eligibility criteria, were included in this post hoc analysis.

Sample characteristics were summarized as mean and standard deviation (SD) or absolute and relative frequencies, as appropriate. To evaluate potential differences in baseline characteristics, we compared the intention-to-treat (ITT) population of the CERP trial (i.e., all the randomized patients with no major violations of the eligibility criteria and with at least two pain evaluations) according to switch. The Wilcoxon test and chi-square test were used for continuous variables and categorical variables, respectively.

Statistical significance was set at $p < 0.05$ for a bilateral test. Analyses were done with SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Forty-four centers took part in the study, 520 patients were randomized in the CERP trial to receive a WHO step III opioid as background treatment, and 498 ITT patients were included in this analysis [2].

Table 1 shows the baseline demographic and clinical characteristics (tumor and metastases site, ongoing anticancer therapy, neuropathic and/or breakthrough pain, average and worst intensity pain, background opioid therapy) for patients who switched or not switched during the follow-up: a higher proportion of patients with neuropathic or mixed pain at baseline was recorded for patients who switched during the follow-up (24% vs 14.8%).

During the observation, the opioid was switched in 79 patients (15.9%) for a total of 87 events (Table 2). The numbers and reasons for switches were correlated with each starting opioid in Table 3.

Table 4 shows the changes in the average pre- and post-switch daily doses, for each starting opioid and

Table 2 Number of switches and reasons for switching

Characteristics of switch	*n* (%)
Number of patients switching	79 (15.9)
Number of events	87
Number of events/patient	
1	72 (91.1)
2	6 (7.6)
3	1 (1.3)
Reasons for switch	
Uncontrolled pain	45 (52.3)
Severe ADRs	19 (22.1)
Pain and ADRs	4 (4.7)
Dysphagia	18 (20.9)[1]
Unknown	1

[1] Dysphagia required a switch only for patients taking oral opioids

ADRs adverse drug reactions

Table 1 Main demographic, clinical characteristics, and opioid background treatments of the CERP patients according to switch at baseline

	No switch population $N = 419$	Switch population $N = 79$	All patients $N = 498$	*p* value[1]
Age (years), mean (SD)	67.0 (11.6)	66.3 (13.0)	66.9 (11.8)	0.921
Female, *n* (%)	188 (44.9)	33 (41.8)	221 (44.4)	0.611
Primary tumor, *n* (%)				
Lung, pleura	117 (27.9)	24 (30.4)	141 (28.3)	0.993
Colon, rectum	96 (22.9)	18 (22.8)	114 (22.9)	
Genitourinary	81 (19.3)	13 (16.5)	94 (18.9)	
Breast	55 (13.1)	10 (12.7)	65 (13.1)	
Head-neck	35 (8.4)	7 (8.9)	42 (8.4)	
Other	35 (8.4)	7 (8.9)	42 (8.4)	
Metastases, *n* (%)	361 (86.2)	63 (79.7)	424 (85.1)	0.142
Ongoing anticancer therapy	151 (36.0)	24 (30.4)	175 (35.1)	0.334
Pain, *n* (%)				
Breakthrough pain	186 (44.4)	37 (46.8)	223 (44.8)	0.689
Neuropathic or mixed pain	61 (14.8)	19 (24.1)	80 (16.3)	0.041
Average pain				
NRS, mean (SD)	6.0 (1.4)	5.9 (1.2)	6.0 (1.4)	0.525
NRS > 7, *n* (%)	152 (36.3)	25 (31.6)	177 (35.5)	0.430
Worst pain				
NRS, mean (SD)	8.0 (1.5)	7.9 (1.5)	8.0 (1.5)	0.939
NRS > 7, *n* (%)	350 (83.5)	67 (84.8)	417 (83.7)	0.778
First opioid therapy, *n* (%)				
Oral morphine	95 (22.7)	27 (34.2)	122 (24.5)	0.152
Oral oxycodone	109 (26.0)	16 (20.3)	125 (25.1)	
Transdermal fentanyl	108 (25.8)	16 (20.3)	124 (24.9)	
Transdermal buprenorphine	107 (25.5)	20 (25.3)	127 (25.5)	

[1] Wilcoxon was used for continuous variables and chi-square test for categorical variables

SD standard deviation, *NRS* Numerical Rating Scale

Table 3 Number of switches and correlated reasons depending on the pre-switch opioid

Starting opioid[1]	Total switches	Inadequate analgesia *N* = 45	Adverse reactions *N* = 19	Inadequate analgesia and adverse reaction *N* = 4	Dysphagia *N* = 18
Oral morphine, *n* (%)	27 (31.8)	9 (33.3)	7 (25.9)	1 (3.7)	10 (37.0)
Oral oxycodone, *n* (%)	19 (22.4)	7 (36.8)	1 (5.3)	3 (15.8)	8 (42.1)
TD buprenorphine, *n* (%)	21 (24.7)	14 (66.7)	7 (33.3)	0 (0.0)	0 (0.0)
TD fentanyl, *n* (%)	18 (21.2)	14 (77.8)	4 (22.2)	0 (0.0)	0 (0.0)

[1] Two switches after the first switch, with another starting opioid, were not included

TD transdermal

independently of the reason for the switch. We excluded two outlier patients, in treatment with oxycodone and buprenorphine before switching, in whom an increase of about 700% in the opioid dose was observed after the switch.

All the opioids were considered together in the analysis of analgesic efficacy. The API score ranged from 5.0 (± 2.0 SD) to 3.7 (± 1.6 SD) before and after the switches, thus decreasing on average by 31.2%, and the WPI varied from 6.4 (± 2.6 SD) to 5.4 (± 1.7 SD) with a 13.3% decrease. The type of response, considering a pain reduction of at least 30% as positive [5], comprised 51.5% of R and 48.5% of PR or NR. The responders achieved on average a 52.8% reduction of pain intensity.

Table 5 shows the number of good, poor, and negative responses after a switch for severe opioid toxicity, evaluating each type of adverse event separately. The positive and negative responses are distributed similarly.

Finally, we focused on the 23 switches due to severe toxicity, evaluating the type of response for each side effect in each patient (Table 6). Unexpectedly, we found positive responses for all the adverse events in seven patients: a full negative response in four cases and mixed responses, positive for some adverse events and negative for others, within the same patient, in nine cases. For example, the switch 2 induced a total negative response for nausea, vomiting, and constipation but complete positive responses for dry mouth and confusion. Switches 10, 11, and 20 are listed in the table, as the switches were done for severe toxicity, but the responses were not described since the drugs were switched at the last follow-up visit, so we could not measure the outcomes.

Discussion

Part of this analysis examined some aspects related to the opioid switching in cancer patients, since the literature gives some conflicting results. In this analysis, 15.9% of patients were treated with strong opioids, and switched over 4 weeks of observation. This frequency is similar to the results of two other studies: 17% and 14.5% [21]. The most common reason for switching was lack of analgesia in 52.3% of the patients. This reason prevailed in other studies too, although at frequencies ranging from 70 to 83% [22, 23].

Other aspects as well emerged from our analysis. The number of switches varied depending on the starting opioid. Excluding the switches due to dysphagia, oxycodone gave the lowest need for switching solely for uncontrolled pain. Switches for inadequate analgesia were more often needed with transdermal opioids while morphine was substituted similarly for both uncontrolled pain and adverse reactions. A worthy of note consideration is that no switch to methadone was made, even if this drug can be considered the gold standard in opioid switching.

Overall, the advantages expected from the switch, namely, better analgesia and less toxicity, were scant. The

Table 4 Opioid daily dose (as OMEDD) before and after the switch depending on the starting opioid

Starting opioid *n* (%)	Opioid daily dose (mg), mean (SD)			
	Pre-switch	Post-switch	Absolute difference	Relative difference
Oral morphine 27 (31.8)	56.3 (34.7)	76.8 (41.7)	18.4 (28.8)	45.3% (60.5)
Oral oxycodone 19 (22.4)	64.6 (29.0)	86.3 (37.4)	19.7 (31.8)	27.6% (31.8)
TD buprenorphine 21 (24.7)	76.9 (25.6)	65.6 (54.4)	− 11.5 (46.3)	− 17.1% (52.5)
TD fentanyl 18 (21.2)	124.7 (114.5)	70.0 (56.1)	− 42.4 (103.0)	− 19.2% (41.7)

TD transdermal, *mg* milligrams, *SD* standard deviations

Table 5 Responses after switch for severe and unmanageable adverse events

Opioid adverse events, *n* (%)	Responders	Poor responders	Non-responders
Nausea	6 (46.2)	0 (0.0)	7 (53.8)
Vomiting	6 (60.0)	1 (10.0)	3 (30.0)
Constipation	5 (41.7)	0 (0.0)	7 (58.3)
Dry mouth	3 (30.0)	1 (10.0)	6 (60.0)
Drowsiness	4 (36.4)	3 (27.3)	4 (36.4)
Confusion	5 (50.0)	1 (10.0)	4 (40.0)
Hallucinations	1 (50.0)	0 (0.0)	1 (50.0)
Myoclonus	0 (0.0)	0 (0.0)	1 (100.0)
Total	30 (43.5)	6 (8.7)	33 (47.8)

average reduction of API score was 1.3 points, which is close to 30% of pain intensity, considered clinically significant [4, 24], but this positive response was achieved in only 51.3% of the patients. The change of WPI after the switch was definitely poorer (13.3%). Thus, results were good only in half the switched patients. This unsatisfactory outcome contrasts with the positive impression from a previous study, where patients reached on average a pain reduction greater than 35% [25]. We acknowledge that no conclusions can be drawn regarding tolerance since the data we collected did not include tolerance as one of the reasons for switching. No conclusions can be drawn about neuropathic pain as well, since we did not evaluate the response to the switch in this situation because the overall number of enrolled patients was limited and then further divided into the two sub-conditions.

Table 6 Responses to switch carried out for severe and unmanageable ADRs in each patient

Patient (*N*)	Nausea	Vomiting	Constipation	Dry mouth	Drowsiness	Confusion	Hallucinations	Myoclonus
1	NR	–	NR	NR	PR	PR	–	–
2	NR	NR	NR	R	–	R	–	–
3	R	R	NR	–	NR	–	–	–
4	R	R	–	–	R	R	–	–
5	–	–	R	–	R	–	–	–
6	–	–	R	–	–	–	–	–
7	–	–	–	–	R	R	–	–
8	–	–	–	–	NR	NR	–	–
9	NR	R	NR	NR	PR	NR	–	–
10[1]	–	–	–	–	–	–	–	–
11[1]	–	–	–	–	–	–	–	–
12	NR	PR	R	NR	–	–	–	NR
13	NR	–	NR	NR	–	–	–	–
14	R	–	–	PR	NR	R	–	–
15	–	–	NR	R	PR	R	–	–
16	NR	–	NR	NR	–	–	–	–
17	NR	NR	–	–	–	–	–	–
18	R	R	–	–	–	–	–	–
19	–	NR	R	–	–	NR	NR	–
20[1]	–	–	–	–	–	–	–	–
21	–	–	–	NR	NR	NR	R	–
22	R	R	–	–	R	–	–	–
23	R	R	R	R	–	–	–	–

[1] In these cases, the switch was made at the last follow-up visit so we could not measure the outcomes; therefore, the response is not reported

R responders, *PR* poor responders, *NR* non-responders

The efficacy of the switch because of severe opioid toxicity was first analyzed for each adverse event. There were more than 50% R among patients with vomiting and confusion, whereas NR prevailed in the case of constipation and dry mouth. These symptoms do generally tend to improve slightly during lengthy treatment with opioids due to the missed onset of tolerance [26]. Our observation indicated that these side effects often did not improve even after changing of the opioid. The analysis by single patient concerned the situations where a patient had more than one adverse event at the same time. The question was whether the switch would produce the same response positive or negative for all the side effects. The responses were variable and in seven cases out of 20, all were positive responses; four cases gave only negative responses for all the adverse events reported, thus indicating that switching can induce "all-or-nothing" responses. However, nine cases gave mixed responses, positive for some adverse events and negative for others. For example, the switch in patient 2 induced total negative responses for nausea, vomiting, and constipation and complete positive response for dry mouth and confusion. The reduction of nausea and vomiting was general though in patient 9 the response was negative for nausea and positive for vomiting. These observations suggest that the switch sometimes induces a "light and shade" response in an individual. All these results indicate that the outcomes of switching are a priori unpredictable in clinical practice.

As regards the drugs and doses before and after the switches, morphine and oxycodone were switched starting from quite low doses (about 60 mg daily), independently from the reason for the substitution; their absolute daily doses increased averagely by around 20 mg/daily after the switch. In contrast, the transdermal opioids were substituted starting from higher doses then the oral opioids, and their average doses tended to be reduced, by 11.5 mg/daily for buprenorphine and 42.4 mg/daily for fentanyl from the pre-switch dose.

This analysis presents some limitations. The primary study [2] aimed to describe the number and features of the switches during follow-up. The number of switches actually done was not predictable in advance and in the end was quite low. Moreover, the follow-up of this study lasted 4 weeks that is not a very long but realistic period of observation in advanced cancer patients. It is worth acknowledging that many cases of opioid switching might occur in a longer period.

This issue agreed with the principle, expressed in the original protocol, that the physicians could decide the drug schedule completely independently after the initial randomization, to optimize pain management in their patients, thus including the decision of whether and how to switch to an opioid. Their decisions reflected personal attitudes and procedures for the switch, sometimes indicating only partial observance of rules and recommendations. For example, they were fairly far from the indications of the equi-analgesic charts that suggest the correct conversion of doses between opioids when switching [27]. Our analysis was necessarily based on these professional approaches and the collected data represent a picture of real-world opioid switching.

Conclusions

Opioid switching makes available a better pain relief or adverse reactions control in about 50% of patients who "are not doing well" with opioid treatment.

A more original contribution of the findings concerns the variability of the response for any adverse event, so each of them may be controlled in one patient and uncontrolled in another. The second interesting aspect is that in the same patient the switch may lessen the intensity of some adverse events leaving the severity of others unvaried all that in a completely unpredictable way.

We must therefore conclude that the switch can help in the management of some clinical cases, but with many limits and uncertainties. Moreover, future studies should deeply explore how practitioners decide to switch, considering not only scientific but also external reasons.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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