Opioid Switching: a Descriptive Analysis

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Rodízio de Opioides: uma Análise Descritiva

Rotación de Opioides: un Análisis Descriptivo

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ABSTRACT

Introduction: The use of opioids must be individualized and changing for another opioid may be necessary (opioid switching). **Objective:** Identify how the opioid switching was performed and whether the desired effect was achieved in patients admitted at a public palliative oncologic care specialized hospital. **Method:** *Post hoc* analysis of the profile study of patients admitted to a public oncologic palliative care hospital in Rio de Janeiro between September and November 2016. Hospitalizations were followed longitudinally by reviewing the charts with daily collection of the numeric rating scale (NRS). Pain was considered controlled when NRS = 0. Doses, route of administration, switch (drugs and motif) of the opioids were observed. The time for pain control was calculated when this was the reason. **Results:** 104 opioid switching were observed in 90 hospitalizations (22.5%), 49% of which were strong opioids and 43%, from mild to strong. Main reasons were pain (40%) and dyspnea (36%). The time to NRS = 0 was 1.6 days (+/-1.8; 95% CI 1.0-2.1), taking longer to switch to methadone (mean 2.7 days +/-2.5; 95% CI 1.0-4.4). Comparing the dose of oral morphine by analgesic equipotency, a 10% increase in the target opioid dose occurred, and when rotating due to dyspnea (38%), the increase was greater. **Conclusion:** Although pain control was higher than described in other studies, the increase in the equipotent dose of opioid is not corroborated by protocols. Extensive surveillance and other studies are recommended in the unit.

Key words: Palliative Care; Pain Management; Analgesics, Opioid/administration & dosage; Medication Therapy Management.

RESUMO

Introdução: O uso de opioides deve ser individualizado e a troca por outro opioide pode ser necessária (rodízio de opioide). **Objetivo:** Identificar como foi realizado o rodízio de opioide e se o efeito desejado foi atingido em pacientes internados em uma unidade especializada em cuidados paliativos oncológicos. **Método:** Análise *post hoc* do estudo de perfil de pacientes internados em um hospital público de cuidados paliativos oncológicos no Rio de Janeiro, entre setembro e novembro de 2016. As internações foram acompanhadas longitudinalmente por revisão de prontuário com coleta diária da escala verbal numérica (EVN). A dor foi considerada controlada quando EVN = 0. Doses, via de administração e rodízio (fármaco e motivo) dos opioides foram observados. O tempo para controle da dor foi calculado quando este foi o motivo. **Resultados:** Foram observados 104 rodízios de opioides em 90 internações (22,5%), sendo 49% entre opioides fortes e 43% de fraco para forte. Principais motivos foram dor (40%) e dispneia (36%). O tempo para EVN = 0 foi 1,6 dias (+/-1,8; IC95% 1,0-2,1), sendo mais demorado na troca por metadona (média 2,7 dias +/-2,5; IC95% 1,0-4,4). Comparando a dose de morfina oral por equipotência analgésica, houve aumento de 10% na dose do opioide de destino, sendo esse aumento maior quando no rodízio por dispneia (38%). **Conclusão:** Embora o controle de dor tenha sido superior ao descrito por outros trabalhos, o aumento da dose equipotente do opioide não é corroborado por protocolos. Maior vigilância e outros estudos são recomendados na unidade.

Palavras-chave: Cuidados Paliativos; Manejo da Dor; Analgésicos Opioides/administração & dosagem; Conduta do Tratamento Medicamentoso.

RESUMEN

Introducción: El uso de opioides debe ser individualizado y puede ser necesario cambiarlo por otro opioide (rotación de opioides). **Objetivo:** Identificar cómo se realizó la rotación de opioides y si el efecto deseado se logró en pacientes ingresados en una unidad especializada en cuidados oncológicos paliativos. **Método:** Análisis post hoc del estudio de perfil de pacientes ingresados en un hospital público de cuidados paliativos de oncología en Río de Janeiro, entre septiembre y noviembre de 2016. Las hospitalizaciones fueron seguidas longitudinalmente mediante la revisión de los registros médicos con la recopilación diaria de la Escala Numérica Verbal (ENV). El dolor se consideró controlado cuando ENV = 0. Se observaron dosis, vía de administración, rotación (fármacos y motivo) de los opioides. El tiempo para el control del dolor se calculó cuando esta fue la razón. **Resultados:** Se observaron 104 ruedas de opioides en 90 hospitalizaciones (22,5%), con 49% entre opioides fuertes y 43% de débiles a fuertes. Las razones principales fueron dolor (40%) y disnea (36%). El tiempo para ENV = 0 fue de 1,6 días (+/-1,8; IC del 95%: 1,0-2,1), y tomó más tiempo cambiar a metadona (promedio 2,7 días +/-2,5; IC 95% 1,0-4,4). Comparando la dosis de morfina oral para la equipotencia analgésica, hubo un aumento del 10% en la dosis de opioides objetivos, este aumento fue mayor al rotar debido a la disnea (38%). **Conclusión:** Aunque el control del dolor fue superior al descrito por otros estudios, el aumento en la dosis equipotente de opioide no es compatible con los protocolos. Se recomienda mayor vigilancia y otros estudios en la unidad.

Palabras clave: Cuidados Paliativos; Manejo del Dolor; Analgésicos Opioides/administración & dosificación; Administración del Tratamiento Farmacológico.

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INTRODUCTION

The use of analgesic opioids is one of the bases for pain and dyspnea control in patients in palliative care[1]. The World Health Organization (WHO)[2] created the "ladder for pain relief", classifying the opioids in weak or strong according to its potency. The goal of this protocol is to help the professional to evaluate and adapt the drugs used pursuant to the patient's necessity at every moment sequentially and progressively[2].

Opioids therapy needs to be individualized respecting the required dose for each patient at every moment. In some situations, change to another opioid should be considered, it is called "opioid switching", they are: intolerable adverse effect during titration, poor analgesic management regardless of dose adjustment, limiting drug-drug interactions, necessity to change the route of administration, specific clinical benefits of some opioids (morphine – dyspnea; oxycodone – neuropathic pain)[3].

The new drug should be prescribed at a dose that does not result in adverse effect or withdrawal and is effective in controlling the symptom. There are several instruments to help this process developed to determine the analgesic equipotency among the opioids[4,5].

An evaluation of the profile of hospitalized patients, of drugs with analgesic potential utilized and of the achieved pain control in a public oncologic palliative care unit in the city of Rio de Janeiro[6] was developed. Based in the observation of many opioids switching in the period, a subsequent analysis of this group was prepared. The present study has the objective of identifying how opioid switching was performed and whether the desired effect was reached in patients admitted in a specialized oncologic palliative care unit.

METHOD

From September 1st to November 30th 2016 a cross-sectional study to evaluate the profile of patients and their drug treatment in a public oncologic palliative care hospital in the city of Rio de Janeiro[6] was conducted. A *post hoc* analysis focused to opioid switching was carried out and described in this article.

At the occasion, all the admissions were followed up through chart review. Pain was quantified through Numerical Rating Scale (NRS)[7-10], applied and registered in the chart at the admission and routine medical evolution. The four routine physicians formed the oncologic palliative care clinical team of the unit for at least six years and were previously retrained to be assigned to the shifts.

Typically, the opioids utilized at the unit in that time were tramadol, codeine, morphine, methadone, oxycodone and transdermal fentanyl. Their prescribed doses and routes of administration were observed. Every opioid switching was considered regardless of the potency. The medical evolution provided the rationale for opioid switching.

The opioid doses were converted to oral morphine for study analyzes according to the analgesic equipotency following the guidelines of the National Comprehensive Cancer Network[4].

The admission, called episode and not the patient was utilized to analyze opioid switching. Descriptive analyzes of the variables collected with calculation of frequency, measures of central tendency and dispersion were performed. The measures of association were calculated utilizing the chi-square tests for categorical variables, Mann-Whitney for numerical variables and paired Wilcoxon for paired numerical variables. All the numerical variables collected have non-normal distribution according to the Shapiro-Wilk test. The statistical software R was utilized.

The Institutional Review Board of the National Cancer Institute José Alencar Gomes da Silva (INCA) and of the University Hospital Pedro Ernesto/University of the State of Rio de Janeiro (UERJ) approved the study, report number 1.630.518 (CAAE 54919016.4.0000.5274).

RESULTS

From September 1st to November 30th, 2016, 399 patients were admitted at the unit, totaling 461 episodes of hospitalization. Opioid analgesics were used in 400 of these episodes and switching in 90 (22.5%).

Pain was the main reason for hospitalization. Considering all the episodes, pain was present in 44% (176) of the hospitalizations and motivated 19% (76) of all the admissions. Considering only the episodes with opioid switching, pain was reported in 47.8% (43) of the admissions and was the main motive for 26.7% (24).

The mean time of hospitalization was eight days. It was observed more prolonged hospitalization when opioid switching occurred after analyzing separately the episodes with and without opioid switching (Table 1).

Of the 90 opioid switching episodes, in ten, a second switching was made and in other two, a third, reaching 104 switching. Dyspnea and pain were the main symptoms that motivated opioid switching, being responsible for 77% (80) of them. Table 2 describes the type and reason for switching.

In all the switching cases justified by renal insufficiency, morphine was switched to methadone. In two switching

Table 1. Duration (days) of the episodes of admission using opioid analgesic between September 1st. and November 30th, 2016 in an oncological palliative care unit in Rio de Janeiro (RJ)

	Total Episodes (n=400)		With opioid switching (n=90)		No opioid switching (n=310)	
	Mean (+/-SD)	CI95%	Mean (+/-SD)	CI95%	Mean (+/-SD)	CI95%
Time of hospitalization (days)	8.4 (+/-7.3)	7.7-9.2	10.4 (+/-7.8)	8.8-12.1	7.9 (+/-7.1)	7.1-8.7
			p-value* 0.00			

Captions: SD = Standard Deviation; CI = Confidence Interval; *Test Mann-Whitney.

Table 2. Description of opioids switching performed in the episodes of admission between September 1st. and November 30th, 2016 in an oncological palliative care unit in Rio de Janeiro (RJ)

Motive for switching	Weak opioid to strong opioid		Strong opioid to strong opioid		Strong opioid to weak opioid		Weak opioid to weak opioid		Total
	n	%	n	%	n	%	n	%	
First switching									
Pain	21	48.9	18	43.9					39
Dyspnea	20	46.5	10	24.4					30
Renal insufficiency			10	24.4					10
Adverse effect	1	2.3	1	2.4	3	100	1	33.3	6
Easiness of route of administration	1	2.3	2	4.9					3
Cough							2	66.7	2
Total	43		41		3		3		90
Second switching									
Pain			2	20					2
Dyspnea	2	100	5	50					7
Easiness of route of administration			3	30					3
Total	2		10						12
Third switching									
Dyspnea			2	100					2
Total			2						2

motivated by cough, tramadol was switched to codeine. For dyspnea, it was switched to morphine. When the easiness of the route of administration was the objective, it was switched to transdermal fentanyl.

For pain-motivated switching in use of strong opioids, changes were made for four regular medications adopted at the unit: in two, fentanyl was switched, in four, methadone, in nine, morphine and in five, oxycodone.

Of the six switching motivated by suspicion of adverse effect, the symptoms were delirium, nausea and somnolence. For the symptom nausea in two cases, the drug was switched to tramadol: one to codeine with improvement of the symptoms and other to morphine but nausea continued. In the two cases of delirium, the initial opioid was morphine, one switched to transdermal fentanyl and other to tramadol (both without improvement of the condition). In the two cases of somnolence, where fentanyl was switched to tramadol the condition did not change, and from morphine to tramadol, the symptom improved.

When the motive of switching was pain, it was controlled in 1.6 days in average (+/-1.8, CI95% 1.0-2.1), being faster in switching weak to strong opioid (2.1 days +/-2.1, CI95% 1.1-3.1) than among strong opioids

(1 day +/-1, CI95% 0.5-1.5), but the difference was not statistically significant (p-value 0.11). Figure 1 shows these means.

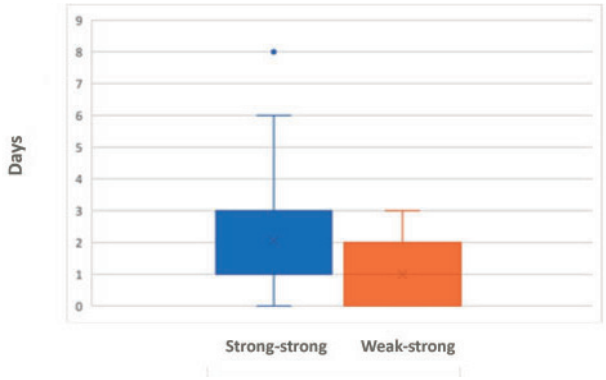

Figure 1. Boxplot* of time (days) necessary to control pain after opioid switching motivated by pain according to analgesic potency in the episodes of admission between September 1st and November 30th, 2016 in an oncologic palliative care unit in Rio de Janeiro (RJ).
Caption: * Mann-Whitney test, p-value 0.11.

In only three of the 39 pain motivated switching, the symptom was not controlled. In two of them, the patient evolved to death (for both, tramadol was switched to morphine) and the other was discharged (fentanyl switched to oxycodone), with pain reported every day.

Evaluating each analgesic isolated initiated as substitute for pain control, the use of morphine was associated with a faster control of the pain and methadone with slower control (Table 3).

Considering the conversion according to the analgesic equipotency for oral morphine of the opioid doses prescribed pre and post switching, a statistically significant increase of the final dose was noticed. The difference of the doses separated by motive of switching was calculated and is described in Table 4.

Table 3. Time for pain control (days) according to the drug after opioid switching motivated by pain in episodes of admission between September 1st. and November 30th, 2016 in an oncologic palliative care unit in Rio de Janeiro (RJ)

Opioid	n	Time for pain control after switching (days)	
		Mean (+/-SD)	CI95%
Morphine	20	1.05 (+/-1.2)	0.5-1.6
Methadone	11	2.7 (+/-2.5)	1.0-4.4
Oxycodone	7	1.3 (+/-0.8)	0.6-2.0
Fentanyl	1	1	

Captions: SD=Standard deviation; CI = Confidence Interval.

DISCUSSION

Pain and palliative care experts have been discussing opioid switching intensely. Its necessity reflects the presence of more complex symptom to control, requiring more expertise of the supervising professional team.

Other authors studied cases where it was necessary to switch opioid. The quantitative findings concluded it is uncommon at home or hospital environment in concurrence with this article. A study of Corli et al.[11] evaluated switching among strong opioids in 15.9% of the patients evaluated. In a study with 1,141 oncological palliative care patients at home with strong opioids, 17% of the cases needed switching[12]. Opioid switching of any potency in the present study corresponded to 22.5% of the episodes. Reducing the analysis to strong opioids switching alone, it was observed in 13.3% (53) of the episodes.

Table 4. Dose equivalent of oral morphine of opioids utilized in switching of the admission episodes in, between September 1st. and November 30th, 2016 in an oncologic palliative care unit in Rio de Janeiro (RJ)

	Origin opioid - equivalent morphine (mg)		Final opioid - equivalent morphine (mg)		p-value
	Mean (+/-SD)	CI95%	Mean (+/-SD)	CI95%	
Global	130 (+/-170.0)	97.7-163.9	143.6 (+/-168.9)	110.8-176.4	0.03
Motive for switching					
Dyspnea	87.0 (+/-111.4)	50.9-123.1	120.7 (+/-141.1)	74.9-166.4	
Pain	175.3 (+/-211.2)	108.6-241.9	189.0 (+/-196.3)	137.0-250.9	
Adverse Effect	70.0 (+/-58.8)	8.2-131.7	36.2 (+/-24.7)	10.2-62.2	
Renal insufficiency	104.4 (+/-78.6)	48.2-160.6	76.0 (+/-33.8)	51.8-100.2	
Cough	12.5 (+/-7.5)	-82.8-107.8	20.0 (+/-9.8)	-68.9-108.9	
Route of administration	180.8 (+/-209.2)	-78.9-440.6	172.2 (+/-201.5)	-78.0-422.4	

Captions: SD = Standard-Deviation; CI = Confidence Interval.

Some authors describe pain as the main motive for opioid switching. This was observed too in this study, being responsible for 39.4% (41) of switching as a whole. If only strong opioids are considered, the figure is 37.7% (20 episodes). The frequency other authors observed is higher, ranging from 52% to 83%[11,13]. Pain management in the present study was higher than described in the literature. In only three episodes (7%) the symptom was not managed. Despite studies showing positive results, failure rate reaches 49%[11,13,14].

Although proportionally the quantity of opioid switching encountered is similar to what other authors observed, while analyzing the cases motived by pain alone, the proportional results found are dissimilar. In the aforementioned studies, only opioids drugs were described excluding adjuvant medications for pain management, which can justify different quantitative findings. Based in the profile analysis of the unit where these data came from[6], the use of common and adjuvant analgesics was higher than other authors described regarding frequency and dose. This difference may be one of the reasons of lower switching due to pain and better pain management in the aftermath.

The participation of the multi-professional team is another unaddressed aspect of pain management in the current article and in the others mentioned. At the unit in study, nurses, licensed practical nurses, psychologists, physiotherapists, social workers, nutritionists and pharmacists, further to volunteers of chaplaincy provide care too. With this, pain can be addressed broadly in all its aspects.

The response of opioid switching motivated by suspicion of drug-related adverse event was poor, only two episodes reported benefits (33%). Other authors also described this conclusion[11]. It can be justified due to the suspicion of drug-related adverse event when in fact the symptom was the result of the basal disease (as delirium, somnolence, nausea etc.).

Although WHO[15] has emphasized the lack of evidences to recommend the elaboration of a protocol addressing the practice of opioid switching, an expert panel suggests reduction from 25% to 50% of equivalent dose of opioid while switching. In cases of uncontrolled pain, a reduction between 5% to 15% is recommended[3].

A multicenter study observed equivalent opioid doses pre and post switching, but considered the initial dose after switching, not evaluating further adjustment[11]. Mercadante et al.[12] noticed the necessity of mean increase of 23% of the initial dose of the new opioid in the first week, remaining unclear whether the initial dose at the moment of switching was equivalent. In the present article, higher final dose was found. However, it was compared the next day with the prescription of the routine which includes occasional adjustments the on-call team has made along the day when switching occurred. It is worth mentioning that there was no report of suspicion of opioid intoxication during the period investigated.

Caution is advised about the increase of the dose observed in the switching in this study. Although collection bias may justify this finding, protocols are unanimous in suggesting a reduction of the equivalent dose. Findings are not sufficient to modify the current guideline.

An evaluation of the analgesic equipotency at the unit after switching to define whether the increase observed was due to the necessary adjustments should be performed and conducted in the subsequent hours the on-call physician switched the medication or if the guidelines were not followed. In case of the first hypothesis, the efficiency of the clinical teamwork must be highlighted with the continuous evaluation of the patient for prompt management of the symptom. On the other hand, if the increase of the equivalent dose of the new drug has been prescribed immediately, the clinical staff should be trained. No suspicion of intoxication should not be reference for failing to investigate the data observed.

At the palliative care unit in study, the patients receive the required pain relief medication for home use as long as it is typically used at the unit. And in this context, it is the main motive of hospitalization. Pain control at home needs to be improved, one of its basic aspects is the access to analgesic medications, specially opioids[16]. Hospitalization, in addition to overloading the health system, is damaging to the quality of life[17]. With low survival expectation, the palliative care team should support the daily fight out the hospital environment and pursue to control the symptoms[18].

The two main limitations of this study were collection of the opioid dose only in the prescription of the following day after the switching and not immediately and the evaluation of the efficacy of the switching restricted to information from the chart and not directly from the patient.

In addition, only outcomes of pain control and suspicion of adverse event were searched. A study with the evaluation of the dose according to the analgesic equipotency immediately before and after switching with monitoring of occasional early adverse event or signs of intoxication is suggested for the unit.

CONCLUSION

Although pain control was higher than described in other articles, the protocols do not corroborate the increase of the equipotent dose of the opioid. Other studies and more surveillance are recommended for the unit.

CONTRIBUTIONS

All the authors contributed for the study conception and/or design, collection, analysis and interpretation of the data, wording, critical review and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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