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Use of off-label drugs and the prevalence of adverse reaction to drugs in the adult intensive care unit of a brazilian public hospital

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Abstract

Objective: To Identify the occurrence of adverse reactions to medications (ADR) in patients using off-label prescriptions admitted in an adult intensive care unit (ICU). **Methods:** Cross-sectional and prospective study evaluated the use of off-label medications and the appearance of ADR in an adult clinical ICU of a Brazilian hospital from March to Aug/2018. The prescriptions were classified as label**,** off-label, and unlicensed, and the NARANJO algorithm assessed ADR occurrence. The suspected cases of ADR were separated into label and off-label. **Results:** The prevalence of off-label use was 73.0%, with 73.9% prescribed after admission to the ICU. Regarding the category of off-label use, 23.6% were due to the volume of the diluent. The predominant drug classification was systemic antimicrobials, accounting for 16.8%. The PHD represented 68.7% of the off-label medicines. Sixty suspected ADR were identified in 26 patients registered with suspected ADRs, from that 85.0% resulted from the use of off-label medications. The most prevalent reactions were classified as probable (81.7%), and diarrhoea was the most frequent symptom. There was a significant association between the use of off-label drugs, PHD prescriptions, and the occurrence of ADR ($p < 0.05$). **Conclusion:** The findings showed that the event of ADR was higher among off-label drugs and PHD prescriptions.

Keywords: Pharmacovigilance; Off-label Drug; Intensive Care.

Uso de medicamentos off-label e a prevalência de reações adversas a medicamentos na unidade de terapia intensiva adulto de um hospital público brasileiro

Resumo

Objetivo: Identificar a ocorrência de reações adversas a medicamentos (RAM) em pacientes em uso de prescrição *off-label* internados em uma unidade de terapia intensiva (UTI) adulto. **Métodos:** Estudo observacional, transversal e prospectivo avaliou o uso de medicamentos *off-label* e o aparecimento de RAM em uma UTI clínica adulto de um hospital brasileiro de março a agosto/2018. As prescrições foram classificadas como *label*, *off-label* e não-licenciadas, e o algoritmo NARANJO avaliou a ocorrência de RAM. Os casos suspeitos de RAM foram separados em *label* e *off-label*. **Resultados**: A prevalência de uso *off-label* foi de 73,0%, sendo 73,9% prescritos após admissão na UTI. Em relação à categoria de uso *off-label*, 23,6% foram devido ao volume do diluente. A classificação de medicamentos predominante foi a de antimicrobianos sistêmicos, com 16,8%. Os Medicamentos Potencialmente Perigosos (MPP) representou 68,7% dos medicamentos *off-label*. Sessenta suspeitas de RAM foram identificadas em 26 pacientes registrados com suspeita de RAM, dos quais 85,0% resultaram do uso de medicamentos *off-label*. As reações mais prevalentes foram classificadas como prováveis (81,7%), sendo a diarréia o sintoma mais frequente. Houve associação significativa entre uso de medicamentos *off-label*, prescrições de MPP e ocorrência de RAM ($p<0,05$). **Conclusão:** Os achados mostraram que o evento de RAM foi maior entre medicamentos *off-label* e prescrições de MPP.

Palavras-chave: Farmacovigilância; Medicamento Off-label; Tratamento intensivo.

Introduction

The off-label use of medicines is an alternative prescription practice different from that of the regulatory agency to register medicines in a country and the package insert description. The use of these drugs implies several safety issues, whether clinical, ethical, or legal. In some countries, the off-label use of medications is widespread, both in the hospitals and outpatient settings[1].

In Brazil, the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária* - ANVISA) is a regulatory agency linked to the Ministry of Health, which has as one of its powers the responsibility for authorizing the registration of medicines and their commercialization in the national territory. The approved use of these drugs is called label[2]. However, ANVISA does not regulate medical practice or how these drugs are prescribed, in addition to not guiding this prescription practice. Nevertheless, this process does not prevent the medication from being prescribed off-label[1,3].

The use of off-label drugs can be guaranteed based on published clinical evidence that supports their use in clinical settings, where the theoretical benefit outweighs the potential risks[1]. As a result, this use must be based on scientific literature, within prescribed standards and norms that are considered reasonable and modern, concerning the relevant bibliography and updated practices of prescription and use of drugs[4].

In the absence of quality evidence for the use of off-label medication and the existence of formal research, such use outside the label is generally not recommended. Failure to approve a drug's use does not indicate that it is ineffective, contraindicated, or disapproved, but it may mean that there is insufficient evidence for approval[5]. The use of off-label drugs is justified, on the other hand, when comparative studies are showing an advantage in efficacy and safety or cost-effectiveness over existing alternatives[6].

Studies indicate a prevalence, in the prescription of off-label medications in the pediatric population and neonatal intensive care units (ICUs), between 23.4% to 45.8%[7-11]. Also, off-label prescription patterns are common in critical adult patients. Studies in North American hospitals show that between 36% to 48% of patients use off-label drugs, the most prevalent being in the classes of gastrointestinal, antibiotic, anti-epileptic, and immunological agents, a practice commonly used in ICUs[1,12].

Due to the severity of the disease and the numerous medications that patients use during hospitalization in the ICU, the concern about the prescribed drugs safety is understandable[13-14].

However, few studies in the scientific literature evaluate the use of off-label drugs with ADR development in critical adult patients[1]. Bearing in mind that the frequency of off-label prescriptions in the ICU is high, and it is a risk factor for ADR, it is necessary to assess this practice's impact on patient safety[15]. Therefore, more studies must be carried out. Thus, this study aimed to determine the prevalence of off-label drugs in adults hospitalized in the ICU and the occurrence of ADR in a population of critically ill patients. Therefore, off-label drugs would be responsible for more adverse drug reactions than label drugs ?

Methods

This is an Cross-sectional and prospective study, carried out in an adult clinical ICU, with eight hospital beds, at the University Hospital, in Fortaleza-Ceará, Brazil, which is integrated with the Brazilian unified health system (*Sistema Único de Saúde* – SUS) from March to August/2018. The study was approved by the Ethics and Research Committee of the Hospital (CAAE: 81729818.5.0000.5045).

The study population consisted of 18 years or older patients admitted to the ICU for 48 hours or more. Age (elderly ≥ 60 years and non-elderly < 60 years), sex, the origin of hospitalization, medical speciality, the reason for admission, comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE II) severity scores and Sequential Organ Failure Assessment (SOFA)[16]. length of stay, hospital outcome and prescribed medications were analyzed. In addition to the pharmacotherapeutic profile, therapeutic indication, dosage, route of administration, diluent, diluent volume, time of administration, and prescription before or after admission to the ICU. This study was approved by the Ethics and Research Committee of the Hospital and followed the rules and guidelines for research established in Resolutions nº466/2012, nº510/2016, and nº580/2018 of the National Health Council/Ministry of Health.

Prescribed drugs were categorized according to the Anatomical Therapeutic Chemical (ATC) classification and described concerning Potentially Hazardous Drugs (PHD)[17-18]. Drug prescriptions were classified as label, off-label and unlicensed.

They were evaluated daily for ADR development and attributed to a causal relationship with drugs, classified into label and off-label. The classification of suspected ADRs was through the Naranjo algorithm for causality: defined or proven, probable, possible, doubtful or conditional[19].

The data were analyzed statistically using Excel® software, version 2016. In investigating the association between the variables, Fisher's exact test was performed, using the statistical program GraphPad Prism, version 8.0d (USA). The level of significance was set at ($p < 0.05$). Study sample calculation was 102, with a confidence interval of 95% and a sampling error of 5%.

Inclusion Criteria

Adult patients (aged ≥ 18 years) using medication in the ICU, accompanied by the intensive care pharmacist/resident pharmacists team, admitted any day of the week, and prescribed at least one drug prescribed.

Exclusion Criteria

Patients with an ICU stay of less than 48 hours and incomplete medical records.

Results

Characterization of the population

The study included 100 patients and 1,31 drug prescriptions. There was a prevalence of males with 51% (n = 51) and elderly with 52% (n = 52), with a mean age of 56.72 years and standard deviation (SD: 17.48) years. From nursing units 48% (n = 48), from the surgical ICU 33% (n = 33) and from external hospital units 19% (n = 19), with the majority of the medical specialty in cardiology 19% (n = 19). The highest three reasons for admission were septic shock 41% (n = 41), sepsis 16% (n = 16) and pneumonia 6% (n = 6). Regarding comorbidities, systemic arterial hypertension 67% (n = 67), diabetes mellitus 45% (n = 45) and renal dysfunction 31% (n = 31) were the most frequent. The assessment of scores for severity/organ dysfunction showed an average of points and standard deviation of 21.21 ± 8.86 (range: 2–46 points) for APACHE II and 6.58 ± 3.73 (range: 1–17 points) for the SOFA. The average length of stay was 14 days, and a majority of the patients had hospital discharge as an outcome 58% (n = 58).

Prevalence of off-label drug use and associated factors

The average prescription analyzed per patient was 13.18 out of a total of 1,318. The mean 34.73 points (SD: 29.60) of the number of off-label medication times per patient represents.

There were 192 different drugs out of a total of 4,041 times they were prescribed. The prescription of drugs with unlicensed use was observed eleven times (0.27%) for the medicine papain, considered a dermatological cream produced in a manipulation laboratory. The use of licensed medication occurred in 99.7% (n = 4,030) of the cases, with 73.0% (n = 2,952) of the prescribed drugs being off-label and 26% (n = 1,049) label. The average number of off-label drugs per patient was 34.73, so that all patients received at least one off-label drug 0.72% (n = 29) of medicines were included in the 'unavailable classification'.

The prescription on the first day of hospitalization revealed that 73.5% (n = 397) of the drugs had already been prescribed off-label before admission to the ICU. After the admission, it was observed that drugs were prescribed off-label in 73.8% (n = 2,555).

Twenty-seven different PHD were prescribed off-label, in which they represented a total of 1,547 of the medications, of these, the amount of off-label was 68.7% (n = 1,064). Fischer's test showed a statistically significant p-value in PHD (p=<0,0001 prevalence ratio 0,8436; IC95%: 0,79–0,89). The five PHD mostly prescribed were: noradrenaline 16.6% (n = 257); potassium chloride 14.0% (n = 218); fentanyl 12.2% (n = 189); midazolam 10.6% (n = 164) and heparin in 7.6% (n = 42).

Fischer's test showed a statistically significant p-value in the elderly and non-elderly category (p = 0.0199; prevalence ratio 0.9294; IC95%: 0.87–0.98), APACHE II (p = 0,0027; prevalence ratio 1.087; IC95%: 1.03–1.14). There was no statistically significant association with the other variables (**Table 1**).

Off-label categories and associated drugs

Among all medications, 23.6% were off-label due to the diluent volume used, which resulted in more concentrated solutions than recommended, and 20.4% due to the therapeutic indication. Some drugs were classified as off-label for more than one reason (the sum of the reasons for off-label use exceeds the absolute value of drugs with off-label use).

Regarding the administration route i n off-label, 92 .27% (n = 717/777) of the drugs were through enteral tubes.

According to the ATC classification, 49 different therapeutic classes were administered, of these, systemic antimicrobials represented 16.7% (n = 489); medication for cardiac therapy, 12.0% (n = 354); psycholeptics 11.6% (n = 343); blood substitutes and perfusion solutions 10.9% (n = 321); and anesthetics 6% (n = 195). These constitute the largest number of off-label prescriptions.

The drugs with the highest prevalence of off-label use in the class of systemic antimicrobials were meropenem with 27.8% (n = 136) and polymyxin B with 19.8% (n = 97), while noradrenaline 6% (n = 257), was the leading representative of the cardiac therapy class.

Noradrenaline also represented the bulk of off-label drug prescribed 8.7% (n = 257), owing to discrepancies in the volume and the type of diluent prescribed; followed by potassium chloride 7.8% (n = 230), due to the route of administration and the volume of the diluent; and fentanyl with 6.4% (n = 189) as a result of the indication and time of administration.

Prevalence of adverse drug reactions associated with off-label use

There were 26 patients with suspected ADR, with a prevalence of 70.4% (n = 18) females (p = 0.0224; prevalence ratio 1.635; IC95%: 1.10–2.36), non-elderly, 53.8% (n = 14) and with a mean age of 58 years old (SD: 17.34) (range: 21–85 years). The assessment of severity/organ dysfunction scores in patients who had ADR showed an average of 22.80 points (SD: 8.08) (range: 10–46 points) for APACHE II and 6.26 points (SD: 3.19) (range: 2–14 points) for the SOFA. Fischer's test showed a statistically significant p-value in the female and male category (p=0.0224; prevalence ratio 1.635; IC95%: 1.10–2.36) (**Table 2**).

Sixty suspected ADRs were identified, of which 85.0% (n = 51) was associated with off-label use, 11.6% (n = 7) with label use, and 3.3% (n = 2) with unavailable classification. These reactions were included in later analyses and attributed to a causal drug dichotomized: label or off-label. As to the classification of NARANJO *et al.*[19] (1981) reactions were classified as probable in 81.7% (n = 49) and possible in 11% (n = 18.3) of patients.

Different PHD were prescribed among suspected ADR drugs (n = 6), with fentanyl being the first 42.8% (n = 6), followed by dexmedetomidine 28.6% (n = 4); midazolam 14.3% (n = 2); methadone 7.1% (n = 1) and heparin 7.1% (n = 1). These drugs represented more than 25% of the total prescribed 28.3% (n = 17), in which approximately 82% were off-label 82.3% (n = 14), and label was only 17.6% (n = 3).

Table 1. Prevalence and gross prevalence ratio of using at least one off-label medication, according to demographic aspects, severity scores (APACHE II and SOFA).

Category	Total = 4.041 N (%)	Off-label (n=2.952) N (%)	Label (n=1.049) N (%)	p[a]	Prevalence ratio	$CI_{95\%}$[b]
Female	2046 (50,63)	1492 (50,54)	537 (51,19)	0,7194	1,013	0,94-1,08
Male	1995 (49,36)	1460 (49,45)	512 (48,80)			
Elderly[c]	2.329 (57,63)	1.735 (58,77)	573 (54,62)	0,0199	0,9294	0,87-0,98
Non-elderly	1.712 (42,36)	1.217 (41,22)	476 (45,37)			
APACHE II ≤ 25[d]	1.630 (40,33)	1.792(41,39)	692 (37,08)	0,0027	1,087	1,03-1,14
APACHE II > 25[d]	2.411 (59,66)	1160 (58,60)	357 (62,91)			
SOFA ≤ 12[e]	3.767 (93,21)	2.740 (92,81)	988 (94,18)	0,135	1,015	0,99-1,03
SOFA > 12[e]	274 (6,78)	212 (7,81)	61 (5,81)			

[a] Fisher's test; p<0,05. [b] CI 95%: confidence interval of 95%. [c] In Brazil, the elderly are individuals aged 60 years or over. [d] *Acute Physiology and Chronic Health Evaluation.* APACHE II's stratification was applied randomly, considering the risk of mortality greater than 50% of mortality for values above 25. [e] *Sequential Organ Failure Assessment.* The SOFA stratification was applied randomly, considering the estimate of organ failure above 50% for values above 12.

Table 2. Comparison of patient and drug characteristics between those with and without adverse drug reactions.

Category	Total (n=100)	No ADR (n=74) N (%)	ADR (n=26) N (%)	p[a]	Prevalence ratio	$CI_{95\%}$[b]
Age	60*	60*	60*	-	-	-
Female	49	31 (41,89)	18 (70,37)	0,0224	1,635	1,10-2,36
Male	51	43 (58,10)	8 (29,62)			
Elderly[c]	52	39 (52,70)	13 (50)	0,8225	1,050	0,82-1,35
Non-elderly	48	35 (42,29)	14 (53,84)			
APACHE II ≤ 25[d]	68	50 (67,56)	(65,38)	>0,9999	0.9677	0,66-1,28
SOFA ≤ 12[e]	93	68 (91,89)	25 (96,15)	0,6729	1,046	0,87-1,16
SOFA > 12[e]	7	6 (8,10)	1 (3,84)			

ADR = Adverse Drug Reaction. *median. [a] Fisher's test; p<0,05. [b] CI 95%: confidence interval of 95%. [c] In Brazil, the elderly are individuals aged 60 years or over. [d] *Acute Physiology and Chronic Health Evaluation.* APACHE II's stratification was applied randomly, considering the risk of mortality greater than 50% of mortality for values above 25. [e] *Sequential Organ Failure Assessment.* The SOFA stratification was applied randomly, considering the estimate of organ failure above 50% for values above 12. [f] PHD, Pot entially Dangerous Drug.

The evaluation of suspected ADR drugs by the ATC classification showed a prevalence of off-label use by the class of systemic antimicrobials in 21% (n = 41.18) and psycholeptics in 15.7% (n = 8), wherein piperacillin + tazobactam and fentanyl stood out.

Regarding the types of suspected ADR that were identified and the frequency of occurrence, diarrhoea was an often outcome with 18.3% (n = 11), and then hypernatremia 11.7% (n = 7) and hypotension 10% (n = 6).

When comparing the drugs received between those patients before and after ADR, patients who had ADR received a more significant number of medications, considered off-label and prescribed as PHD, with a statistically significant p-value (p = 0.0002; prevalence ratio 0.8413; IC95%: 0.76–0.92) (**Table 3**).

Table 3. Comparison of medications received by patients between those with and without an adverse reaction to medications.

Category	Total admission (n=100)	No ADR (n= 74)	RAM (n=26)	p[a]	Prevalence ratio	$CI_{95\%}$[b]
No. of PHD drugs received	1549	914	635	0,565	1,025	0,94-1,12
Nº of drugs off-label	2952	1769	1183			
No of drugs label	1049	719	345	0,0002	0,8413	0,76-0,92
No of drugs PHD and off-label	1088	617	417			

ADR = Adverse Drug Reaction. PHD = Potentially Dangerous Drug [a] Fisher's test; p<0,05. [b] CI 95%: confidence interval of 95%.

Discussion

This study showed a prevalence in the use of off-label medication in 73.05% of prescriptions. The value found was higher, between 36% and 50%, than the use of off-label drugs identified in previous studies with adult patients in the ICU[1,20]. Type characteristics, diluent volume and time of administration of intravenous medications were considered in this study, but they were not in previous ones, which possibly reduced the prevalence of off-label use medications presented by them.

There was a high prevalence of off-label in critical adult patients, with 73.8% of off-label medications prescribed after admission to the ICU. Lat *et al*.[12] (2011) also showed a high prevalence of prescriptions, 89.1%, after admission to ICUs in hospitals in the United States.

The prescription of PHD was associated with greater off-label use of 68.7%. These drugs have a higher risk of causing significant harm to patients if misused. Its use in unregulated conditions tends to have more risks in clinical practice when prescribed off-label[21-23]. However, concerning the clinical severity scores (APACHE II and SOFA), they were not associated with greater off-label use, statistically significant, corroborating the results found in the study by Lat *et al*.[12] (2011), Nevertheless**,** there was a greater risk of mortality in the patients included in this study when considering the APACHE score's stratification. Whereas with SOFA, there was a lower risk or organ failure.

Despite the shortage of evidence supporting off-label medication use Lat *et al*.[12] (2011), prescribing it does not necessarily imply an absence of data. The lack of regulation and scientific evidence suggests a more significant concern with medicines safety, and their high frequency may predispose to an increased risk of adverse reactions.

This paper aimed, above all, to associate the appearance of ADR with the use of off-label medications, which was observed. Moreover, in most registries, the off-label use of medications was associated with suspected ADR cases, 85%, while the minority was of label use. On the other hand, the multicenter study by Smithburger *et al*.[1] (2015) demonstrated 56% of suspected ADR drugs associated with FDA-approved use (label) and 44% were associated with off-label. Although these authors figure, 44%, differs from what was demonstrated in this study, 85%, it is also a significant value. Both results show a high prevalence of off-label use in drugs suspected of ADR, even though it is a single-centre study with differences in the therapeutic arsenal, clinical protocols, and patient profile.

Overall, the prevalence of spontaneous reports of ADR in the study population was 26%, similar to the study by, which found a prevalence of 27.5%[1]. The prevalence of ADR in hospitalized patients ranged from 20% to 23.9%, similar to those found in previous studies[24-25].

ADR's registered notifications mentioned above could explain how the notifications are carried out in hospitals. Voluntary reporting of suspected ADR underestimates the actual rate of adverse reactions and is an underused method. It is necessary to combine passive and active surveillance techniques to prevent and detect ADR.

Studies report low adherence to the spontaneous voluntary notification, evidencing the need for improvements in this area, especially about raising awareness of the importance of spontaneous notification to obtain necessary data for health regulation purposes. Active search strategies improve the detection of suspicious reports of ADR[26-28].

The clinical severity scores (APACHE II and SOFA) in patients who developed ADR indicate that this study population is related to clinically non-severe patients. That is, with less risk of mortality and organ failure.

The five most common classes of drugs involved in developing ADR in this study related to the ATC classification were: antimicrobials for systemic use, psycholeptics, corticosteroids, anaesthetics, alike classes identified in previous investigations[1,26].

The high prevalence of systemic antimicrobials prescribed as off-label and suspected of causing ADR corroborated with a study carried out in the ICUs of North American hospitals[1]. Lat *et al*.[12] (2011) pointed out, as an important reason for the off-label use of antimicrobials, the existence of few drugs approved by the Food and Drug Administration (FDA) for the treatment of severe sepsis, and that antimicrobials represent the mainstay of drug therapy for sepsis, being widely used mainly in critically ill patients. According to Tansarli *et al*.[29] (2012), antibiotics are often prescribed as off-label in adults due to the emergence of antimicrobial resistance to multiple drugs, limiting treatment options for critically ill patients. They are more vulnerable to multidrug-resistant bacteria.

This study detected an association between the use of systemic antimicrobials and diarrhoea's appearance in 18.3%. This ADR is considered typical (≥ 10%). It can easily be found at inserts of antimicrobial drugs.

Furthermore, a strong correlation between the significant number of off-label drugs considered PHD in patients who developed ADR was shown. Therefore, it is noticeable the importance of more studies related to the use of these drugs and the monitoring process, mainly of the PHD, as well as the need for the adoption of preventive measures in the places of health care, on account of the risk of irreversible damage to the patient when misused and cause ADR[18].

According to Lat *et al*.[12] (2011), the frequent use of drugs in an off-label way can discourage well-conducted clinical studies, and the packages insert update by the pharmaceutical industries for economic reasons. Aware of this problem and its risks, the scientific community and health authorities should be concerned. Hence, the present study aimed to guide prescribers to understand better the use of off-label medications in patients admitted to the ICU. The medical team must *acknowledge* that this prescription must be based on studies with strong scientific evidence that supports it.

A limitation of the study concerns the complete data that allow the assessment of causality from the use of the Naranjo algorithm method used to establish cause and effect relationships, the information was not always available in the patients' records in a complete way, making it difficult to adverse reaction classification. Equally important is the result of the spontaneous notification systems of adverse events, mainly characterized by high underreporting. Another limitation is that this is a single-center study carried out over a short period of time, which was only intended to determine the extent of the relationship between off-label drug use and ADRs in critically ill adult patients.

Conclusion

We conclude that the off-label use of medications frequently occurs in the ICU, and the occurrence of ADR was higher in off-label medications. Physicians should be warned that there is a high risk of the patient developing ADR with an increase in the number of drugs received off-label, especially those considered PHD. Patient safety must be prioritized and must be at the forefront of safe medication practices.

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Collaborators

Study design and analysis: Fonteles MM and Moreira LP; Article writing: Moreira LP; Article review: Moreira LP, Peixoto-Junior AA and Francelino EV; Statistical analysis and Discussion: Moreira LP, Perraud EB and Guedes MM.

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Conflict of Interest Statement

The authors declare no conflict of interest, financial or otherwise.

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