Review Article

Drug incompatibility in the ICU: review of implications in nursing practice

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ABSTRACT

This is an integrative review of the literature performed in seven databases, with the aim of analyzing the scientific production on potential drug incompatibilities in ICUs, and mapping the most prevalent incompatible drugs described in the literature. The filters applied were: articles available in full, and publications from 2009 to 2016 in Portuguese, English, and/or Spanish, totaling 11 articles at the end of the selection. From the review, it was observed that the medicines phenytoin and pantoprazole are the main drugs responsible for drug incompatibilities in intensive care units. Blocking of incompatibilities can be achieved through simple measures routinely implemented by the nursing team, such as optimization of drug scheduling, administration of drugs known to be incompatible in separate venous routes, and standardization of drug dilution and administration, focusing mainly on the most prevalent incompatible drugs found in the study.

Descriptors: Nursing Care; Critical Care; Drug Incompatibility; Central Venous Catheters; Administration, Intravenous.

INTRODUCTION

Drug incompatibility results from the simultaneous dilution and/or administration of two or more drugs that interfere with the therapeutic efficacy of the medications and patient safety, visually evidenced by change of solution color, precipitation, or turbidity. This mechanism occurs in vitro, that is, outside the patient's body, which differentiates it from real drug interactions, because these occur in the body[1].

In addition to the presence of incompatibilities between two or more drugs, this event can be observed between drugs and diluents, between drugs and adjuvants, and/or between drugs and the materials of the venous catheters[2].

Such events commonly occur in intensive care settings due to multiple factors, including the large number of drugs prescribed and given daily. Continuous concomitant intermittent administration of medications corroborates the occurrence of drug incompatibilities, especially when care regarding the compatibility and administration scheduling is not considered[1,3-4].

In addition, critically ill patients may present intravenous infusion devices with reduced routes, which lead to concomitant administration of drugs, increasing the risk of incompatibility[1-2]. Y-shaped infusion devices also contribute to incompatibilities, because there is a meeting of the drugs in the final route of infusion[2].

Drug incompatibilities are classified as chemical and physical. The chemical ones occur when there is degradation of more than 10% of molecular alteration, with hydrolysis being the most frequent reaction. This type of reaction is correlated to the temperature and pH of the drug solution. In contrast, physical incompatibilities are evidenced by changes in color and viscosity; precipitation; turbidity of the solution; or release of gases. These reactions can occur immediately after the preparation or later. It is estimated that events such as these are present in 3% to 25% of the treatments administered[2], accounting for 60% of serious problems and adverse events in hospitals[5].

In the intensive care setting, the main route of administration is intravenous[6]. This route offers greater safety and an immediate effect of medications in the body. In this context, the central venous catheter (CVC) becomes the device of preference because of its insertion in deep veins, and for being sutured to the skin, making dislocation difficult. Moreover, the permanence time of the device is greater when compared to peripheral vascular access, which configures its preference in these sectors.

Thus, this study aimed to investigate the most frequent intravenous drug incompatibilities, in order to produce a compilation of evidence that point out the best recommendations to mitigate the potential risks involved in the drug safety process.

Therefore, the purpose of this study was to analyze the scientific production of potential drug incompatibilities in intensive care medicine, and to map the most prevalent incompatible drugs described in the literature.

Studies on the consequences and implications of drug safety in healthcare practice can contribute to improve the quality of nursing care, as well as to reduce the gaps between theoretical precepts and daily clinical practice.

METHODS

This is an integrative review that adopted the PIO strategy, which represents an acronym for Patient, Intervention, and Outcomes. These three elements are fundamental for the formulation of the research question, and for the bibliographic search for evidence, which allows for the definition of information necessary for the resolution of the research clinical question[7].

The integrative review was performed covering the following steps: establishment of guiding

hypotheses or questions; sampling or searching in the literature; categorization of the study; evaluation of the studies included in the review; interpretation of the results; synthesis of the knowledge; or presentation of the review[8].

The guiding question elaborated from the PIO focused on: What are the most frequent intravenous drug incompatibilities described in the literature in the context of intensive therapy?

Subsequently, the survey for articles with the following Descriptors in Health Sciences (Decs) were analyzed: nursing; critical care; central venous catheters; intravenous administration and incompatibility of medications; and Medical Subject Headings (Mesh): nursing; critical care; central venous catheters; and intravenous administration and drug incompatibility.

The selection of articles was carried out by two PhDs in nursing, and two nurses, supported by the guiding question, selected according to the qualifying instrument of scientific productions produced by the authors of the study.

Thus, a survey of scientific publications was made available in the LILACS, SciELO, BDenf, CINAHL, MedLine, PubMed, and SCOPUS databases. The filters used were: articles available in full; and publications from 2009 to 2016 in Portuguese, English and/or Spanish. Inclusion criteria were: observational, descriptive, analytical studies; and those working with human beings in clinical practice, in which the authors are health professionals (physicians, pharmacists, and nurses). Exclusion criteria were: articles that do not treat patients hospitalized for intensive care and duplicates. A total of 1,927 articles were searched, with 11 articles being selected for inclusion in the sample.

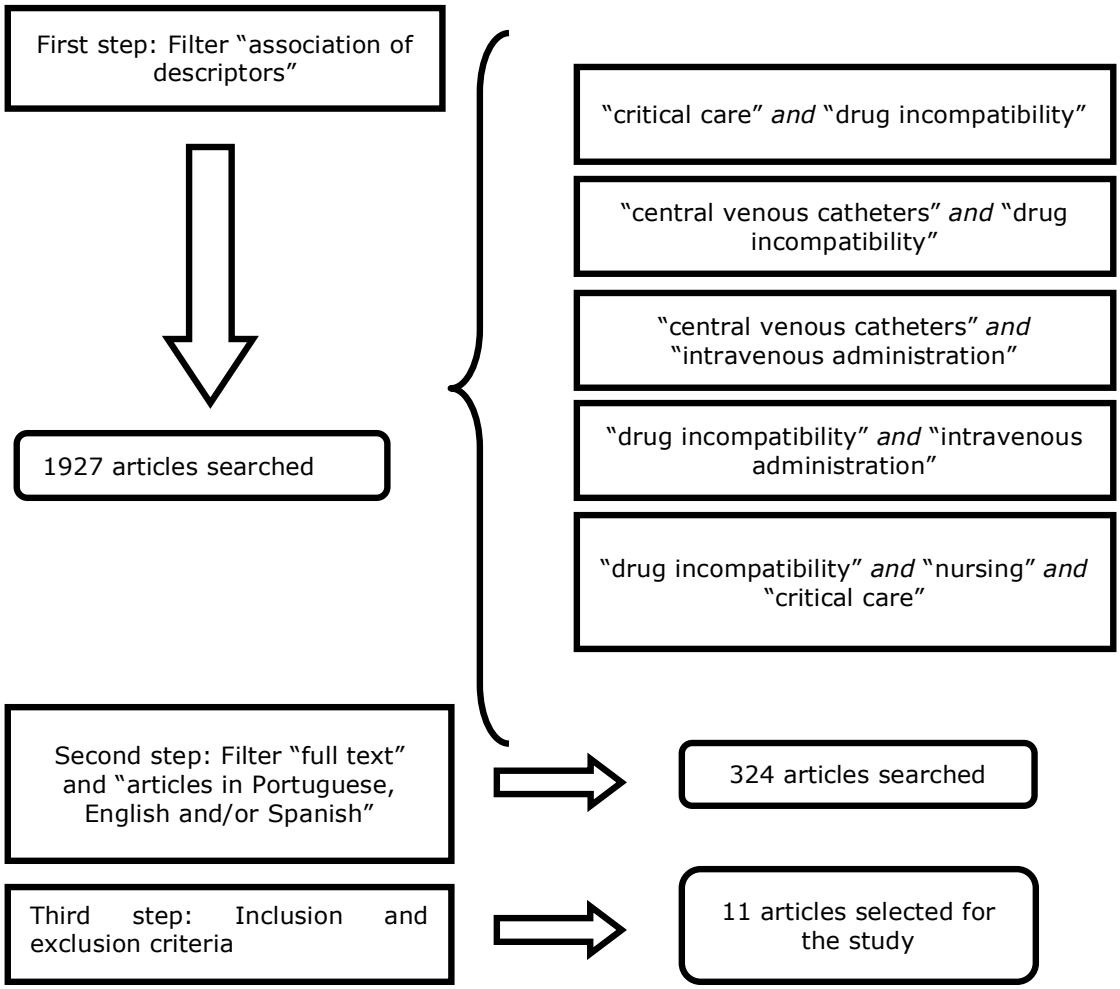

Figure 1: Flow of selection of articles for composing the research.

RESULTS

Of the 1,927 articles surveyed, only 11 met the selection criteria established by this review, being grouped into two categories: predisposing factors for the occurrence of drug incompatibility, and drug incompatibilities in intensive care.

In order to collaborate to optimize the reading of the selected articles, a table was prepared with the main topics related to each article (Table 1).

The productions selected to compose this research sample concentrate on studies produced and published in international journals that are focused on the area of pharmacy. As evidenced in the study methodology, the research found and selected is divided in original studies performed in intensive care units.

With the research progression, it was observed that two main categories emerged in data treatment, which are exemplified in later topics.

Table 1: Synthesis of the articles included in the review.

Authors / Title / Year of publication / Databases / Country of origin	Design	Intervention	Results
Correard F, Savry A, Gauthier-Villano L, Pisano P, Pourroy B / Visual compatibility of defibrotide with selected drugs during simulated Y-site administration / 2014 / CINAHL / United States of America.	The degree of visual compatibility of a defibrotide solution with some types of solutions of 43 drugs in concentrations commonly used in clinical practice was studied.	The following were analyzed: anti-infective drugs; corticosteroids; sedatives; analgesics and cardiovascular agents. The mixtures were observed immediately after and with 60/150/240 minutes. Compatibility was defined as the absence of color change; turbidity; particles; gas generation and precipitation.	Of the 43 solutions tested, 36 were visually compatible with the defibrotide solution over the whole period. Amicacin, furosemide, midazolam, mycophenolate mofetil, nicardipine, tobramycin and vancomycin are incompatible with defibrotide solution.
Kumar A, Mann HJ / Visual compatibility of oritavancin diphosphate with selected coadministered drugs during simulated Y site administration / 2010 / CINAHL / United States of America.	The visual compatibility of oritavancin with various drugs commonly administered to patients in intensive care settings was studied.	The solutions were observed for a period of four hours at room temperature. Compatibility was defined as the absence of any color change, fibers, particles or precipitate.	Of the 37 drugs tested, 23 were visually compatible with the three concentrations of oritavancin during the four-hour study period. Drugs formulated at a basic or neutral pH were more likely to be incompatible with oritavancin.
Vijayakumar A, Sharon EV, Teena J, Nobil S, Nazeer I / A clinical study on drug related problems associated with intravenous drug administration / 2014 / PubMed / India.	A prospective observational study, conducted for a period of four months. Patients receiving more than two intravenous medications were included in the study.	The objectives were to evaluate the problems related to the administration of intravenous drugs and to develop strategies to reduce and prevent the occurrence of errors during administration.	Of the 110 patients studied, 80 (72.72%) reported problems related to medications, with 61 (55.4%) problems being observed in patients receiving intravenous drugs through the peripheral line. **Incompatibilities** (40.9%) were the most obvious problem, followed by administration errors (10.9%) and dilution errors (8%).
Westbrook J, Rob M, Woods A, Parry D / Errors in the administration of intravenous medications in hospital and the role of correct procedures and nurse experience / 2011 / MedLine / England.	A prospective observational study that analyzed the preparation and administration of 568 intravenous medications by 107 nurses in two teaching hospitals.	The objectives were to measure the frequency, type, and severity of errors of intravenous administration in hospitals, and the associations between procedural failures and clinical intravenous errors. The errors were identified and classified by severity.	Of 568 intravenous administrations, 69.7% presented at least one error, with 25.5% being severe. Four types of error (erroneous intravenous rate, mixture, volume, and **drug incompatibility**) were responsible for 91.7%. Error and severity rates decreased with clinical experience. Each year of professional experience reduced risk by 10.9%. **Bolus administration was associated with an increased risk of error by 312%.**
Bertsche T, Münk L, Mayer Y, Stahl R, Hoppe-Tichy T, Encke J, Haefeli WE / One-year follow-up on procedure to prevent IV drug incompatibilities in an intensive care unit / 2009 / MedLine / United States of America.	Validation study of a standard operating procedure (SOP) aiming at reducing drug incompatibilities.	Drug administration to 53 patients in intensive care was evaluated with the aim of mitigation of drug incompatibilities through a SOP.	Of the 2,014 pairs of drugs infused simultaneously across all lumens of available catheters, 24 pairs were incompatible. **The effect of SOP implementation indicated that its institution, followed by a regular meeting of the multiprofessional team, improved the quality of the infusional therapy.** This would be, according to the study, a practical and appropriate method to avoid errors in the administration of medicines.

Authors / Title / Year of publication / Databases / Country of origin	Design	Intervention	Results
Bertsche T, Veith C, Stahl A, Hoppe-Tichy T, Meyer FJ, Katus HA, Haefeli WE / A purging procedure for pantoprazole and 4-lumen catheters to prevent IV drug incompatibilities / 2010 / MedLine / Germany.	Interventional, prospective study. Performed in a cardiovascular intensive care unit, where standard operating protocols on drug compatibility were used.	The objective was to evaluate the number of patients with incompatibilities before and after the implementation of improvement measures to avoid incompatibilities, which consisted of: instruction about pantoprazole and the recommendation to use 4-lumen catheters in replacement of 3-lumen ones, increasing the number of infusion lines available.	In an intensive care setting with good compliance with the standard operating procedure, the incompatibility rate decreases relative to non-compliant environments, while the use of 4-lumen catheters instead of 3-lumen catheters did not achieve the expected benefit in pairs of incompatible drugs.
Cabezas CL, Guerrero L, Molas G, Soy D / Physicochemical compatibility of high concentration drugs usually Y-site administered in intensive care units / 2014 / SCOPUS / England.	Experimental study. The drug incompatibilities were studied, and defined by the presence of turbidity, precipitation, or color change.	Study demonstrated the physical-chemical compatibility in Y of: dopamine or dobutamine-methadone in glucose 5% and saline solution; dobutamine-midazolam in 5% dextrose; methadone-midazolam in 5% dextrose and saline solution; and methadone-esomeprazole in physiological solution.	The results demonstrated the incompatibility of: dobutamine with furosemide in saline solution; and midazolam with esomeprazole in saline solution.
Foinard A, Décaudin B, Barthélémy C, Debaene B, Odou P / The impact of multilumen infusion devices on the occurrence of known physical drug incompatibility: a controlled in vitro study / 2013 / SCOPUS / United States of America.	Experimental study. Three drugs were studied: furosemide; midazolam; and saline solution at different concentrations and infusion rates in various intravenous devices.	Physical incompatibility was evaluated through two tests: visual inspection and visible particle counting test according to the European Pharmacopoeia.	The characteristics of the infusion device seem to have an impact on the physical compatibility of the two drugs. Under specific conditions, the multiple-lumen infusion access device prevented the incompatibility between furosemide and midazolam.
Delaloye VH, Gryllaki MB, Voirol P, Gattlen L, Pannatier A / In vitro compatibility of various cardioactive drugs during simulated Y-site administration / 2013 / SCOPUS / England.	Experimental study. The drugs were diluted in the usual way performed in intensive care units.	Compatibility was checked by visual inspection and by chemical assays, and simulated in in vitro Y administration. The solutions were considered compatible in the absence of any visual change, and in any significant variation in pH value and drug concentration at each point in the study.	When combined, the cardioactive amines were stable over 24 hours, provided they were protected from light.
Marsilio NR, Silva D, Bueno D / Incompatibilidades medicamentosas em centro de tratamento intensivo adulto de um hospital universitário / 2016 / SCOPUS – SCIELO / Brazil.	A prospective, quantitative, cross-sectional study was carried out from July to September, 2015. The probable incompatibilities were identified based on the analysis of the patients' prescriptions available in the hospital's online system.	A pharmaceutical intervention was performed using the guidelines for the preparation and administration of incompatible drugs. Compliance to these guidelines was later evaluated by the nursing team. On hundred prescriptions were analyzed.	Two hundred seventy-one drug incompatibilities were found, with an average of 4 incompatibilities per prescription. The most common were: midazolam-hydrocortisone (8.9%), cefepime-midazolam (5.2%) and hydrocortisone-vancomycin (5.2%). Most of them occurred when one drug was administered continuously and another intermittently (50%).
Fang BX, Li P, Shi XY, Chen FC, Wang LH / Incompatibilities of lornoxicam with 4 antiemetic medications in polyolefin bags during simulated intravenous administration / 2016 / PubMed / United States of America.	Experimental study. The compatibility and stability of solutions containing lornoxicam with antiemetic agents in combination for patient-controlled analgesia, usually performed in the postoperative period, were evaluated.	Mixtures of analgesics and antiemetics with lornoxicam were visually inspected for precipitation, turbidity, and discoloration at each sampling interval; if evident, the incompatibility between the medicinal products was shown.	After storage for 4 to 48 h, the presence of a slight precipitate was observed in all combinations. The results indicate that combinations of lornoxicam with droperidol, ondansetron, granisetron, or tropisetron in infusion solution during simulated intravenous administration were incompatible.

Drug incompatibilities in intensive care settings

In this category we selected the main drug incompatibilities described in the current literature; all those described in Table 2 have the same chemical nature[9].

Table 2: Main drug incompatibilities described in the searched literature[10-14].

Basic drug	Secondary drug for incompatibility	Basic drug	Secondary drug for incompatibility
Phenytoin	Amicacin	Pantoprazole	Amicacin
	Calcium gluconate		Phenytoin
	Acyclovir		Calcium Gluconate
	Ciprofloxacin		Ciprofloxacin
	Clindamycin		Clindamycin
	Dexamethasone		Dexamethasone
	Furosemide		Hydrocortisone
	Hydrocortisone		Mannitol
	Mannitol		Metoclopramide
	Metoclopramide		Vancomycin
	Pantoprazole		Furosemide
	Sodium bicarbonate		Methadone
	Vancomycin		
	Potassium chloride		
	Ranitidine		
	Fentanyl		
	Midazolam		
	Noradrenaline		
Azithromycin	Ciprofloxacin	Ciprofloxacin	
	Clindamycin		
	Amicacin		
	Furosemide		
	Potassium chloride		
Acyclovir	Ciprofloxacin	Furosemide	Ciprofloxacin
	Pantoprazole		Azithromycin
	Phenytoin		Phenytoin
			Pantoprazole
			Vancomycin
			Dobutamine
			Midazolam
Midazolam	Hydrocortisone	Hydrocortisone	Midazolam
	Cefepime		Vancomycin
	Omeprazole		Calcium chloride
	Phenytoin		Vitamin B1
	Defibrotide		Sulfamethoxazole-trimethoprim
	Dopamine		
	Dobutamine		
	Esomeprazole		
Defibrotide	Amicacin	Lornoxicam	Ondansetron
	Furosemide		Droperidol
	Midazolam		Granisetron
	Mycophenolate mofetil		Tropisetron
	Nicardipine		
	Tobramycin		
	Vancomycin		
	Furosemide		

The most frequently mentioned drug incompatibilities in the literature are related to the medicines

phenytoin and pantoprazole. These drugs have a differentiated indication in intensive care centers.

Phenytoin, as an anticonvulsant drug, has a restricted indication for patients who present with some neuropsychic disorder. Pantoprazole, as a proton-pump inhibitor drug[15] and, therefore, providing gastric protection, is indicated for all patients admitted to intensive care centers as a form of protection against stress-induced peptic ulcers.

Factors predisposing the occurrence of drug incompatibility

In the survey carried out in this research, the factors that potentiate the appearance of drug incompatibilities in intensive therapies were included. Corroborating with the literature, this review provided the grouping of the most common causes of drug incompatibility.

One finding discusses bolus drug administration compared to continuous administration, highlighting that there is a 312% increased risk of drug incompatibility on bolus administration[16]. Another important factor that contributes to the occurrence of drug incompatibilities is the reduced number of venous lines for the administration of multiple drugs[17].

In addition, it is mentioned that there is no clinical reasoning for the best indication of the number of lumens individualized to each patient, so that in some cases a number of medications is far higher than the capacity of administration by the catheter is administered, to the detriment of another in where there is a higher number of venous routes for the administration of reduced numbers of medications[10-11]. Another study deals with the occurrence of drug incompatibilities due to the material with which the catheter is made, interacting with the drug and leading to possible incompatibilities[10].

DISCUSSION

Incompatibility is characterized as an error associated with the use of medication, an event that presents a risk with the possibility of causing harm to the patient hospitalized in the intensive care unit, because it compromises the efficacy of the therapy, interfering negatively in drug safety.

Thus, the importance of approaching this issue with the nursing care in intensive care units is highlighted. Drug incompatibilities are directly related to the preparation and administration of medications, with the procedures being mainly performed by nursing professionals and, therefore, knowledge about the best way to do it should be reiterated.

The categorization of the studies was necessary for a better analysis of the data. The first category entitled “drug incompatibilities in intensive care settings” showed the main incompatible drugs according to the literature, with emphasis on phenytoin and pantoprazole.

Phenytoin is an anticonvulsant drug, indicated for the treatment of epilepsy. It has a precise use for intensive care patients regarding the treatment of seizures, but it should be administered in isolation, because its potential to lead to incompatibility is high. Eighteen drugs stood out that, if administered simultaneously with phenytoin in the same venous route, will generate a drug incompatibility reaction.

Medications listed as incompatible with phenytoin include the class of antibiotics, diuretics, anti-emetics, gastric protectors, sedatives, and vasoactive amines[12-13].

However, this drug is not indicated for routine use in intensive care units, in contrast to pantoprazole. Patients admitted to the ICU are constantly under organic stress, which may lead to the onset of stress-induced gastric ulcers. Thus, the administration of drugs that prevent such pathology is routinized and, therefore, there is an indication for the daily administration of proton-pump inhibitors such as omeprazole and/or pantoprazole[15].

It is empirically observed that nursing scheduling for these drugs, including omeprazole and pantoprazole, occurs at six o'clock, minimizing possible interactions with feeding, called drug-nutrient interaction.

Scheduling this medication for six o'clock can compromise the identification of possible reactions due to an incompatibility because the transfer of care/shift changes occur around this time. Such a situation may imply failure by the team administering the drug to observe chemical reactions arising from incompatibilities, and the staff working on the next shift will rarely associate the observed reactions with an incompatibility reaction, adding the signs presented to clinical findings.

Nevertheless, it is also observed that nursing scheduling in intensive care units has followed a routine pattern, in which a large cluster of medications is scheduled for the same time, impairing drug safety, because the risk for drug incompatibilities increases proportionally to the number of drugs prescribed and administered together[1-2].

Thus, observation becomes nursing care, in order that nursing schedules minimize such unwanted events. At present, there is a tendency to avoid standardized systems of scheduling, in which there is a fixed timetable, in order to optimize the routine in the intensive care unit. In this way, the appearance of incompatibilities due to concomitant administration of several drugs at the same time is facilitated[4].

Pantoprazole was also presented as a drug prone to the incompatibility process, according to the literature, being evidenced in 12 drug incompatibilities. This fact becomes important when we observe that such incompatibilities reduce the therapeutic efficacy of critically ill patients, who depend primarily on the effect of the drugs so that their clinical condition can be reversed and restored. The reduction in the effect of pantoprazole can cause perforating gastric ulcer, leading to high gastrointestinal bleeding, reduced hematocrit and circulating red blood cells, making the weaning from mechanical ventilation difficult. Therefore, it is crucial that the knowledge about the incompatibilities comprise daily nursing care.

Among the drugs that are incompatible with pantoprazole, we can list the class of diuretics, antibiotics, corticoids, antiemetics, and electrolyte solutions. Such drugs are extremely important in intensive care units and need to have their therapeutic potential within the normal parameters in order to produce the desired efficacy.

As a way to mitigate the incompatibilities found, the nursing staff has the responsibility of scheduling medication times based on their peculiarities, focusing on the reactions of drug incompatibilities. The

development and implementation of standard operating procedures has also proved to be an effective strategy for minimizing the incompatibilities found[17].

In the second category that emerged in the study, entitled "Factors predisposing to the occurrence of drug incompatibility," the importance of the best choice of venous access, and of the knowledge regarding the administration of drugs to block drug incompatibilities, is demonstrated. The critical patient, due to the risk of hemodynamic instability, clinical severity, and the use of irritant medications, is strongly indicated for the insertion of central venous catheters. These catheters have a precise indication in the context of intensive care, but may present undesired situations arising from their use.

A study[11] has shown that multiple-lumen infusion devices directly influence drug incompatibility by blocking midazolam and furosemide[11]. Therefore, it is important that an evaluation of the health status of each patient admitted to the intensive care unit is performed, as well as the observation of the number of drugs prescribed and their particularities, in order to provide a better choice for infusion device and amount of lumens, providing an increase in drug safety, because this blocks the risk of incompatibilities.

Simultaneously, it is important to observe the medications that are administered continuously to patients so that there is no incompatibility between them in the deep venous access routes. In situations where the number of prescribed drugs is greater than the number of administration routes, one can observe the use of "Y" or three-way devices. These devices allow the infusion of more than one drug through the same route of central venous access, but these drugs are infused concomitantly. Attention must be paid to the compatibility among drugs that are infused simultaneously, because this form of infusion may lead to drug incompatibilities[2].

As the final product of a drug incompatibility, we can observe the formation of precipitates in the infusion set, dilution vessel, or venous catheter pathway, change of solution color, turbidity, and gas formation. It should be emphasized that such reactions may decrease the therapeutic efficacy and interfere negatively in the treatment provided to patients in the intensive care unit.

CONCLUSION

Drug incompatibility is an event that, despite the dissemination of knowledge in the field of pharmacology, still requires an in-depth study, as evidenced in this research. Of the articles, in 11 that were selected, nursing productions were not highlighted, with the focus only on the area of pharmacovigilance.

Drug incompatibilities with medications routinely used in intensive care units, such as gastric protectors (pantoprazole), anticonvulsants (phenytoin), and antibiotics, occur more commonly. However, there is a large gap in terms of studies seeking to investigate how nursing staff could minimize such risks to patients.

Blocking of incompatibilities can be accomplished through simple measures routinely implemented by the nursing team, such as a schedule based on the physicochemical characteristics of the medications, adequate drug distribution in the central venous catheter, the selection of central venous access for each

drug, and the standardization of dilution and form of drug infusion.

Thus, investments in the area of healthcare professionals' training are essential, so that these professionals are able to identify medicines that influence the drug incompatibility process, and intervene in their mitigation.

We hope that this study may contribute to the clarification of the occurrence of drug incompatibilities and their peculiarities in order to help the nursing team to minimize such events in intensive care units.

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