ABSTRACT
The goals of the research were to assess the pharmaceutical form of medicinal preparations administered through catheters and identify the profile of errors that occur during their preparation. This is a cross-sectional study of an observational nature, conducted in an intensive care unit with a sample of 350 doses of medication prepared by 56 nursing technicians. Data collection occurred in March 2010. The results showed that 92% of the drugs were in the solid form. The errors were divided into two categories for liquid forms: dilution and mixing, and grinding was added as an error possibility for a solid form. The error rates were greater than 40% in all categories. The conclusions are that grinding can compromise the therapeutic effect of coated controlled-release tablets, not diluting syrups may contribute to the obstruction of catheters, and mixing medication during grinding may increase the risk of drug interactions.

DESCRIPTORS
Intensive Care Units
Medication errors
Safety measures
Nursing

RESUMO
Esta pesquisa teve como objetivo identificar a forma farmacêutica dos medicamentos preparados para serem administrados por cateteres e o perfil dos erros cometidos durante o preparo. Trata-se de estudo epidemiológico transversal, de natureza observacional, conduzido em uma unidade de terapia intensiva com amostra de 350 doses de medicamentos preparados por 56 técnicos de enfermagem. A coleta de dados ocorreu no mês de março de 2010. Os resultados mostram que 92% dos medicamentos eram sólidos. Os erros foram agrupados nas categorias diluição e mistura para formas líquidas, acrescidos de trituração para sólidos. As taxas de erro foram superiores a 40% em todas as categorias. Conclui-se que: a trituração indevida pode comprometer o resultado terapêutico em comprimidos revestidos e de liberação controlada; não diluir xaropes pode contribuir para a obstrução de cateteres; misturar medicações ao triturá-las pode aumentar o risco de interações farmacêuticas.

DESCRIPTORES
Unidades de Terapia Intensiva
Erros de medicación
Medidas de seguridad
Cuidados de enfermagem

RESUMEN
Se apuntó a identificar la forma farmacéutica de los medicamentos preparados para ser administrados vía catéter y el perfil de errores cometidos durante la preparación. Estudio epidemiológico transversal, de tipo observacional, desarrollado en unidad de terapia intensiva sobre muestra de 350 dosis de medicamentos preparados por 56 técnicos de enfermería. Datos recolectados en marzo de 2010. Los resultados expresan que 92% de los medicamentos eran sóli- dos. Los errores se agruparon en las categorías: dilución y mezcla para formas líquidas, agregados de trituración para sólidos. Las tasas de errores superaron el 40% en todas las categorías. Se concluye en que: la trituración inapropiada pudo comprometer el resultado terapéutico con comprimi- dos revestidos y de liberación controlada; no diluir jarabes pudo haber ayudado a obstruir catéteres, y mezclar medicamen- tos al triturarlos puede aumentar el riesgo de interacciones medicamentosas.
INTRODUCTION

Patients in Intensive Care Units (ICU) frequently receive medicine through catheters. Most solid drugs prescribed for administration through catheters need to be ground and diluted. When solid controlled-release drugs with a coating or in gelatin capsules are ground, the pharmacological properties of the drug may not be maintained. In such cases, an error is considered to have occurred.

The National Health Surveillance Agency (ANVISA) adopted the medication error concept of the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), which is defined as:

- any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.

Medication errors are frequent in hospitals and are classified as preventable adverse events, which may or may not result in patient harm. On average, a hospitalized patient is a victim of at least one medication error per day. For example, when a nursing professional opens controlled-release capsules, the active ingredient of the medication is immediately released, whereas the pharmaceutical formulation was developed to release the active ingredient over time.

Recently, specific orientations focused on the particularities of administering medications through catheters have occurred in hospitals, instead of focusing on other relevant aspects such as the preparation of medications prior to their administration.

Several studies examining errors when giving medications through catheters have been published, considering drug interactions with enteral nutrition and issues related to maintaining catheter patency. New approaches are needed to investigate the potential errors in medication preparation, centering on three aspects: the grinding, diluting and mixing of a medication.

To prepare solid drugs, it is important to know how to grind, when not to grind, what solvent to use, what volume to use, and the impossibility of grinding certain drugs together. If the medication is a liquid, it is necessary to know what diluent to use, how much solvent to use, and whether to mix different liquid drugs in the same syringe.

Physical-chemical and physiological factors, such as the degree of compression when grinding and the hydro- or liposolubility of the active ingredient, should be addressed when studying the potential errors made during the preparation, including grinding, mixing and diluting. Preparing a medication without analyzing the impact of these variables can cause therapeutic errors and potentially harm patients.

In this study, the focus was only medication administration through catheters in order to assess the pharmaceutical formulation of the drugs prepared for administration through catheters and identify the profile of errors committed during their preparation.

To reduce medication preparation errors and develop cooperative strategies regarding safe preparation practices for medications to be administered through catheters, several variables need to be investigated and evaluated to determine how they influence the safe use of medication and how this process can be improved.

METHODS

This study was a cross-sectional observational nature without interventions. It was undertaken in the ICU of a large private hospital in Rio de Janeiro. The observations concerned three possible categories of errors that are committed during the preparation of a medication: errors made during grinding, mixing or diluting medications.

In the grinding category, improper or insufficient grinding was possible. Improper grinding involves the grinding of gelatin capsules and coated controlled-release pills. Grinding was considered insufficient when simple pills were not ground into a fine powder. In the mixing category, mixing two or more drugs in the grinding mortar or two or more liquid drugs in the same syringe was considered an error. In the dilution category, not using sterile water for dilution, using less than 20 ml for dilution or not diluting liquid drugs were considered errors.

On average, a hospitalized patient is a victim of at least one medication error per day.

All data collection was based on a systemized observation checklist. The prepared dose was considered as the error analysis unit. For each dose, only two mutually exclusive categories were possible: correct or incorrect preparation. For each dose, however, various types of errors could occur.

The number of doses administered per month in the unit was used to calculate the appropriate sample size for observed doses. The sampling calculation formula for cross-sectional studies of finite populations was used, with a 95% confidence level, \( \alpha = 0.05 \) and a critical value of 1.96, considering that 20% of professionals commit some type of error, according to a preliminary survey of the Nursing Service. To account for potential losses, 5% was added, and the number of doses was rounded off to 350, thus guaranteeing the appropriate number of doses for the sample size.

Fifty-six nursing technicians who met with the selection criteria were observed. The criteria were as follows: worked at the institution for longer than six months; signed the Informed Consent Form; prepare medications as a routine task; and had at least one year of experience in intensive care. To reach 350 doses, each ICU employee...
was observed preparing at least six doses. The observations took place in March 2010, after receiving approval from the Research Ethics Committee at Universidade do Estado do Rio de Janeiro under protocol 004/2010.

The study was based on the error classification used by National Coordinating Council for Medication Error Reporting Prevention (NCC MERP)\(^2\), a North American entity created in 1995 to maximize rational and safe medication use. The aims of this entity are to encourage reporting of medication errors and discuss strategies to prevent their occurrence in all phases of the medication process.

These errors are characterized according to their potential harm to the patient. In this study, interest was focused on type B errors, which according to the NCC MERP, do not affect the patient. An example is the preparation of clarithromycin using distilled water (reconstitution error). The error is detected, the dose is discarded, and a new dose is prepared using the correct solution.

In this study, because nursing professionals were monitored directly to observe whether an error had occurred, the choice was made to intervene whenever a type B error occurred. In these cases, the observed error was recorded, and the researcher intervened by explaining the mistake in preparation and asking the technician to perform the procedure correctly.

The data were organized in an Excel database, and statistical analysis was conducted using central trend and dispersion measures. The Junior Statistics Incubator at Universidade do Estado do Rio de Janeiro also provided support.

**RESULTS**

*Pharmaceutical form of drugs prepared*

The population consisted of 39 patients hospitalized in the ICU. The patients were predominantly women (51.28%) and the elderly (89.74%) with a median age of 78 years and a median hospitalization time of 24 days. Most patients (76.92%) were not sedated at the time of data collection and were not under any fluid restrictions (82.05%).

The observations consisted of 350 doses of 52 different drugs. Solid drugs were 92% of the doses (n=322), predominantly simple pills (79.19%), hard gelatin capsules, coated pills, and controlled-release drugs in addition to one powder drug (acetylcysteine), as shown in Figure 1.

The highest number of liquid doses were in the form of syrup (57%), followed by solutions (32%) and emulsions (11%). As for the medication groups, drugs affecting the cardiovascular and kidney systems (CVKS) were predominant. The most commonly administered individual drugs were as follows: amiodarone hydrochloride (n=39), captopril (n=33), amloidipine (n=30), and acetylcysteine (n=23).

*Profile of medication preparation errors*

The dose preparation error rate was 67.71%, considering both solid and liquid drugs. The error distributions among the categories grinding, mixing and diluting associated with the pharmaceutical form are shown in Table 1. Please note that no dilution errors for the solid drugs or mixing errors for the liquid medications are shown.

<table>
<thead>
<tr>
<th>Table 1 – Error distribution per category and pharmaceutical form at in the Intensive Care Unit of a private hospital - Rio de Janeiro, 2010</th>
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<tr>
<td><strong>Forma farmacêutica</strong></td>
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<tr>
<td>solid (n=322)</td>
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<td>liquid (n=28)</td>
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* for each prepared dose, errors could occur in more than one category.

** does not apply to the liquid pharmaceutical form.
For the solid drugs, the error rate in the grinding category was 45.47%, distributed between insufficient (39.87%) and improper (5.6%) grinding, and the error rate in the mixing category was 39.25%. Among liquid pharmaceutical formulas, only one error type was found, an error in dilution (67.85%). Among solid drugs, the prevailing error was in grinding, including improper grinding of hard gelatin capsules (19.35%) and of all controlled-release and coated pills. The insufficient grinding errors (not producing a fine powder) involved folic acid (73.33%), amiodarone hydrochloride (58.97%) and bromopride (50.00%). The error of mixing a drug with other drugs mainly involved bromopride (66.66%), amiodoine besylate (53.33%), bamifylline (43.47%), folic acid (40.00%) and acetylsalicylic acid (33.33%). For the liquid drugs, the only error category was lack of dilution, which occurred for 67.85% of the doses. The error rates for solid drug preparation are shown in Figure 2.

\[Error rate in solid medication preparation. UTI 2010\]

\[Figure 2 – Error rate in solid medication preparation - (n=322)\]

**DISCUSSION**

**Pharmaceutical form of the drugs**

Fifty-two different drugs were found to be administered through catheters, 47 of which were solid (92%), consistent with other studies and demonstrating the clear predominance of solid forms in prescribers’ indications\(^6\). In this study, simple pills represented 72.86% of the drugs, which is similar to the value of 71.90% found in another study\(^7\). These data indicate that prescribers frequently use the solid oral pharmaceutical form, mainly simple pills, without complying with the recommendation to replace a solid formulation with a liquid formulation if possible\(^8\).

Liquid oral pharmaceutical formulations are known to be most appropriate for administration through catheters. Therefore, research on whether this alternative is available for the prescribed solid drugs is needed.

The prevalent drugs in this study were amiodarone hydrochloride, captopril, amiodopine besylate, acetylcysteine, bamifylline, folic acid, acetylsalicylic acid, bromopride, potassium chloride syrup and rivastigmine hydrochloride. Only one drug, KCl syrup, was prescribed in the liquid form. A liquid oral alternative was available for 15 of the 47 oral solid drugs, including the following: solutions in the form of drops for ascorbic acid, clonazepam and paracetamol; syrups for acetylcysteine and ferrous sulfate; and solutions for folic acid, bromopride, rivastigmine hydrochloride, phenytoin, risperidone and ritonavir. Amiodarone, nitrofurantoin and zidovudine are available as solutions, and digoxin is available as an elixir.

Solid formulations need to be ground prior to administration through catheters, but the ground drug may adhere to the catheter wall. When this occurs, the amount of active substance reaching the blood compartment may be sub-therapeutic\(^9\).

Another possible consequence of grinding is that it may cause drug modifications through different types of interactions, which can lead to a change in the bioavailability of the drug’s active ingredient. The bioavailability percentage of a drug depends on the speed and magnitude of its absorption and on the intensity of its pre-systemic extraction, that is, its extraction before it reaches the circulation.

When a medication is consumed, it passes through the portal system and consequently into the liver, where it will...
suffer the effect of the first liver passage before reaching systemic circulation. The quantity of absorbed drug that reaches the circulation also depends on what fraction of the drug is metabolized by the liver. One example that demonstrates the effect of the first passage of a drug through the liver is propanolol because the standard intravenous dose is 5 mg, whereas the oral dose needed to reach a similar blood concentration is between 40 and 80 mg; therefore, the dose needs to be adjusted depending on the route of the administration.

As for liquid pharmaceutical formulations, the results indicate that despite recommendations, viscous and hyperosmolar medicines such as syrups and emulsions are still prescribed for administration through catheters, the predominant route examined in this study.

It should be emphasized that although the liquid forms are the most appropriate for administration through catheters, limitations exist that are related to viscosity, osmolarity (many liquid preparations are hyperosmolar) and the excipients present in the formulations, mainly sorbitol, which increase the risk of gastrointestinal tract intolerance. Sorbitol is an excipient used to improve the taste and stability of preparations and is present in some solutions and syrups. Depending on the preparation for which it is used, it can cause gastrointestinal disturbances, which are also observed with hyperosmolar drugs. At doses of less than 7.5 g/day, sorbitol has a laxative effect; between 7.5 and 10.0 g/day, it can cause aerophagia and abdominal distension; and at doses of approximately 20 g/day, abdominal spasms occur.

Therefore, the total daily quantity of drugs containing sorbitol that the patient is receiving should be assessed, and in the case of diarrhea, another pharmaceutical form or other drug that is therapeutically equivalent needs to be considered.

High viscosity can hamper the drug’s passage through the catheter, which is why diluting a drug in 15 to 20 ml of water is recommended. When preparing a hypertonic medication, nursing personnel need to know that these drugs may not be well tolerated when administered through post-pyloric catheters. One alternative is to dilute the medication in more water if no other pharmaceutical formulation is available. Drugs with an osmolarity of 1,000 mOsm/kg or more need to be diluted in 100 ml of water. Examples of drugs with an osmolarity of 300 mOsm/kg or more are dexamethasone solution (1 mg/ml), liquid ferrous sulfate (60 mg/ml), lactulose syrup (0.67 g/ml), and liquid potassium chloride (10%).

Some solid drugs found in this study of catheter-administered drugs were inappropriate for catheter use, such as folic acid, calcium carbonate, rivastigmine hydrochloride, flunarizine dihydrochloride, trimetazidine dihydrochloride MR, galantamine hydrobromide, nimodipine, pentoxifylline, ritonavir and ferrous sulfate.

Medication grinding errors

Errors with the potential for patient harm were registered for more than half (62.2%) of the 350 doses of 52 drugs but only concerned the solid pharmaceutical formulations.

The proportion of grinding errors was 45.47%, including insufficient and improper grinding. Insufficient grinding, i.e., not grinding the solid drug into a fine powder, occurred in 128 simple pill doses. The most affected drugs were folic acid (73.33%), amiodarone hydrochloride (58.97%), amiodipine besylate (43.33%), captopril (39.39%) and acetylsalicylic acid (8.33%). All of these drugs can be ground without altering the active ingredient or the therapeutic response.

The consequence of insufficient grinding is that drug particles can obstruct thin-caliber tubes by combining with the diet in the catheter lumen, which can affect the catheter, the patient, the drug and the nursing personnel. This may be the most studied aspect of medication errors to date. Washing catheters before and after administering a medication is known to be an effective practice to prevent obstruction.

Hard gelatin capsules, coated pills and prolonged-release drugs were improperly ground. The coated drugs that were erroneously ground were hydralazine hydrochloride (n=11) and pentoxifylline (n=10).

Enteric-coated pills possess an external protective layer of substances that prevent their early disaggregation in the gastric environment. The enteric coating is used to mask undesirable organoleptic characteristics, protect the active substance from destruction in the stomach, avoid irritation of the gastric mucosa by direct contact with irritating and necrosing substances, impede the dilution of the active ingredient by the gastric juice to favor its intestinal action (antibiotics, anthelmintics) and favor the release of the medication at the appropriate absorption site.

The characteristics of gastro-resistant coatings permit resistance against the action of enzymes and the gastric pH (1.0 to 3.5) for up to six hours. After reaching the small intestine, the enteric coating is expected to disintegrate or dissolve at intestinal pH (5.0 and 6.0), releasing the active ingredients in the jejunum, where absorption is more effective.

When a coating to protect the active ingredient from the gastric environment is present, the pill cannot be ground and administered through a gastric catheter. If it is, the drug may not behave as expected.

In this study, almost all of the catheters were placed in the post-pyloric position, where the pH is less acidic. This fact may have contributed to reduced therapeutic effectiveness of the drugs. The effect of grinding on a drug’s active ingredients should also be considered. No studies were found that analyzed this aspect of the pharmacological effectiveness of an active ingredient.
Specifically considering grinding of coated hydralazine hydrochloride pills, grinding may have caused the degradation of the active ingredient and consequently reduced the effectiveness of the drug. When ground, the active ingredient of pentoxifylline pills is exposed, resulting in immediate release into the intestine.

The hard gelatin capsules in this study all contained the drug omeprazole. In this pharmaceutical formulation, the powdered drug is placed into a hard gelatin container. These are specifically produced for oral administration.

Proton pump inhibitors (omeprazole, lansoprazole, and pantoprazole) are absorbed in the intestine but are inactivated by gastric acid; therefore, they are given in the form of granules with an enteric coating, which is a contraindication for grinding. When administered through gastric catheters, they need to be mixed with orange or apple juice, which is acidic, to protect the granules until they reach the intestine. With respect to intestinal catheters, a suspension of these granules can be prepared using a 8.4% sodium bicarbonate solution. In Brazil, omeprazole pills manufactured using the Multiple Unit Pellet System technology are available, which permits their administration through catheters. However, at the hospital where this study was undertaken, this form was not available\(^{[15]}\).

The prolonged-release drugs that were ground were galantamine hydrobromide and trimetazidine dihydrochloride MR in solid forms.

In a recent study undertaken at a general hospital in Brazil to identify the techniques used for preparing medication for catheter administration, the grinding of controlled-release drugs was also observed\(^{[14]}\). The controlled-release forms of drugs, characterized by the gradual release of a drug and the maintenance of its plasma concentration at therapeutic levels over an extended period, thereby permitting fewer daily doses, cannot be ground\(^{[14,16]}\). Therefore, grinding these forms for administration through catheters is not acceptable.

Hard gelatin capsules contain slow- or enteric-release micro-granules. Microencapsulation differs from other coating techniques because it can be used with particles whose diameters range from tenths of microns to 5000 microns.

One measure used in hospitals to avoid this type of error is the development of labels with a figure demonstrating that the drug should not be ground\(^{[19]}\).

**Errors due to medication mixing**

Mixing drugs during grinding occurred in 39.25% of the drugs. The technicians mixed two or more drugs in the mortar during grinding. The most frequent mixtures were amiodipine besylate with bamifylline, bromopride, amiodarone hydrochloride or acetylcysteine. Another frequent mixture was bamifylline and bromopride, captopril or acetlycysteine. The mixture of captopril with aspirin was also found. Liquid medicines were not mixed.

When not using a solid pharmaceutical form, the dissolution or suspension of a drug in a compatible vehicle may require grinding. Hence, the chemical and physical-chemical properties of the drug and its initial formulation, which determine its stability and pharmacokinetic profile, need to be known to avoid jeopardizing the effectiveness and safety of the treatment. Because this is a physical-chemical interaction, whether changes occurred in the expected therapeutic effect could not be evaluated.

Nursing technicians prepare drugs by grinding various drugs in the same receptacle, without considering potential incompatibilities that may result from this practice. This practice may have harmed the patients.

**Medication dilution errors**

The dilution errors that were found involved liquid drugs, and all of the errors were that the technician did not dilute the liquid drug. This error occurred with emulsions and syrups. The first group included mineral oil, and lactulose and potassium chloride were in the latter group.

It should be noted that emulsions\(^{[7-18]}\) are diseminations of small water droplets in oil, or of oil in water, maintained by emulsifying agents such as sodium lauryl sulfate, gelatin or gum arabic. Syrups consist of medicinal agents dissolved in a concentrated sugar solution, usually sucrose. The sweetener is specifically used to hide the bitter taste of the drug\(^{[7-18]}\).

When preparing drugs for administration through catheters, one should know that liquid pharmaceutical forms are the most effective because they are easily absorbed and less often result in catheter obstruction. Despite being the most appropriate, the liquid forms also have limitations, including viscosity and osmolarity-related problems as well as the presence of excipients in the formulations, mainly sorbitol, which increase the risk of intolerance by the gastrointestinal tract\(^{[7-18]}\).
Mineral oil (emulsion) has been prescribed to treat constipation. It is a mixture of liquid hydrocarbons obtained from petroleum, which are indigestible and only partially absorbed. Its administration is recommended on an empty stomach or two hours before meals. Mineral oil should not be administered through catheters because it swells and obstructs the route when it mixes with fluids.

The syrups prepared were potassium chloride at 1,400 mOsm/Kg and hyperosmolar lactulose, at approximately 3,600 mOsm/Kg, which can cause diarrhea, abdominal distension and vomiting. Undiluted syrups are not recommended for administration through catheters due to their viscosity and the amount of sorbitol in their formulae. Syrup administration through catheters demands previous dilution in 10 to 100 mL of water to minimize gastrointestinal effects. Dilution in water is required, depending on the pharmacological effect desired.

Syrups are less preferred than other liquid forms because their pH is below 4. They may cause physical incompatibility problems with enteral nutrition as well as catheter obstruction due to the viscosity of the binding solution. In addition, syrups and emulsions are highly viscous, hampering their administration through catheters and increasing the risk of obstruction. To improve administration of these liquids, adequate dilution is necessary before administration in most cases.

The osmolarity of the syrup is one of the physical characteristics determining the organism’s tolerance. The closer the osmolarity of the drug is to that of the gastrointestinal secretions, the better the tolerance will be. The osmolarity of gastrointestinal secretions varies between 100 and 400 mOsm/Kg, whereas liquid pharmaceutical forms exist with osmolarity levels up to 6,000 mOsm/Kg, which can cause problems depending on the location of the catheter. pH is another important physical-chemical parameter in the selection of pharmaceutical forms for administration through catheters. Elixirs and suspensions are preferable to syrups.

When nurses evaluate prescriptions and find that liquid drugs need to be administered through catheters, they need to take care to choose elixirs or suspensions. They need to check the sorbitol contents and osmolarity before administering the drugs, dilute hypertonic drugs in 10-30 mL of water, and check the drugs’ pH because drugs with pH levels below 3.5 may precipitate when intestinally administered, due to the neutral or alkaline pH of the environment. Although the indicated form for a medication is liquid, particularities are involved that if not respected, can result in gastrointestinal intolerance, diarrhea and obstruction of the catheter.

**CONCLUSION**

As verified, liquid alternatives were available for some of the solid drugs that required grinding for administration through catheters in the ICU under study. A high error rate was observed, revealing that the nursing team in this ICU had not been appropriately trained regarding the preparation of medication, although they handle medications routinely.

Improving the knowledge of medication preparation among professionals involved in patient care can decrease issues with the safety and effectiveness of pharmacological treatments and nutritional support and prevent medication-induced disorders in the patients.

Methods to prevent errors can be implemented, such as labels warning that some drugs cannot be ground and readily available tables listing the solid drugs for which liquid alternatives are available and recommended by the hospital.

The intent of this study was to contribute to Brazilian scientific research on safe medication management by investigating preparation techniques for drugs administered through catheters. Adequate technical criteria for medication preparations need to be disseminated and knowledge on this topic needs to be improved among nursing professionals to avoid errors that reduce the effectiveness and safety of pharmacological treatments.

Nurses need to be encouraged to discuss the best pharmacological practices for medication preparations with pharmacists, and skills need to be shared to guarantee patient safety.

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Research on preparation techniques for drugs administered through catheters by intensive care nursing

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