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Original Article

Incompatibility between intravenous drugs in an adult intensive care unit of a large Brazilian hospital

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Abstract: This study aimed to identify the use of High-Alert Medications (HAM) and other drugs, and to estimate the frequency of medication errors involving intravenous (IV) incompatibilities in an adult Intensive Care Unit (ICU) of an urgency-emergency general public hospital in Belo Horizonte, MG, southeast Brazil. Data on medications administered intravenously, incompatibilities between co-administered drugs and physicochemical instabilities were collected through direct observation of the drugs being administrated to the patients and review of the prescription orders. IV medications were defined as HAM according to the ISMP's list of HAMs. Incompatibilities and instabilities were identified using the Trissel/Micromedex software. A total of 100 patients were included in the study, to which an average of 9.5 IV medications was prescribed. From the total of 947 drugs prescribed for IV administration, only 37.5% were administered during the period of observation. In total, 99% of patients used at least one HAM during the period of observation and 34% of the drugs administrated intravenously exhibited potential instabilities. Based on the review of the prescription orders, 726 potential incompatibilities were detected for co-administered IV drugs (15.2%). One drug-diluent incompatibility and four drug-drug incompatibilities were detected during the observation. This disparity between the rate of incompatibility through direct observation and prescription evaluation indicates the need for direct pharmaceutical intervention regarding the clinical status of the patient, being not limited to the analysis of prescription orders. **Keywords:** medication errors; incompatibilities; intravenous medications; intensive care unit

Introduction

Medication Errors (ME) are defined as any actual or potential avoidable event that can lead to the incorrect use of drugs, and that may or may not involve harm to the patient, regardless of whether the medication is under the control of health professionals, patients or consumers[1]. ME are a growing concern in health care. According to the World Health Organization, additional hospitalization, litigation costs, disability, lost productivity and other medical expenses due to ME have an estimated cost in some countries of US$ 19 billion annually[2].

Important ME tend to involve medications administered intravenously, which expose patients to a higher risk of injury owing to their immediate bioavailability, what makes measures to correct mistakes less effective and more urgent[3,4]. The immediate bioavailability of IV drugs is a highly advantageous pharmacokinetic feature, particularly in the

treatment of critically-ill patients. However, the rapid onset of action of these medications also implies partial or total irreversibility of errors, especially in view of the fragile health of this group of patients for which is more difficult to balance the effects of MEs and also slight under or overdoses may have major consequences[5-7].

Considering the high number of comorbidities of patients at the ICU, the frequent administration of parenteral drugs, the need for constant drugs continuous infusion and the limited number of separated IV lines in critically-ill patients, the occurrence of drug incompatibilities compose a worrisome scenario[8]. Incompatibilities are also referred as pharmaceutical interactions, and are defined as undesired physicochemical interactions that happen due to the combination of two or more drugs in solutions that are not proper for the patient, as far as they can affect treatment efficacy and safety[9,10]. Incompatibilities can happen between two drugs or a drug and a solute, adjuvant, recipient or medical device, and may take place during the preparation or administration of drugs[11].

In this context, incompatibilities between IV medications are recognized as a priority ME for improving the quality of healthcare. However, the scarcity of specific information on the prevalence of this kind of MEs in ICUs raises the need of conducting studies such as the present investigation. Here we investigated the use of IV drugs and the frequency of incompatibility-related MEs, focusing in identifying potential obstacles for the safe administration of drugs in intensive care settings.

Material and Methods

Setting and design

We conducted a cross-sectional observational study on drug incompatibilities involving drugs administered intravenously in a 37-bed adult ICU of a large Brazilian hospital for urgency and emergency services. The hospital is one of the largest Brazilian emergency hospital, the largest in Minas Gerais State, and presented a total of 425 beds at the time of the study. The study was approved by the Research Ethics Committee of the institution where the study was carried out (021B/2011).

Study population

We included a total of 100 adult patients (aged 18 years or older) admitted to the ICU during the period of study (37 days) in the study sample.

Observational data collection

All patients were directly observed during their second day at the ICU during busy hours with frequent drug administration from 7 a.m. to 7 p.m. The observation was centered on drugs administered intravenously. We registered all drugs administered to these patients intravenously using a specific formulary previously validated in a pilot study, along with specifications regarding dilution (type of diluent, volume and final concentration), rate of infusion, site of puncture and type of intravenous connection.

We screened the following types of potential incompatibilities: drug-diluent incompatibility, drug-drug incompatibility in the same IV drip bag device; and drug-drug incompatibility administered via the same Y connector (two-way connector) or three-way connector. In addition, any potential instabilities of infusion solutions were detected after evaluating the diluents used, final concentration of the drugs in solution, infusion rate and total infusion time. All potential incompatible and unstable combinations were accepted as plausible or rejected according to the Trissel IV incompatibility database, available on Micromedex® database (Drugdex system, Thomson Reuters (Healthcare) Inc.)[12].

Prescription order reviews

Prescription order reviews were conducted in parallel with the direct observation of the IV administered drugs. We reviewed all prescription orders considered valid at the day of observation for the patients included in the study. The ICU explored in this study has a prescription order electronic system, and the final prescriptions are printed in the pharmacy. We analyzed the printed version of the prescription orders regarding the prescribed intravenous drugs, dilution (type of diluent and volume) and infusion rate. All intravenous drugs were analyzed, including drugs with conditional or "when required" administration status. The same type of potential incompatibilities were identified from the reviewed prescriptions, considering that all the drugs could, at some point, could be co-administered in solution (same IV drip bag device) or via the same connector device (two-way connector or three-way valve). Drug-diluent incompatibilities were only assessed when the diluent was present in the prescription order, once this is an optional information in the prescribing system.

Data analysis and processing

We generated a database using the EpiInfo® 7.0 (2011) software program for data organization and analysis. The data were initially descriptively analyzed based on frequency, central tendency (mean and median) and dispersion (range and standard deviation) measurements of demographic variables and use of drugs. We compared the proportions of drug-drug incompatibilities detected by direct observation and review of prescription orders using Pearson´s Chi-square test or Fisher´s exact test, where appropriate. A level of significance of 5% was adopted for all comparisons.

Results

Profile of sample and use of intravenous drugs

During the period of study, 77 men and 23 women were observed, and their ages ranged from 18 to 94 years old (average = 44.8±17.8 years). An average of 1.4 puncture accesses per patient was observed (median 1, ranging from 1-5), and peripheral access was the most frequently detected (50.4%), followed by subclavian (29.3%), jugular (13.8%), and femoral (n = 8; 6.5%). From a total of 132 connector devices, 49.2% (n = 65) consisted in three-way valve type, 45.5% (n = 60) were Y-type, and the remainder were simple connectors (n = 7; 5.3%).

Data collected by direct observation indicated an average of 3.6 drugs administered per patient intravenously (median 3, ranging from 1-9). Based on the reviews of the prescription orders, an average of 9.5 IV drugs were prescribed per patient (median 9.5, ranging from 1-17). The most frequently used drugs during the observation period were: glucose (25.1%), fentanyl (16.1%), midazolam (15.8%), norepinephrine (11.5%), potassium chloride and thiamine (7.6% each), vitamin B complex (6.2%) and magnesium sulphate (3.7%).

The most frequently prescribed drugs were: dipyrone (also called metamizole) (10.1%), glucose (10.0%), metoclopramide (9.3%), ranitidine (9.1%), fentanyl (8.9%), midazolam (8.8%), norepinephrine (6.0%), phenytoin (5.4%), regular human insulin (3.6%), thiamine (3.4%) and potassium chloride (2.9%).

Assessment of incompatibilities using the observational approach

One drug-diluent incompatibility (nitroglycerine in sodium chloride at 0.9%) (n = 1; 0.3%) was identified by direct observation. Among the 494 potential drugs pairs co-administered via the same IV line, three drug-drug incompatibilities (n = 3; 0.6%) were identified, and the incompatibilities were detected in Y-type connectors in all cases. Potential instability was also detected for nitroglycerine in sodium chloride at 0.9% (n = 1; 0.3%) and for sodium nitroprusside in glucose at 5% (n = 1; 0.3%) (Table 1).

Table 1 – Details of physico-chemical drug-diluent and drug-drug incompatibilities detected by direct observation.

Type of incompatibility	Drug pair involved in incompatibility	Description of incompatibility	Absolute frequency (n)
Drug-diluent	Nitroglycerine + sodium chloride 0.9%	Physically compatible but chemically unstable: potential nitroglycerine loss	1
Drug-drug	Sodium bicarbonate + Thiamine	Incompatible: potential chemical decomposition	1
	Regular human insulin + midazolam	Physically incompatible: turbidity, particles and/or change in color detected.	1
	Dobutamine + midazolam	Physically incompatible: Development of particles.	1

Source: MICROMEDEX® (accessed in May 2012)[12].

Assessment of incompatibilities by prescription order review

From the prescriptions orders that specified the diluent to be used, 10 drug-diluent incompatibilities were detected (0.9%) (Table 2). Amidst the 4791 IV drugs potential pairs prescribed, 726 potential drug-drug incompatibilities were found (15.2%), 11.5% of which (n = 550) involved Y connectors (average 13.6 per patient) and 3.7% (n = 176) consisted in co-solubilization (mean 2.4 per patient). The most frequent drug interactions in which the site of incompatibility was the Y connector, included phenytoin with the following drugs: metoclopramide (n = 49, 8.91%), ranitidine (n = 49, 8.91%), fentanyl (n = 46, 8.36%), midazolam (n= 45, 8.18%), and norepinephrine (n = 34, 6.18%). For solubilization in the same IV drip bag device, the most frequent interactions were between norepinephrine and ranitidine (n = 52, 29.55%), phenytoin and norepinephrine (n = 34, 19.32%), potassium chloride and midazolam (n = 22, 12.50%), sodium chloride and mannitol (n = 17, 9.66%), as well as phenytoin and regular human insulin (n = 13, 7.39%). A statistically significant difference ($p<0.0001$) was detected between the rates of drug-drug incompatibility detected in potential co-administered drugs in the reviewed prescriptions and in the observational data.

Table 2 – Details of physico-chemical drug-diluent incompatibilities detected by prescription order review

Drugs involved in incompatibility	Description	Absolute frequency (n)
Amoxicillin and clavulanic acid + sodium chloride 0.9%	Physically compatible but chemically unstable: potential clavulanic acid loss.	7
Cefepime + sodium chloride 0.9%	Physically incompatible and chemically unstable: darkening of solution and potential loss of cefepime.	1
Phenytoin + sodium chloride 0.9%	Physically incompatible: crystalline precipitation of phenytoin.	1
Nitroglycerine + glucose at 5%	Physically compatible but chemically unstable: potential nitroglycerine loss.	1

Discussion

During the observational collection, a similar average of puncture accesses per patient was found to that observed by Angelieri in 2007[13] (1.4 versus 1.7, respectively) in a study performed in São Paulo University teaching hospitals, which sought to determine the incidence of blood-borne infections in patients admitted to the ICU in use of central venous catheter. Regarding the insertion site, the frequency we found confirmed that most of venous accesses in the ICU are attained using peripheral catheters, whereas for central catheters, the site of insertion for access is predominantly the subclavian vein[13-15].

Venous access limitations, in the case of patients requiring therapy involving a large number of drugs, require the use of sets with multiple lines (Y type or three-way connectors), allowing simultaneous infusion of compatible solutions into the same access vein. However, the solutions to be infused concomitantly are not always compatible; therefore, incompatibilities are likely, once the drugs will be combined before reaching the blood stream[16-17]. Here, most of the patients were in use of multiple lines (94.7%). By contrast, lower rates of multiple lines were described in the studies carried out by Mesiano and Merchán-Hamann[14] (78.5%) and Angelieri[13] (66.9%).

On our observational collection of data, the average number of IV drugs being administered per patient (3.6 drugs) was lower than the one observed in the study of Bertsche et al.[8], who detected an average of 6.7 ± 2.4 IV drugs administered per patient in a prospective study. Beyond the scarcity of studies on ICUs based on direct observation of patients, the studies differ in several aspects such as the methodology used, the time at which patients were assessed and their clinical status, with a remarkable influence in the number of drugs used in the pharmacotherapy of critically-ill patients. Bertsche et al.[8], detected a high proportion of patients on mechanical ventilation at the ICU where the studies were conducted, while patients diagnosed with cardiac disorders (such as acute myocardial infarct) and non-transplanted post-surgical patients were not included in their study. This explains the disparities with the present study, given that the leading cause of ICU admission were external causes and no restrictions were set regarding post-surgical patients in this study.

Considering the prescription orders valid at the time of observation, a greater average (9.6) and range (1-17) was detected on the prescription order review than on the observational data collection (3.6; 1-9). This was an expected finding, given that the observation covered a single period of time. Similar results were described by Kopp et al.[18], in which an average of 8 drugs was prescribed per patient (range 0-18). In a study conducted by Lima and Cassiani[19], 1 to 19 drugs per patient were prescribed on the second day of admission, encompassing drugs administered by any route.

Other prescription-based studies performed in Brazilian adult ICUs are of limited comparative value since these investigations assessed more than one prescription order per patient and expressed results as a mean based on the total drugs used in all reviewed prescription orders per patient. Cardinal et al.[20] reported a mean of 14.28 ± 6.31 drugs per prescription order (minimum 1, maximum 28 - based on analysis of 844 prescription order of 72 patients). By contrast, Moraes et al.[21] and Marsilio et al.[22] identified lower means 7 ± 1.6 and 6.5 ± 2.4 IV drugs per prescription order. In these studies, IV drugs were excluded if prescribed for use only when necessary.

In the present study, out of the 947 IV drugs prescribed, 37.5% were administered during the observation period (n = 355). This disparity between the number of drugs prescribed and administered was also highlighted by Reis[23] that identified an average of 21.4 prescribed drugs per patient, whereas a mean of only 12 drugs were actually administered.

The most prescribed drugs in the ICU (dipyrone, glucose 50%, metoclopramide, ranitidine, fentanyl, midazolam, norepinephrine and phenytoin in order of frequency of prescription) are similar to that detected by Mazzola et al.[24], consistent with ICU patients profile. The most frequently used medications during the period of observation were not the same as the most frequently prescribed (the most administered drug was glucose 50%, followed by fentanyl, midazolam, norepinephrine, potassium chloride, thiamine, vitamin B complex and magnesium sulphate). It was evident that the drugs usually administered by direct IV route (such as dipyrone, metoclopramide, ranitidine and phenytoin) were substituted by drugs typically administered by continuous infusion. This represents a limitation of the study, since the nursing team was not questioned regarding the route used to administer these drugs, precluding the assessment of potential incompatibilities.

The frequency of incompatibilities detected in the present study (0.3%) was similar to that observed by Fahimi et al.[25] (0.2%). In an assessment of different pharmaceutical services of two German and one British hospital. Wirtz et al.[26] identified compatibility problems in 10% of doses observed, with the majority of these errors registered in a German ICU. At the Czech Republic, Machotka et al.[27] identified ratios of 6.8% and 2.16% in two different ICUs. Conversely, Tissot et al.[4] identified an even higher incompatibility rate of 18.6%. It is important to mention that, although these studies were based on direct observations, nurses were observed at the time of drug preparation, which did not occur in the present study.

A higher number of drug-drug incompatibilities was detected on the prescription order review (n = 726; 15.2% of potential combinations). This disparity in incompatibility rates detected using the different methods of analysis was statistically significant ($p<0.05$), an expected finding considering that the observational collection was performed at a single timepoint. Similar proportions of incompatibility among the potential drug pairs was detected in another Brazilian study[22] that performed prescription order reviews (14.6% of potential drug combinations).

Amidst the prescription orders that contained specifications of the diluent to be used, 10 drug-diluent incompatibilities were detected (0,9%), the most frequent of which (n = 7) was amoxicillin in association with clavulanic acid and sodium chloride 0.9%. The results of a study analyzing the frequency of antimicrobials prescribed in a Belo Horizonte ICU revealed that 47.3% of antimicrobial dilutions were not prescribed and, among those prescribed, 63.7% were incorrect, where the errors found included insufficient diluent (72.1%), incorrect diluent (18.6%) and incomplete diluent (9.3%)[28].

It is important to mention that the most frequent potential incompatibilities identified in the prescription order review were not detected during the observational collection of data. This indicates that the pharmacist assessment of incompatibilities should not be a practice limited to the prescription order review, but should also comprise the real clinical context. It should involve patient monitoring and observational visits made at least on a daily basis at bedside.

The number of potential instabilities detected was also low. However, in the study conducted, the instabilities were calculated based on the infusion rates registered on the pump and the total volume of the drip bag. Consequently, in cases where the infusion rate had been reduced only after infusion of most of the bag device contents, this analysis would not be applicable and instabilities would be irrelevant, representing a limitation of the direct observation at a single timepoint. Conversely, instabilities of solutions for administration by continuous infusion can be easily prevented, for which the pharmacist has a key role in adjusting the dilutions for drugs that the stability profile is well known.

In this context, preventative strategies such as the implementation of protocols for drug administration, training and most importantly, the presence of a clinical pharmacist as an active member of the healthcare team, co-responsible for the pharmacotherapy of critically-ill patients, represent feasible alternatives to promote the correct use of drugs, reducing considerably the potential of serious MEs, raising standards of patient care as well as enhancing safety in drug use.

Conclusion

A small proportion of the prescribed IV drugs were administered during the period of observation. The majority of patients used at least one HAM during the period of observation. Based on the review of the prescription orders a much higher number of potential incompatibilities was detected than during the observation. This disparity between the rate of incompatibility through direct observation and prescription evaluation indicates the need for direct pharmaceutical intervention regarding the clinical status of the patient, being not limited to the analysis of prescription orders.

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