

Analysis of extemporaneous oral liquid from commercially available drugs in hospital

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The objective of this study was to identify drugs that received dose adjustments (DA) and pharmaceutical alternatives (PA) that avoid DA, and calculate the economic percentage of this replacement. A descriptive, observational and cross-sectional study was performed in a second level hospital. The pharmacy and nursing services was accompanied to identify the drugs that received DA and the compounding techniques. After identifying all the drugs that received DA, was identified in the Brazilian market the corresponding pharmaceutical alternative, with the Drugs Price List of Brazilian Health Regulatory Agency. For those drugs that was not available any PA, was performed a research of studies that describe compounding techniques in international scientific databases. Was identify 88 drugs that received DA, and these, 50 do not have any PA. Were identified compounding techniques to 40 drugs. Although any drug has your own particularity of compounding, the compounding techniques can be grouped in five categories. The standardization of 29 drugs can reduce in 28% the DA procedure and cost saving of 34,85%/month. We can conclude that every three drugs prescribed, one received DA and every three DA, one can be avoided by the selection of 29 PA, saving cost as well. The use and standardization of five techniques would attend the pharmaceuticals recommendations for better dissolution, bioavailability and patient safety.

Uniterms: Pharmaceutical preparations/hospitals. Patient safety. Pharmacoeconomics. Drugs/descriptive study/ Off-Label Use.

INTRODUCTION

Dose adjustment (DA) is performed to supply a patient's therapeutic needs when non-standard dosages are needed (Brasil, 2007; FDA, 2013). The lack of liquid pharmaceutical forms for oral use on the market has become a problem for the pharmacotherapy of patients that primarily uses liquid formulations, such as pediatric patients, the elderly, patients receiving drugs via probe, patients with dysphagia, and patients with dementias, Parkinson's, or Alzheimer's disease (Haywood, Glass, 2013; Thombre, Berchielli, Rogers, 2014). Patients with these problems require extemporaneous oral preparations in order to ensure the patient's therapy. DA is common in health systems; however, there are no guarantees regarding

the quality, effectiveness, and safety of drugs after DA and DA can expose the patient to adverse events (Glass, Haywood, 2006).

With the aim of ensuring the pharmacotherapy of the patient, contributing to the culture of patient safety, and objectively identifying drugs that underwent DA and pharmaceutical alternatives (PAs) that could avoid DA, we compared DA to the compounding techniques described in the literature and calculated the economy of PAs.

METHODS

Study design

This was a pharmaco-epidemiological, descriptive, and observational cross-sectional study based on the guideline *Strengthening the Reporting of Observational studies in Epidemiology* (STROBE) (Von Elm *et al.*, 2008).

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Study site

This study was conducted at the State Hospital Américo Brasiliense (HEAB) in Américo Brasiliense, São Paulo state. The hospital assists patients from 24 cities in the region.

Study period

Patient prescriptions were monitored in July 2013.

Data collect

Patient prescriptions were monitored daily. The nursing staff's work was monitored to check the drug manipulation techniques, administration, and storage after DA. The PAs and the costs were identified in the Brazilian market with the Drugs Price List of ANVISA (ANVISA, 2015). The DAs were classified into derivation or subdivision of the pharmaceutical form, according to the current legislation (Brasil, 2007). For those drugs without available PAs, studies that describe compounding

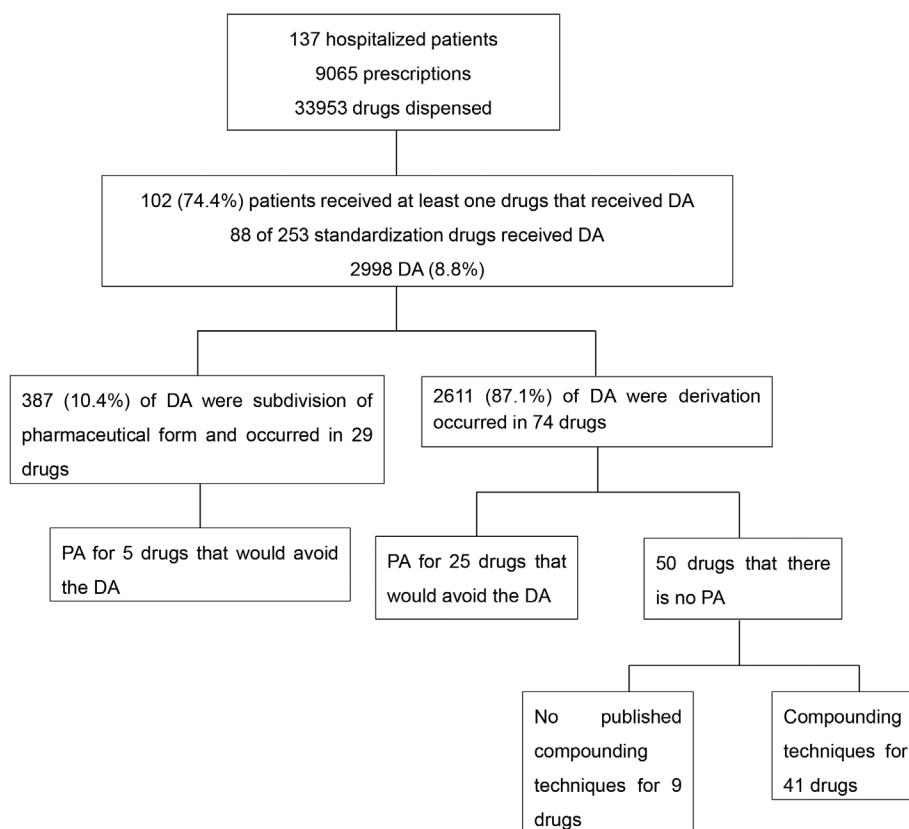
techniques were studied, using the descriptors: "Drug name" – for each drug; "Drug Compounding"; "Drug Stability"; and "Pharmaceutical Preparations" in the databases LILACS, SciELO, and PubMed.

Ethical considerations

The study was approved by the ethics committee of the Institute Lauro de Souza Lima as the project "Proposta de implantação de um serviço de farmacovigilância no Hospital Estadual de Américo Brasiliense" under protocol E-015/10; it was also approved by the hospital board.

RESULTS

DA was identified in 88 (34.7%) different drugs of the 253 standardized drugs in the hospital pharmacy (Figure 1). The technique of derivation was standardized and described in the standard operating procedure as crushing the solid dosage form with the aid of a pestle, followed by immediate administration. The subdivision of the pharmaceutical form occurred in the hospital



NOTE: DA: Dose Adjustment; PA: Pharmaceutical alternatives.

FIGURE 1 - Flowchart analysis of prescriptions of hospitalized patients, identification of dose adjustments, and pharmaceutical alternatives in the Brazilian market and the compounding techniques available in the literature.

pharmacy and was performed by the pharmacy team. The subdivision technique used specialized equipment for this purpose, followed by packing and labeling with product information, including the active ingredient, expiry date, and batch number. Subdivisions of liquid dosage forms occurred in the ward in drug handling rooms by the nursing team. Only a portion of the ampoule contents were administered, corresponding to the desired concentration. No DA exceeded the shelf life of 48 hours.

In the Brazilian market, 29 PAs were identified for the 88 drugs that received DA, possibly decreasing DAs by 28.5% (856 / 2,998) (Table I).

For the 50 drugs that lacked PAs, 40 had known compounding techniques (Table II); the following ten drugs (or drug combinations) had no published compounding techniques: bisacodyl; citalopram; a combined dose of rifampicin, isoniazid, pyrazinamide, and ethambutol; doxazosin; finasteride; isosorbide; ivermectin; paracetamol and codeine combined; quetiapine; and sertraline.

Regarding the microbiological quality, studies show the necessity of adding parabens, such as methylparaben and propylparaben, in the extemporaneous formulations and refrigerated storage to avoid microbiological growth (OPAS, 1997; Haywood, Glass, 2013; Alemón-Medina *et al.*, 2014).

Furthermore, the hospital spent US\$ 3,458.39 on performing DA. The economic analysis was calculated through the difference between the sum of DA (considering the frequency and cost for dosage form unity for each drug - for solid drugs, it was considered one tablet or capsule, and for liquid drugs, one milliliter) and the sum of the corresponding PA dosage (Table 1).

Through economic analysis, standardizing PAs could generate a cost savings of US\$ 1,205.59. Only one drug (piperacilin + tazobactam powder for injection 4 g + 0.5 g) is responsible for US\$ 1,190.41 of this cost savings.

DISCUSSION

DA is an indispensable practice in hospitals because many patients often have specific needs that require the administration of drugs in various dosage forms (Haywood, Glass, 2013; Thombre, Berchielli, Rogers, 2014).

Generally, these patients are those who make use of catheters, have dysphagia, and/or require different doses of commercialized drugs. Therefore, of every four hospitalized patients, three patients require at least one PA to one or more prescribed drugs; however, the standardization of 29 PAs may reduce DA practices by one-third.

Nevertheless, the Pan American Health Organization/World Health Organization recommends preparing reduced therapeutic forms in order to facilitate the logistics (acquisition, storage, and distribution) of drugs, promoting the drug's rational use, avoiding duplication and saving money by avoiding waste (OPAS, 1997).

On the other hand, ensuring the safety, efficacy, and quality of pharmaceutical forms is given by the pre-registration of drugs through stability studies (short and long), pharmaceutical equivalence studies, such as dissolution profiles and other pharmacopoeia analysis, and *in vitro* studies of bioequivalence aspects (Mastroianni, Lucchetta, 2011). These issues are no longer guaranteed after DA.

In addition, it is recommended that therapeutic forms be updated every two years, not just for the inclusion or exclusion of drugs, but also to review the submissions to ensure the best posology for the patient profile (OPAS, 1997). Once the drugs were available to patients in the most appropriate pharmaceutical form and without manipulation (Catalán *et al.*, 2001; Habib *et al.*, 2014), patients would not be exposed to the inherent risks of DA (Paparella, 2010); this would also decrease costs.

Therefore, the data from this study highlight the importance of continuous expansion and revision of therapeutic forms, considering not only the managerial and administrative aspects of hospital pharmacy (selection, acquisition, and distribution of drugs), but also the management of patient safety at the institution.

For those drugs that do not have available commercial alternatives, DA is often inevitable. Every DA is considered off-label use, because it is a manipulation and formulation of extemporaneous doses from the marketed drugs (Kairuz *et al.*, 2007; ANVISA, 2010; EMA, 2014; Carvalho, 2016); therefore, DA should be discussed by the health team and be provided in the clinical protocols of the service.

Additionally, it was observed that derivation is standardized in the hospital and was based on the tablet dispersion technique, respecting the period of lateness (48 hours) set by ANVISA (Brasil, 2007), showing conformity (Glass, Haywood, 2006). However, studies (Allen, 2012; Alemón-Medina *et al.*, 2014; Shoosanglertwijing *et al.*, 2015) demonstrate that the validity of the PA is often greater than seven days, under certain criteria for manipulation and storage.

Glass and Haywood (Glass, Haywood, 2006) suggest a decision-flow for choosing the DA procedure. If there is need for an extemporaneous preparation of liquid, one must seek a commercially available alternative to avoid the DA. If none are available, the second option

TABLE I - Standard drugs that received dose adjustment and their classification and pharmaceutical alternatives available in the Brazilian market, which would avoid the need for dose adjustments

Standardized drugs	DA	Available commercially alternative
amiodarone (tablet 200 mg)	SPF	amiodarone (tablet 100 mg)
	D	amiodarone (oral solution 200 mg/mL)
amoxicillin + clavulanate (tablet 500 + 125 mg)	D	amoxicillin + clavulanate (powder for oral solution suspension 50 mg/mL + 12.5/mL)
azithromycin (tablet 500 mg)	D	azithromycin (powder for oral solution suspension 40 mg/mL)
carbamazepine (tablet 200 mg)	D	carbamazepine (oral solution 20 mg/mL)
carvedilol (tablet de 25 mg)	SPF	carvedilol (tablet 12.5 mg)
clonazepam (tablet 0,5 mg)	D	clonazepam (oral solution 2.5 mg/mL)
clonazepam (tablet 2 mg)	D	clonazepam (oral solution 2.5 mg/mL)
complex B® [tablet - vitamin B1 (5mg); B2 (1mg);B3(30mg); B5 (4mg); B6 (3mg)]	D	Complex B® [oral solution - vitamin B1 (3 mg/mL); B2 (3 mg/mL); B3 (10 mg/mL); B5 (25 mg/mL); B6 (10 mg/mL)]
dexamethasone (tablet 4 mg)	D	dexamethasone (elixir 0,1 mg/mL)
digoxin (tablet 0,25 mg)	SPF	digoxin (tablet 0.125 mg)
	D	digoxin (pediatric elixir 0,5 mg/mL)
domperidone (tablet 10 mg)	D	domperidone (oral solution 1mg/mL)
ferrous sulphate (tablet 250 mg)	D	ferrous sulphate (syrup 50 mg/mL)
fluoxetine (tablet 20 mg)	D	fluoxetine (oral solution 22,4 mg/mL)
folic acid (tablet 5 mg)	D	folic acid (oral solution 0.2 mg/mL)
haloperidol (tablet 5 mg)	D	haloperidol (oral solution 2 mg/mL)
lamivudine (tablet 150 mg)	D	lamivudine (oral solution 10 mg/mL)
levodopa + benserazide (tablet 200 mg + 50 mg)	SPF	levodopa + benserazide (tablet 100 mg + 25 mg)
lopinavir + ritonavir (tablet 200 + 50 mg)	D	lopinavir + ritonavir (oral solution 80 + 20 mg/mL)
loratadine (tablet 10 mg)	D	loratadine (oral solution 1 mg/mL)
metronidazole (tablet 400 mg)	D	metronidazole (oral solution 40 mg/mL)
oseltamivir (capsule 75 mg)	D	oseltamivir (powder for oral suspension 12 mg/mL)
piracetam (tablet 400 mg)	D	piracetam (oral solution 60 mg/mL)
phenobarbital (tablet 100 mg)	D	phenobarbital (oral solution 40 mg/mL)
piperacillin + tazobactam (powder for injection solution 4 g + 0,5 g)	SPF	piperacillin + tazobactam (powder for injection solution 2 g + 0,25 g)
risperidone (coated tablet 1 mg)	D	risperidone (oral solution 1 mg/mL)
risperidone (coated tablet 2 mg)	D	risperidone (oral solution 1 mg/mL)
scopolamine (dragee 10 mg)	D	scopolamine (oral solution 10 mg/mL)
tramadol (capsule 50 mg)	D	tramadol (oral solution 100 mg/mL)
valproic acid (capsule 250 mg)	D	valproic acid (oral solution 50 mg/mL)

Note: **DA:** Dose Adjustment; **D:** Derivation; **SPF:** Subdivision of pharmaceutical form.

would be to search for a therapeutic equivalent. If there is no therapeutic equivalent with the same efficacy and safety, the third option would be the preparation of an extemporaneous solution, according to the pharmacopoeia. When lacking the monograph of preparation, it is recommended to research a validated formulation. Without

this, the literature should be used to find DA techniques specific to the drug. In a final decision, the standardized tablet dispersion technique should be used.

The advantage of technique standardization, as found in the literature review, is that it increases the stability of extemporaneous solutions and improves the dissolution

TABLE II - Categories of manipulation techniques available in the literature regarding the medicinal dosing adequacy for 40 drugs

Compounding techniques	Drugs
Crush SDF, dispersion with water and immediate administration.	acetylsalicylic acid (Jamal, Dumke, 2012).
Crush SDF, adding suspending agent and SQT with syrup.	amlodipine (Loyd, 2006); amitriptyline (Gupta, 2009); ciprofloxacin (Johnson <i>et al.</i> , 1988); clopidogrel (Skillman, Caruthers, Johnson, 2010); diazepam (Newton, Schulman, Becker, 1976; Strom, Agbai, 1986); lamotrigine (Nahata, Morosco, Hipple, 1999); levodopa and carbidopa (Nahata, Morosco, Leguire, 2000); pyrimethamine (Nahata, Morosco, Hipple, 1997); prednisone (Gupta, Gibbs, Ghanekar, 1978).
Crush SDF, adding suspending agent and other agents (humectants, binders and / or acidifying) and SQT with syrup.	atenolol (Patel, Doshi, Desai, 1997); baclofen (Johnson, Hart, 1993); gabapentin (Nahata, 1999); lorazepam (Wan-Man <i>et al.</i> , 2004); losartan (Allen, 2012); metoprolol (Allen, Erickson, 1996); norfloxacin (Boonme <i>et al.</i> , 2000); topiramate (Loyd, 2009).
Crush SDF, adding agents (humectants, binders, acidifiers and thickeners) and SQT with syrup.	captopril (Lye <i>et al.</i> , 1997); diltiazem (Allen, Erickson, 1996); tenofovir (King <i>et al.</i> , 2011).
Crush SDF, adding other agents (humectants, binders, acidifying, alkalizing and thickeners).	carvedilol (Yamreudeewong, Dolence, Deborah, 2006); clobazam (Buontempo <i>et al.</i> , 2013); clonidine (Ma, Decarie, Ensom, 2014); donepezil (Yamreudeewong, Dolenc, Pahl, 2006); spironolactone (Salgado <i>et al.</i> , 2005); enalapril (Nahata, Morosco, Hipple, 1998); phenytoin (Viriyaraj <i>et al.</i> , 2009); fluconazole (Yamreudeewong, Lopez-Anaya, Rappaport, 1993); furosemide (Shoosanglertwijit <i>et al.</i> , 2011); hydralazine (Okeke <i>et al.</i> , 2003); hydrochlorothiazide (Santoveña, Hernández-Paiz, Fariña, 2012); levothyroxine (Alexander, Kothapalli, Dollimor, 1997); metformin (Alemón-Medina <i>et al.</i> , 2014); omeprazole (Kaufman <i>et al.</i> , 2002); propranolol (Ensom <i>et al.</i> , 2013); sulfadiazine (Pathmanathan <i>et al.</i> , 2004); warfarin (Haywood, Glass, 2013);
They should not be administered by gavage (tube obstruction, lack of information or instability)	calcium carbonate (Jamal, Dumke, 2012); simvastatin (Jamal, Dumke, 2012).

Note: SDF: solid dosage form; SQT: sufficient quantity to.

of the drugs, thereby ensuring greater bioavailability and absorption, ensuring therapeutic effectiveness, and preventing adverse drug events. Moreover, changes in drug dosage forms can lead to changes in the polymorphic and morphological behaviors of drugs, which may cause therapeutic ineffectiveness, because while medicines are produced and stored, they tend to seek the most stable form, which is not always the more active and safe form (Glass, Haywood, 2006; Capucho, Mastroianni, Cuffini, 2008; Paparella, 2010; Glass, Haywood, 2013).

The techniques found for the production of extemporaneous solutions are generally characterized by choosing the most appropriate vehicle (water or simple syrup) and the addition of pharmaceutical adjuvants, such as those used for suspending, thickening, binding, and acidifying. Other commercial alternatives, such as galenical bases, could be used to prepare extemporaneous solutions. This option for the preparation of DA, in order to ensure the quality of freshly-prepared solution and

promote increased patient safety, will require periodic review.

A limitation of the study was the data collection time, a month, which can be a limitation for DA frequency analysis; however, the analysis period was not qualitatively limiting to identify the drugs that received DA, and other studies showed similar numbers of patients and prescriptions analyzed (Joosub *et al.*, 2015; Mahmood *et al.*, 2016). We believed that many of the 88 different drugs undergo DA in other hospitals, and the 40 techniques described in the literature may contribute to the stability, safety, and quality of such preparations.

Thus, data from this study suggest the need to change the selection process and standardization of drugs and the need for cost-effectiveness and cost-benefit studies to evaluate the effectiveness and safety of DA.

These data close a gap in the literature, contributing to our understanding of the inherent risks of DA and identifying potential cost savings.

For every three dispensed drugs, one received DA, and three of every four patients needed at least one of their drugs to undergo DA in their drug therapy, highlighting the importance and relevance of this practice in hospitals. Furthermore, for every three DA, one could be avoided with the selection of a PA. Each drug has its peculiarities for ensuring dissolution, bioavailability, and absorption of the drugs, consequently promoting safe and effective pharmacotherapy.

Therefore, data from this study corroborate the need for cost-benefit studies to evaluate the effectiveness, safety, and economy generated by the DA process.

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