

Adverse drug events related to extemporaneous compounding medicines

DE FREITAS SANTANA G¹, MASSAE TOMA M¹, RUBENS DE NADAI T², BENZI JRL³, DE CARVALHO MASTROIANNI P¹

1 Department of Drugs and Medicines, School of Pharmaceutical Sciences, São Paulo State University (UNESP), Araraquara (Brazil)

2 Department of Public Health, Bauru School of Dentistry, University of São Paulo (USP), Bauru (Brazil)

3 Department of Clinical, Toxicological and Bromatological Analyses, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto (Brazil)

4 Department of Drugs and Medicines, School of Pharmaceutical Sciences, São Paulo State University (UNESP), Araraquara (Brazil)

Fecha de recepción: 26/06/2021 - Fecha de aceptación: 05/07/2021

DOI: <http://dx.doi.org/10.4321/S1699-714X2023000200008>

SUMMARY

In the present study, we investigated the causality between adverse drug events and extemporaneous compounding from spontaneous reports generated by a healthy team in a medium-complexity public hospital in São Paulo state, Brazil. An observational cross-sectional study was conducted between August/2017 to July/2018. All adverse drug events spontaneous reports, which mentioned extemporaneous compounding, were evaluated. The selected variables were patient's clinical history, pharmacotherapy, adverse drug reactions, medication error and type of extemporaneous compounding. Causality assessment between the adverse drug reaction and extemporaneous compounding was performed by World Health Organization – Uppsala Monitoring Center algorithm and medication error analysis was performed by the National Council for Coordination of Reporting

and Prevention of Medication Errors algorithm. 3,211 spontaneous reports were evaluated. Only 144 (4.5%) reports mentioned extemporaneous compounding, being 110 eligible for analysis. The causality assessment showed that in 27 (24%) reports the adverse drug reaction and medication error identified were possibly related to extemporaneous compounding, with an underreporting index of 0.87. From these 27 reports, 3 adverse drug reactions were classified as “probable” and 23 as “possible” whereas 4 medication error were classified as “error, harm: category E”. Although extemporaneous compounding is a common practice in hospitals, only a small portion of the reports included it. Future studies may investigate the use of extemporaneous compounding as a trigger tool for adverse drug reactions since this study shows that one out of four reports that mentioned it leads to patient harm.

Key words: **Extemporaneous compounding, oral suspension, adverse drug reaction, patient safety, underreporting.**

Eventos adversos a medicamentos relacionados a adequações posológicas

RESUMO

No presente estudo, foi investigada a causalidade entre eventos adversos a medicamentos (EAM) e adequações posológicas (AP) a partir de notificações espontâneas geradas pela equipe de saúde de um hospital público de média complexidade no estado de São Paulo, Brasil. Foi conduzido um estudo observacional transversal entre agosto/2017 a julho/2018. Todas as notificações de EAM, que mencionavam AP, foram avaliadas. As variáveis selecionadas foram história clínica do paciente, farmacoterapia, reações adversas a

medicamentos, erro de medicação e a técnica de manipulação extemporânea. A avaliação da causalidade entre a EAM e a AP foi realizada pelo algoritmo da Organização Mundial da Saúde – Centro de Monitoramento de Uppsala e a análise do erro de medicação foi realizada pelo algoritmo do Conselho Nacional para Coordenação de Notificação e Prevenção de Erros de Medicação. Foram avaliadas 3.211 notificações espontâneas. Apenas 144 (4,5%) notificações mencionaram AP, sendo 110 elegíveis para análise. A avaliação de causalidade mostrou que

em 27 (24%) notificações, a reação adversa ao medicamento e o erro de medicação identificados estavam possivelmente relacionados à AP, com um índice de subnotificação de 0,87. Destas 27 notificações, 03 reações adversas a medicamentos foram classificadas como “prováveis” e 23 como “possíveis”, e 04 erros de medicação, classificados “erro com dano: categoria E”. Embora as AP seja uma prática comum em hospitais, são escassas as notificações que as descrevem. Estudos futuros podem investigar o uso de AP como uma ferramenta para rastrear EAM, porque observamos que um em cada quatro notificações com relato de AP estava relacionado a EAM.

Palavras chaves: **Preparações extemporâneas, suspensão oral, reações adversas a medicamentos, segurança do paciente.**

Patricia de Carvalho Mastroianni ♦ Department of Drugs and Medicines, School of Pharmaceutical Sciences, São Paulo State University (UNESP) ♦ Rod. Araraquara - Jaú, Km 1 ♦ 14801-902 Araraquara – São Paulo (Brazil)

patriciamastroianni@yahoo.com.br

INTRODUCTION

The manipulation of industrialized pharmaceutical forms is often necessary in hospitals to ensure that inpatients receive adequate treatment according to their pathophysiological needs. In addition, this procedure needs to be safe and effective, not exposing the patients to an unnecessary risk¹. Extemporaneous compounding (EC) aims to meet this need and can be understood as preparing a drug for a specific individual in response to an identified need, usually performed for pediatric and geriatric patients, patients with invasive devices such as nasogastric tube, patients with dementia and rare diseases^{2,3}. EC occurs when there is no other option available on the market, when the product available is inappropriate⁴ or when it is necessary to improve patient adherence and effectiveness of a drug, especially in patients with dysphagia and neurodegenerative diseases⁵.

EC is common worldwide. In an Ireland hospital elderly care unit, about 35.1% of patients received at least one EC medication, which were most commonly modified to facilitate fractional dosing. Moreover, of the 44 unlicensed modifications, 14 were evidence-based and 30 were not⁶. According to Fodil *et al.* (2017),⁷ 40.3% of geriatric patients receive EC medication in long-term care units in teaching hospitals in Paris, France. In 104 cases, at least one medication could not be safely modified, including 26 cases in which none of the prescribed drugs were safe to crush or open. Recent data shows that three out of four patients hospitalized in a Brazilian hospital receive at least one medication that needed EC⁸. EC was identified in 88 different drugs of the 253 standardized drugs in the hospital pharmacy. However, there are 29 pharmaceutical alternatives in the Brazilian market for the 88 modified drugs, possibly decreasing EC by 28.5%⁹. This process can affect the pharmaceutical characteristics of the product and its therapeutic result, increasing the possibility of occurring adverse drug reaction (ADR), specially for drugs with a narrow therapeutic index, cytotoxic, teratogenic, hormones, steroids and for drugs that may irritate the gastrointestinal tract⁹.

Adverse drug events (ADE) can be defined as any harm caused to patients arising from drug use, such as medication errors (ME), ADR, allergic reactions, and overdoses¹⁰. EC can generate ME, since approximately 60% of the medications are not commercially available in the concentration required by the patient and there is no standardization of the final concentrations in extemporaneous preparations¹¹. In this context, the aim of this study was to assess the causality between ADR and EC and to analyze ME related to the EC using the spontaneous reports generated by the healthy team in a medium sized general hospital.

MATERIAL AND METHODS

Ethical approval

The study was approved by Américo Brasiliense State Hospital Research Ethics Committee and by the School of Pharmaceutical Sciences, São Paulo State University (UNESP) Ethics Committee (CEP/FCFAR number: 05752818.1.0000.5426).

Study design

An observational cross-sectional study was performed in a medium-complexity public hospital, based on the guideline Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)¹². The institution has an electronic health record, which includes, patient's medical history, diagnoses,

medications, treatment plans, allergies, radiology images and laboratory test results. All health professionals register their assessments, such as physicians, psychologists, physiotherapists, speech-language pathologists, pharmacists, nurses, nursing technicians and social workers.

In a cross-sectional study, the researcher measures the outcome and the exposures in the study participants at the same time and the participants are selected based on the inclusion and exclusion criteria set for the study. Cross-sectional studies are faster and are inexpensive, when compared with other studies like cohort. These types of study give information about the prevalence of outcomes or exposures, which can be useful for designing the cohort study. In contrast, since this is a one-time measurement, it is difficult to originate causal relationships. The prevalence of an outcome depends on the incidence of the disease as well as the length of survival following the outcome¹³.

Participants and data collection

ADR and ME spontaneous reports registered between August 2017 and July 2018 were collected, covering 53 beds in all hospital's wards. Inclusion criteria for causality assessment comprised all reports with any reference to an EC performed for patients in the hospital wards. The exclusion criteria included reports with no reference to EC, lack in data necessary for causality assessment and those that came from other sections and services of the hospital, since no patients would be hospitalized there. After that, it was performed a retrospective search for ADR, ME and changes in biochemical and hematological profile in the electronic health record. Finally, it was conducted the causality assessment between the ADR and the EC and the analysis of ME.

Data analysis

After data collection, the causality between the triggered ADR and the EC was performed using the World Health Organization – Uppsala Monitoring Center (WHO-UMC) algorithm since it is more suitable for monitoring ADR in a hospital environment¹⁴. The algorithm includes the categories "certain", "probable/likely", "possible", "unlikely", "conditional/unclassified" and "unassessable/unclassifiable"¹⁵. The causality assessment of ADR was performed by using clinical judgment, that considered the temporal relationship between the occurrence of the event and drug use; ADRs previously described in medication package insert; pharmacologic plausibility, whether the mechanism of action of the drug may produce the event and exclusion of confounding variables that may explain the case, such as clinical condition of the patient and other drug-related problems.

The analyses of potential ME related to the EC were performed by the National Council for Coordination of Reporting and Prevention of Medication Errors (NCCMERP) algorithm, which includes stratified categories: "no error: A", "error, no harm: B, C and D", "error, harm: E, F, G and H" and "error, death: I"¹⁶. The following information was used in both analysis: date of the incident, description of the report, mentioned medication, incident identified in the medical record, type of diet that the patient was receiving, patient's sex, height, weight, age and body mass index, period of hospitalization, pharmacotherapy, biochemical and hematological profile. Extemporaneous compounding techniques were classified in tablet dispersion and splitted tablet¹⁷.

Furthermore, studies comparing the pharmacokinetics between the administration of the intact tablet and the extemporaneously prepared drug or splitted tablet as well as drug polymorphism in solution were searched on PubMed to complement the analysis. The MeSH terms searched were: [(oral solution) AND tablet] AND "name of the drug"; [(Nasogastric) AND "name of the drug"]; [(Bioavailability) AND "name of the drug"]; [(Absorption) AND "name of the drug"]; [(Splitting) AND "name of the drug"]; [(Pharmacokinetics) AND "name of the drug"]; [(Crushed) AND "name of the drug"]; [(Solid-state) AND "name of the drug"]; [(Crystalline structure) AND "name of the drug"]; [(Crystalline) AND "name of the drug"]; [(Polymorph) AND "name of the drug"]. The medication package insert were also used to search for ADR.

The following equations were used to estimate the incidence and the underreporting of ADR and ME related to EC, respectively:

$$\text{Incidence of ADR and ME related to EC} = \frac{\text{Number of reports related to EC with harm}}{\text{Total of reports with EC registry}} \times 100$$

$$\text{ADR and ME related to EC underreporting index} = \frac{\text{no. of ADR and ME detected by triggers} - \text{no. of ADR}}{\text{Total of ADR and ME}} \times 100$$

RESULTS AND DISCUSSION

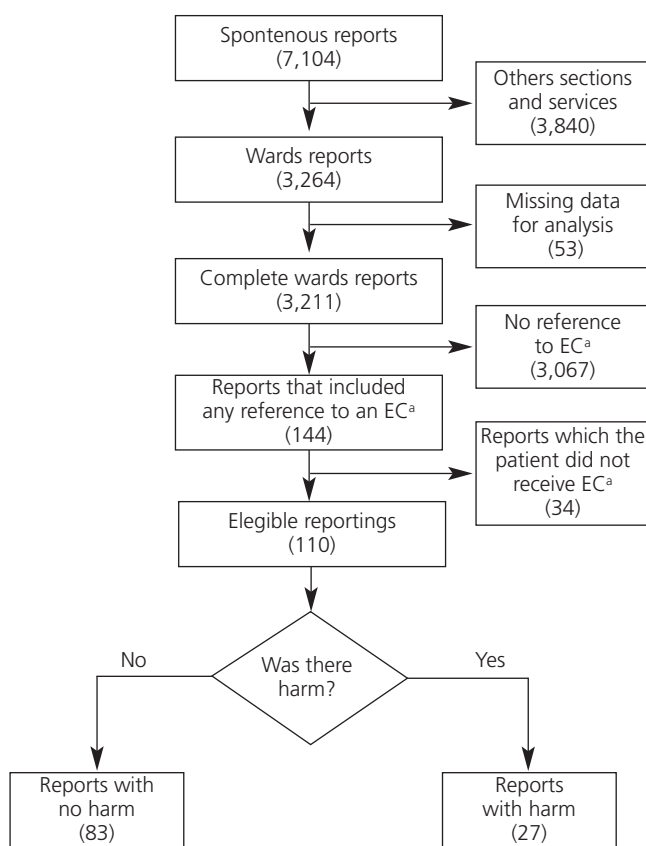
During the period, the hospital team generated 7,104 spontaneous reporting, of which only 144 were related to EC (Figure 1; Table 1). Thirty-four reports were excluded because the patient did not receive the EC preparation due to clinical pharmacist action suggesting pharmaceutical alternatives or changes in the administration route (Table 1). Then, from the 110 reports that mention EC analyzed, 85 described the tablet dispersion technique and 25 described splitted tablet technique.

The EM and ADR causality assessment showed that 83 reports resulted in no harm to patients whereas 27 resulted in harm (Figure 1). From these 27 reports were possible to classify 3 ADR as "probable" and 23 ADR as "possible" related to the EC whereas 4 EM were classified as "error, harm: category E" (Supplementary file).

Only 4.5% (144/3,211) of the reports mentioned EC. ADR and ME possibly associated to EC was estimated in 24% (27/110) of the reports. Furthermore, only 4 EM were described in the analyzed reports giving an underreporting index of 0.87 (26/30).

Little is known about the relation between ADR, ME and EC even though this procedure is quite often in hospitals. The ADR causality assessment and the EM analysis showed relationship to EC of some drugs leading to harm to the patient such as changes in patient's biochemical and hematological changes, mental confusion, agitation, constipation and vomiting. Few studies highlight the risk of EC. In one of them¹⁸, the EC practice had negative effects on medication use, causing minor to severe harm such as diarrhea, stomach perforation and can lead the patient to death. Other authors¹⁹ reported the death of a patient after daily administration of a crushed prolonged-release nifedipine tablet by nasogastric tube, concluding that procedure caused severe hypotension due to the high plasma concentration of nifedipine generated by the immediate release of the entire 90 mg dose. The EC of enteric coated drugs are specially linked to the incidence and severity of ADR in upper and lower gastrointestinal tract²⁰. Yet, conventional-

Figure 1. Flowchart of data collection



^a: extemporaneous compounding.

coated drugs can also cause ADR due to EC, since this process can increase the speed of absorption and bioavailability²¹.

The rate of spontaneous reporting by health professionals is low worldwide and is not a mandatory requirement in most countries²². In Brazil, according to Varallo *et al.* (2018)²³, the perception and the cause of underreporting by the health team are indifference, distrust, ignorance and guilt. In addition, professionals believe that only the nursing team must report. This present study evidence the underreporting of ADR and ME possibly related to EC since only 4 ME were reported. Only 4.5% of the reports mentioned EC, whereas ADR and ME possibly associated to EC was estimated in 24% of the reports.

Studies about EC pharmacokinetics/pharmacodynamics and drug polymorphism in solution are scarce yet essential to complement the causal assessment and to discriminate if the ADR and ME came from the EC procedure or the drug itself. A clinical study demonstrated that the preparation of amlodipine in suspension and the intact tablet are bioequivalent, despite the need to observe EC stability²⁴. However, another clinical study showed lack of bioequivalence between preparing a clopidogrel solution and the intact tablet. The patients that received the EC preparation showed an increase in the absorption speed in 40 minutes, and an almost two-fold increase in the area under the curve²¹. Nonetheless, EC can also promote adherence and can improve the pharmacotherapeutic effectiveness in elderly patients with dysphagia and neurodegenerative diseases, as reported by Mastroianni and Forgerini (2018).

Table 1. Description of reports excluded

| Description | n |
|--|-------|
| Reports that not came from the hospital wards (3,840) | |
| Surgery center | 3,148 |
| Surgical clinic | 651 |
| Ambulatory | 11 |
| Image diagnostics center | 3 |
| Material and sterilization center | 1 |
| Endoscopy center | 5 |
| Board of directors | 1 |
| Financial section | 2 |
| Stabilization room | 13 |
| Tomography center | 5 |
| Reports with missing information (53) | |
| No incident date | 2 |
| No incident location | 22 |
| No patient registration | 29 |
| Reports that not included any reference to an EC a e add* (3,067) | |
| Process error | 1,711 |
| Medication error | 914 |
| Deviation from drug quality | 46 |
| Adverse drug reaction | 140 |
| Problems with invasive diapositives | 172 |
| Hospital-acquired pressure injury | 46 |
| Falls | 38 |
| Reports which the patient did not receive EC (34) | |
| Suspended medication | 34 |

*: extemporaneous compounding

EC are indispensable to treat a range of conditions and it occurs in health services worldwide. However, there seems to be a lack of knowledge about EC safety. Data of this study shows that only a small number of reports includes the EC. However, one out of four reports that mentioned EC leads to patient harm. The hospital's guideline for EC practice allows the procedure under some circumstances, such as the unavailability of the active pharmaceutical ingredient in the market or a basic dosage form absent in the concentration compatible with the needs of the patient¹⁷.

The professional continuing education as well as periodic training seems to develop abilities and skills to ensure the quality of EC preparation, to improve the professionals' perception of this practice and the culture of spontaneous reporting²³. Additionally, Glass and Haywood (2006)²⁵ and others²⁶ provide a management guideline for EC practice. In the absence of the proper pharmaceutical form, a therapeutic alternative should be dispensed. If none is available, a pharmacopeia formula should be dispensed. The third op-

tion would be a research for stability-validated formulation. The final decision relays on the use of scientific principles and tablet dispersion.

This study has some limitations. Data collection was conducted in a general medium-complexity public hospital. Hence, data may not be generalizable to other types of institutions. The causality assessments were conducted using medical record from patients that had already been discharged. This approach could delay the identification of potential confounding variables that were not described in the medical records. The algorithms used were not developed to evaluate the use of EC. To reduce the error of analysis, it was necessary to complement it with studies of pharmacokinetics and polymorphism. Many inpatients that necessitated EC had poor health conditions or several comorbidities and polypharmacy. These factors might confound causality assessment for ADR. Further studies are necessary to evaluate the efficacy and safety of EC. Future studies may investigate the use of EC as a trigger tool for ADR since this study shows that one out of four reports that mentioned EC leads to patient harm.

CONCLUSION

Extemporaneous compounding are rarely mentioned in spontaneous reports (4.5%). One out of every four reports that mentioned EC is linked to ADR and ME (24%). Furthermore, there are an underreporting index of 0.87 of ADR and ME related to EC. That is, among 10 events triggered, 8 were underreported. This is, to the best of our knowledge, the first study that associate the ADR and ME to EC, a very common practice in hospital pharmacy. Considering that EC are indispensable to meet inpatients' pharmacotherapeutic needs, the data suggest triggering EC to identify underreporting of ADR and EM.

Acknowledgements: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) – finance code 001 " to This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brasil (CAPES)—Finance Code 001

Conflicts of interest: The authors declare that they have no conflict of interest.

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Supplementary file**Table 2. Description and frequency of adverse drug events based on the reports with records of extemporaneous compounding**

| Adverse drug event | Number of occurrences | Suspected drug(s) | Prescribed dose | Type of extemporaneous compounding | References |
|--|------------------------------|---|---|---|---|
| Hypotension | 1 | Furosemide | 20 mg BID | Splitting tablet | 1, 2, 3 |
| Increased creatinine | 1 | Furosemide | 20 mg BID | Splitting tablet | 1, 2, 3 |
| Agitation | 1 | Morphine | 10 mg QID | Dispersed tablet | 4, 5 |
| Constipation | 4 | Simvastatine, Hydrochlorothiazide, Morphine, Carvedilol and Doxazosin | Simvastatine: 40 mg QD; Hydrochlorothiazide: 25 QD; Morphine: 5 mg q4h; Carvedilol: 12,5 mg BID; Doxazosin: 2 mg QD | Dispersed tablet | Simvastatine (6, 7); Hydrochlorothiazide (8, 9, 10); Morphine (4, 5); Carvedilol (11, 12, 13); Doxazosin (14) |
| Confusion | 2 | Clopidogrel and Simvastatin | Clopidogrel: 225 mg QD; Simvastatin: 20 mg QD | Dispersed tablet | Clopidogrel (15, 16, 17, 18); Simvastatine (6, 7) |
| Agitation | 2 | Acetaminophen + Codeine, Morphine | Acetaminophen + Codeine: 500 mg + 30 mg QID; Morphine: 5 mg QID | Dispersed tablet | Acetaminophen + Codeine (19, 20, 21, 22); Morphine (4, 5) |
| Hypotension | 2 | Clonidine, Clopidogrel, Carvedilol and Doxazosin | Clonidine: 300 g QID Clopidogrel: 75 mg QD; Carvedilol: 12,5 mg BID; Doxazosin: 2 mg QD | Dispersed tablet | Clonidine (23, 24); Clopidogrel (15, 16, 17, 18); Carvedilol (11, 12, 13); Doxazosin (14) |
| Somnolence | 1 | Morphine | 5 mg QID | Dispersed tablet | 4, 5 |
| Hyperglycemia | 1 | Clonidine | 150 µg QID | Dispersed tablet | 23, 24 |
| Hypoglycemia | 1 | Losartana | 25 mg BID | Splitting tablet | 25, 26 |
| Acute renal failure | 1 | Rifampicin and Sulfamethoxazole + Trimethoprim | Rifampicin: 600 mg QD; Sulfamethoxazole + Trimethoprim: 800 mg + 160 QD | Dispersed tablet | Rifampicin (27, 28, 29); Sulfamethoxazole and Trimethoprim (30, 31, 32) |
| Vomiting | 1 | Quetiapine | 25 mg BID | Dispersed tablet | 33 |
| Gastric irritation | 1 | Hydrochlorothiazide and Simvastatin | Hydrochlorothiazide: 25 mg QD; Simvastatin: 40 mg QD | Splitting and dispersed tablet | Hydrochlorothiazide (8, 9, 10); Simvastatin (6, 7) |
| Increase in liver enzymes | 1 | Lorazepam | 2 mg QD | Dispersed tablet | 34 |
| Epigastric pain | 1 | Prednisone, Morphine and Simvastatin | Prednisone: 10 mg QD; Morphine: 5 mg QID; Simvastatin: 40 mg QD | Dispersed tablet | Prednisone (35); Morphine (4, 5); Simvastatin (6, 7) |
| Insomnia | 1 | Simvastatin | 20 mg QD | Dispersed tablet | 6, 7 |
| Disorientation | 1 | Morphine | 5 mg q4h | Dispersed tablet | 4, 5 |
| Hyponatremia | 1 | Hydrochlorothiazide | 25 mg QD | Dispersed tablet | 8, 9, 10 |
| Fainting | 1 | Doxazosin | 2 mg QD | Dispersed tablet | 14 |
| Lack of appetite | 1 | Hydralazine | 25 mg TID | Splitting tablet | 36 |
| Lack of prescription of a necessary medication | 2 | Nicotine patch | Not applicable | Not applicable | Not applicable |
| Bronchoaspiration | 1 | Not applicable | Not applicable | Not applicable | Not applicable |
| Choking | 1 | Not applicable | Not applicable | Not applicable | Not applicable |

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