Brief Communication

Drug Therapeutic Failures as a Cause of Admission to an Intensive Care Unit at a University Hospital

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Abstract

Objective: Drug therapeutic failures (TFs) are included in pharmacovigilance reporting, as some authors consider them a type of adverse drug reaction. Given their high frequency in Colombia, we studied their importance as a cause of admission to an intensive care unit (ICU). **Methods:** This was a cross-sectional observational study. Clinical records of patients who arrived at the emergency service of a third-care level university hospital were reviewed. Information was collected by a resident in clinical toxicology, and each case was validated and analyzed by a research team using the algorithm proposed by Vaca González and Schumock and Thornton criteria for preventability to evaluate the existence of possible medication errors. **Findings:** In total, 697 clinical records were evaluated and 18 patients presented TFs (2.6%, 95% confidence interval 1.5%–4.1%) as the cause of admission to the ICU. The most frequent TFs were seizures (56%) and hypertension (28%). The most commonly associated medications were valproic acid (28%) and losartan (28%). Ten cases (56%) were associated with drug misuse and the same number of cases was preventable, according to Schumock and Thornton criteria. **Conclusion:** This is the first study assessing TFs as a cause of admission to the ICU in the Colombian population. The frequency of TFs in our study was similar to that described in the literature; being the most common cause the inappropriate drug use, particularly for drugs with complex kinetics, such as antiepileptic drugs.

Keywords: *Drug-related side effects and adverse reactions, intensive care units, patient admissions, pharmacovigilance, postmarketing, product surveillance*

Received: 30-08-2018.
Accepted: 20-03-2019.
Published: 16-10-2019.

Introduction

Adverse drug reactions (ADRs) are recognized as a public health problem, and their prevalence is estimated to be between 1% and 60%.[1] Between 0.2% and 15% of hospital admissions are considered to be related to ADRs, increasing the length of hospital stay, and doubling health-care costs.[2] Similarly, ADRs increase the number of readmissions between 16% and 37% with an increase in mortality between 9% and 13%.[3]

Therapeutic failure (TF) is a term widely used in clinical practice. Its inclusion as ADR was proposed by Hartigan-Go and Wong.[4] in the year 2000, considering it a type F reaction within the alphabetical classification of ADRs. Figueras *et al*.[5] stated that the inclusion of this term in pharmacovigilance programs deserves special consideration because it helps to identify possible pharmaceutical defects in drug production processes preceding prescription (manufacture, transport, and storage). The World Health Organization (WHO) defines a lack of efficacy as the "unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation."[6]

TFs increase the length of hospital stay, promote disease persistence, reduce the quality of life, and increase

Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_18_69

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How to cite this article: Ruiz-Garzón JA, Rojas-Velandia CA, Calderon-Ospina CA. Drug therapeutic failures as a cause of admission to an intensive care unit at a university hospital. J Res Pharm Pract 2019;8:168-73.

social costs of the disease. TFs have been estimated to increase health-care costs by approximately US $100 million per year.[7] In Colombia, TFs accounted for 10% of all ADRs reported in 2005 and 3.3% in 2014 according to the reports of the National Institute of Food and Drug Monitoring (INVIMA, for its acronym in Spanish), which operates as the medicines regulatory agency in Colombia.[8] In the study by Chaves.[9] that assessed ADR reports in adults over 44 years of age recorded in the database of the Bogota District Drug Monitoring Programme during 2012, TFs were the cause of 5.5% of all cases. Another study conducted in hospitalized Colombian patients found a frequency of TFs of 18.8%.[10]

More than two decades ago, Hallas *et al*. proposed an algorithm to determine the cause of TFs; however, its usefulness is very limited. Recently, in response to the public health problem posed by the number of TF reports in Colombia, Vaca González *et al*.[8] proposed an instrument for assessing this drug-related problem by including different dimensions, such as pharmacological, biopharmaceutical, and even marketing aspects. However, few studies have used this TF assessment tool, and its performance is unknown to evaluate TFs as a reason for admission to the intensive care unit (ICU).

This study aimed the importance of TFs as a cause of admission to an ICU of a third-level care hospital and the degree of concordance between Vaca González *et al*. algorithm and the Schumock and Thornton preventability criteria to assess TF cases.

Methods

This was a cross-sectional observational study, part of a bigger one.[11] We evaluated the medical charts of patients who were admitted to the ICU during a 4-month period between September and December 2012; the objective was to identify patients who were consuming one or more drugs at the time of admission, whose hospitalization was considered to be drug-related, and who were admitted to the ICU of the Hospital Universitario Mayor, a tertiary-level care hospital in Bogota, Colombia. All patients were admitted to the ICU on the day of their admission, and most of them were brought by ambulance from their homes. Additional information was obtained through personal interviews with the patients' relatives or treating physicians.

For the purposes of the study, the definition of TF proposed by the WHO was used, which is an "unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation."[6] Suspected cases of TFs were identified by a resident in clinical toxicology, through the systematic evaluation of the totality of clinical histories of the patients who were admitted to the ICU during the study period. The data abstracted and evaluated were gender, age, TF (e.g., status epilepticus), record of all medications consumed by the patient including dosage, frequency and duration of treatment, comorbidities, and paraclinical examinations if available. Data related with medication adherence and use of a generic (or specific trademark) brand were asked directly to the patients or their relatives. Patients with incomplete medical charts or missing information (e.g., without data about treatment adherence) were excluded of the study.

Each case was later validated and analyzed by a research team composed of two pharmacologists, two emergency department physicians, and five general practitioners; this team used the algorithm proposed by Vaca González *et al*.[8] and Schumock and Thornton criteria for assess preventability.[12] In a consensus meeting, we evaluated each case, answering each of the questions of the Vaca González algorithm and the Schumock and Thornton criteria, respectively. This assessment allowed us to classify TFs as preventable or nonpreventable and the causality categories that they belonged.

Statistical methods included descriptions of categorical variables by percentages, using 95% confidence intervals (CIs).

Clinical records were only reviewed, without any intervention or modification of the treatment received by the patient. Confidentiality of the information was ensured, and the study protocol was approved by the Ethics Committee of Research of the Universidad Del Rosario and the Hospital Universitario Mayor. The ethical approval code of the study was CEI-ABN026-000450.

Results

During the assessment period, 697 patients were admitted to the ICU, of which 18 had a TF as their cause of admission (2.6%, 95% CI 1.5%–4.1%). Ten cases (55.6%, 95% CI 33.7–75.4) were seizures related to antiepileptic drugs and five (27.8%, 95% CI 12.5–50.9) were hypertensive emergencies related to antihypertensive drugs. The other three cases were one (5.6%, 95% CI 1.0–25.8) of diabetic ketoacidosis related to insulin, one (5.6%, 95% CI 1.0–25.8) of ascites related to furosemide and spironolactone, and one (5.6%, 95% CI 1.0–25.8) of ischemic cerebrovascular disease related to warfarin. All TF cases are described in Table 1.

Regarding the assessment of disease history that could interfere with the pharmacokinetics and pharmacodynamics of drugs associated with TFs, the

presence of renal failure, liver failure, pregnancy, hypoalbuminemia, malnutrition, and morbid obesity were systematically assessed. Only one patient had a history of renal failure (TF related to antiepileptic therapy with phenytoin), but this condition was not considered a predisposing factor for TF.

With regard to the preventability of TFs assessed by the Schumock and Thornton criteria,[12] 55.6% (95% CI 33.7–75.4) of the cases were found to be preventable, 38.9% (95% CI 20.3–61.4) were classified as not preventable, and 5.6% (95% CI 1.0–25.8) could not be classified according to the available information.

According to the algorithm of Vaca González *et al*.,[8] ten cases (55.6%, 95% CI 33.7–75.4) were associated with inappropriate drug use (affirmative answer to questions 1–6 of the algorithm of Vaca González *et al*.,). On the other hand, in four of the cases reported (22.2%, 95% CI 9.0–45.2), there was not enough information for the analysis. Two of the cases assessed (11.1%, 95% CI 3.1–32.8) were cases of drug-resistant epilepsy that could have been explained by the idiosyncrasies of the patient, whereas the two remaining cases were considered to be induced by market competition (11.1%, 95% CI 3.1–32.8).

Discussion

TF is a complex and multifactorial phenomenon that may cause admission to the ICU. The strengths of our study consisted in the systematic evaluation of TF cases as a cause of admission to the ICU, through an intensive pharmacovigilance method, and to the best of our knowledge, it was the first study of this nature to use a validated algorithm for the evaluation of their causes. An approximate frequency of 3% was identified, and this value is not negligible given that these were serious and potentially fatal adverse events.

During the assessment period, TFs represented 2.6% of all ICU admissions and 19% of all ADR cases. The average age was 58 years, and the condition was equally distributed between women and men. This result is like that reported by Hallas *et al*.,[13] in which ADRs and TFs were assessed as a cause of hospital admission to the medical department of the University Hospital of Odense in Denmark over a period of 2 months. Of the total admissions, TFs represented 2.7% and were defined as probable and definitive according to the algorithm proposed by the researchers. Two years later, Hallas *et al*.[14] conducted a second study, in which they assessed both ADRs and TFs as a cause of admission

Table 1: Description of cases of therapeutic failures including the category of causality to which they belong (*n*=18)

Age (years)	Sex	Drug related with TF	TF	Causality category (Vaca González *et al*.[8])
60	Female	Valproic acid	Seizures	Possible report induced by business interest
49	Female	Carbamazepine	Seizures	Possible association with drug misuse
50	Female	Carbamazepine Phenobarbital	Seizures	Possible association with drug misuse
41	Male	Valproic acid Phenytoin	Seizures	Possible association with drug misuse
46	Male	Phenytoin	Seizures	Possible association with drug misuse
17	Male	Valproic acid	Seizures	Possible report induced by business interest
61	Male	Warfarin	Ischemic cerebrovascular disease	Possible association with drug misuse
79	Female	Losartan Clonidine	Hypertension	Not enough information for the analysis
63	Female	Valproic acid	Seizures	Possibly associated with an idiosyncratic response
74	Female	Furosemide Spironolactone	Ascites	Possible association with drug misuse
20	Female	Valproic acid	Seizures	Possibly associated with an idiosyncratic response
76	Male	Insulin	Diabetic ketoacidosis	Possible association with drug misuse
44	Male	Carbamazepine	Seizures	Possible association with drug misuse
62	Male	Carbamazepine	Seizures	Possible association with drug misuse
89	Male	Losartan	Hypertension	Not enough information for the analysis
88	Female	Losartan Spironolactone Furosemide Amlodipine	Hypertension	Not enough information for the analysis
60	Male	Losartan	Hypertension	Not enough information for the analysis
60	Female	Losartan	Hypertension	Possible association with drug misuse

TF=Therapeutic failure

to six different medical departments of the same hospital (geriatrics, infectious diseases, endocrinology, cardiology, respiratory medicine, and gastroenterology). The assessment criteria were the same as those used in the previous study, and a frequency of 3% for TFs as a cause of admission to these departments was reported, which is similar to that described in our study.

Franceschi *et al*.[15] determined the frequency of TFs as a cause of admission to the emergency department, assessing 123 admissions. Of these admissions, 48.8% (60 patients) coincided with the definition of TF proposed by the authors. These cases were assessed with the algorithm of Hallas *et al*.,[13] and the results revealed that one-third of the cases were suspected TFs. This condition was similar between genders and more frequent in elderly patients, being the distribution like that found in our study. Of these cases, 24.4% were considered serious TFs.

In the study by Baena *et al*.[16] performed in the emergency department of a university hospital in Granada, Spain, between November 2000 and October 2001, drug-related problems were actively assessed as a cause of admission to the hospital's emergency department. Of the 2261 patients admitted to the emergency department during the assessment period, therapeutic ineffectiveness was the most common ADR, accounting for 19.8% of the cases, being practically the same figure as in our study.

Another study was conducted by Andreazza *et al*.,[17] in which drug-related problems were assessed as a cause of admission to the emergency department of the Hospital de Clinicas of Porto Alegre, Brazil, through the active search of cases by an experienced team. Of all 335 patients admitted for drug-related problems, TFs accounted for 54.5% of the cases, involving drugs that required continuous monitoring by the health team. Similarly, 17.9% of drug-related problems were secondary to an inappropriate dosage regimen.

It is possible that the increased frequency of TFs in the studies of Franceschi *et al*.[15] and Andreazza *et al*.[17] is attributed to the type of department assessed (emergency departments) and the working definition for detecting TFs. On the other hand, our study assessed the impact of TFs as a cause of admission to the ICU, which means a greater severity of the condition of the patient to justify the admission to a department of such a level of complexity, which could have a negative impact on the frequency of cases identified.

In our study, most TFs corresponded to patients receiving anticonvulsants who were admitted to the ICU for status epilepticus and represented approximately half of the cases assessed, and valproic acid was the most commonly implicated drug. The TFs that followed in frequency included hypertensive crises (related to antihypertensive drugs) in a quarter of the cases, in which the drug most commonly involved was losartan. These results are like those described by Hallas *et al*.[13] who found that most TFs were secondary to anticonvulsant drugs, but the mechanism leading to TF was not clear. At this point, it is important to remember that given the natural history of the disease, approximately one-third of epileptic patients suffer from a refractory form of the disease, which is resistant to drug treatment, including combination drug schemes.[18] Thus, two (9.5%) cases in our study were classified as being related to the idiosyncratic factors of the patient (drug-resistant epilepsy).

It is also accepted that different anticonvulsant drugs (including valproic acid) require close therapeutic monitoring given their complex pharmacokinetics. The main objective of this monitoring must be to avoid TFs and the adverse effects of these drugs, allowing the design of an individualized dosing regimen.[19,20]

Age is one factor frequently related to TFs, as demonstrated in the study conducted by Kaiser *et al*.[21] who determined the frequency and factors associated with TFs as a cause of hospitalization in patients older than 65 years using the TF Questionnaire developed by the authors. The study was based on three critical elements: the lack of application of evidence-based pharmacotherapy for a given medical condition, inadequate drug dosing related to a problem of prescription or adherence of the patient, and pharmacological interaction interfering with the effectiveness of the prescribed drug. The study was conducted in 11 veterans' centers, demonstrating that 40 (37.7%) of the 106 assessed patients were classified as possible TFs and 12 (11.3%) were classified as probable.

In our study, age and exogenous factors could be predisposing factors for TF. Age is one of the factors most commonly associated with the presence of TF due to pharmacokinetics and pharmacodynamics changes in the elderly.[22,23] Similarly, the number of drugs taken by a patient has been reported to be directly related to the risk of developing adverse drug events, including TFs, given the possible drug interactions that might lead to a decrease in plasma concentration of some drugs or cause antagonistic interactions among them.[24,25]

When assessing the causality of TFs with the algorithm of Vaca González *et al*.,[8] most cases were possibly associated with inappropriate drug use, which is consistent with the results reported by the authors of the algorithm in their validation study. Similar results were

also reported in the study by Henao *et al*.,[10] in which 42% of TFs were attributed to inappropriate drug use.

More than half of the cases (56%) in our study could be explained by inappropriate drug use based on the criteria described by Vaca González *et al*. in their algorithm,[8] including insufficient monitoring of drugs with complex kinetics, inappropriate drug use, inappropriate prescription, lack of patient training, and drug interactions. This figure coincides exactly with the percentage of cases considered preventable according to the Schumock and Thornton criteria,[12] which highlights the high degree of concordance between these ADRs evaluation systems.

Using subtherapeutic doses is another important component of inappropriate drug use that might lead to TF, as demonstrated in the study by Schnurrer *et al*.[26] conducted on physicians belonging to the department of internal medicine at three university hospitals and four municipal hospitals in Germany. Schnurrer *et al*. found that 15% of the drugs were formulated at subtherapeutic doses to patients in whom these drugs were commonly prescribed. In our study, we found that 18% of TF cases could be explained because of using subtherapeutic doses.

Finally, lack of compliance should always be considered when a drug seems ineffective, understanding compliance as "the degree to which the patient's behavior, in terms of taking the drug, following the diet, or making lifestyle changes, agrees with the clinical prescription."[27] According to the study by Kaiser *et al*.,[21] lack of compliance is a very common cause of TFs (58%). Similarly, in our study, we found that more than half of TF cases could be explained by inadequate use of the drug.

Regarding the limitations of this study, it was retrospective in nature and based on medical records. As we explored the occurrence of TFs in a single hospital and a specific service with unique characteristics (the ICU), the results cannot be generalized to other settings.

TF is a complex and multifactorial phenomenon that may cause admission to the ICU. This study is the first attempt to systematically assess TFs as a cause of admission to the ICU of a third-level university hospital. An approximate frequency of 3% was identified. This value is not negligible given these are serious adverse and potentially fatal events. Given that more than half of the cases were related to inappropriate drug use (including lack of adherence) and were associated to antiepileptic drugs, it highlights the importance of ensuring patients' access to these drugs in the outpatient setting, educating patients about taking the drug and its continuous use, and ensuring therapy monitoring (e.g., periodic monitoring of plasma levels), making pharmacotherapy more effective and safer and optimizing the risk/benefit ratio.

As main conclusions of our study, we found that the frequency of TFs as the reason for admission to the ICU of a Colombian University Hospital of third level of complexity is around 3%. Almost half of the cases of TFs were preventable, because they were associated with inappropriate use of medication. Finally, more than 50% of TFs were associated with antiepileptic drugs, which highlight the relevance of the therapeutic drug monitoring.

Authors' Contribution

Jair-Antonio Ruiz-Garzon designed the work, analyzed the data, drafted the manuscript, and approved the final article. Carlos-Alberto Calderon-Ospina interpreted the data for this work, revised the manuscript and approved the final manuscript. Camilo-Andrés Rojas-Velandia collected the data, revised, and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Miguel A, Azevedo LF, Araújo M, Pereira AC. Frequency of adverse drug reactions in hospitalized patients: A systematic review and meta-analysis. Pharmacoepidemiol Drug Saf 2012;21:1139-54.
2. Hohl CM, Nosyk B, Kuramoto L, Zed PJ, Brubacher JR, Abu-Laban RB, *et al.* Outcomes of emergency department patients presenting with adverse drug events. Ann Emerg Med 2011;58:270-9. e4.
3. Walter SR, Day RO, Gallego B, Westbrook JI. The impact of serious adverse drug reactions: A population-based study of a decade of hospital admissions in new South Wales, Australia. Br J Clin Pharmacol 2017;83:416-26.
4. Hartigan-Go KY, Wong JQ. Inclusion of therapeutic failures as adverse drug reactions. Side Eff Drugs Annu 2000;23:27-33. Available from: http://www.sciencedirect.com/science/article/pii/S0378608000800069. [Last accessed on 2018 Jul 10].
5. Figueras A, Pedrós C, Valsecia M, Laporte JR. Therapeutic ineffectiveness: Heads or tails? Drug Saf 2002;25:485-7.
6. World Health Organization, The Uppsala Monitoring Centre. The Importance of Pharmacovigilance. Uppsala: World Health Organization, The Uppsala Monitoring Centre; 2002.
7. Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: Updating the cost-of-illness model. J Am Pharm Assoc (Wash) 2001;41:192-9.

8. Vaca González CP, Martínez RP, López Gutiérrez JJ, Sánchez Pedraza R, Figueras A. Algorithm for the evaluation of therapeutic failure reports – Proposal and pilot analysis. Pharmacoepidemiol Drug Saf 2013;22:199-206.
9. Chaves M. Characterization of adverse drug reactions in adults over 44 years of age in Bogota, January-December, 2012. Biomedica 2015;35:34-42.
10. Henao Y, Parrado IY, Ospina M, Botero PL. Description of the Causality Categories of possible therapeutic failures reported to the Parmacovigilance Program of AUDIFARMA S.A. Pharm Care Esp 2016;18:55-66.
11. Rojas-Velandia C, Ruiz-Garzón J, Moscoso-Alcina JC, Vallejos-Narvaéz Á, Castro-Canoa J, Bustos-Martínez Y, *et al*. Characterization of adverse drug reactions causing admission to an intensive care unit. Br J Clin Pharmacol 2017;83:1134-40. doi:10.1111/bcp.13199.
12. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992;27:538.
13. Hallas J, Harvald B, Gram LF, Grodum E, Brøsen K, Haghfelt T, *et al.* Drug-related hospital admissions: The role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med 1990;228:83-90.
14. Hallas J, Gram LF, Grodum E, Damsbo N, Brøsen K, Haghfelt T, *et al.*Drug-related admissions to medical wards: A population-based survey. Br J Clin Pharmacol 1992;33:61-8.
15. Franceschi A, Tuccori M, Bocci G, Vannozzi F, Di Paolo A, Barbara C, *et al.* Drug therapeutic failures in emergency department patients. A university hospital experience. Pharmacol Res 2004;49:85-91.
16. Baena MI, Faus MJ, Fajardo PC, Luque FM, Sierra F, Martinez-Olmos J, *et al.* Medicine-related problems resulting in emergency department visits. Eur J Clin Pharmacol 2006;62:387-93.
17. Andreazza RS, Silveira De Castro M, Sippel Köche P, Heineck I. Causes of drug-related problems in the emergency room of a hospital in Southern Brazil. Gac Sanit 2011;25:501-6.
18. Galindo-Mendez B, Mayor LC, Velandia-Hurtado F, Calderon-Ospina C. Failure of antiepileptic drugs in controlling seizures in epilepsy: What do we do next? Epilepsy Behav Case Rep 2015;4:6-8.
19. Johannessen SI, Tomson T. Pharmacokinetic variability of newer antiepileptic drugs: When is monitoring needed? Clin Pharmacokinet 2006;45:1061-75.
20. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disord 2014;16:409-31.
21. Kaiser RM, Schmader KE, Pieper CF, Lindblad CI, Ruby CM, Hanlon JT. Therapeutic failure-related hospitalisations in the frail elderly. Drugs Aging 2006;23:579-86.
22. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 2011;50:99-110.
23. Sera LC, McPherson ML. Pharmacokinetics and pharmacodynamic changes associated with aging and implications for drug therapy. Clin Geriatr Med 2012;28:273-86.
24. Raschetti R, Morgutti M, Menniti-Ippolito F, Belisari A, Rossignoli A, Longhini P, *et al.* Suspected adverse drug events requiring emergency department visits or hospital admissions. Eur J Clin Pharmacol 1999;54:959-63.
25. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag 2008;4:269-86.
26. Schnurrer JU, Stichtenoth DO, Frölich JC. Knowledge on drug dosages of ward physicians. Eur J Clin Pharmacol 2002;58:65-7.
27. Haynes RB, Sackett DL. Introduction. Compliance with Therapeutic Regimens. Baltimore: Johns Hopkins University Press; 1976. p. 1-6.