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Detection of Adverse Drug Reactions in hospitalized patients: a network analysis approach

Detecção de Reações Adversas a Medicamentos em pacientes hospitalizados: uma abordagem de análise em rede

Detección de Reacciones Adversas a Medicamentos en pacientes hospitalizados: un enfoque de análisis de redes

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Keywords: Drug-Related Side Effects and Adverse Reactions; Inpatients; Drug Therapy; Observational Study.

ABSTRACT

Objective: We aimed to investigate whether network analysis can be used to estimate patterns of Adverse Drug Reactions and drugs involved. Methods: Patients admitted from 18 years of age or older, hospitalized for more than 24 hours, and using at least one drug during hospitalization were included. Results: 8060 patients were observed, and 358 cases of Adverse Drug Reactions were identified (4.43%). The network graph shows that the occurrence of hypotension induced by furosemide, spironolactone and enalapril is related to serum changes in potassium and the occurrence of renal failure. Centered around nausea and vomiting node, there is a great variety of drugs from different classes involved with this Adverse Drug Reaction and without other connections. Conclusion: Network analysis is a promising strategy for identifying patterns that correlate adverse reactions to drugs administered during hospitalization.

Descritores: Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Pacientes Internados; Terapia Medicamentosa; Estudo Observacional.

RESUMO

Objetivo: Nosso objetivo foi investigar se a análise de redes é capaz de estimar padrões de Reações Adversas a Medicamentos e medicamentos envolvidos. Métodos: Foram incluídos pacientes admitidos a partir de 18 anos de idade ou mais, hospitalizados por mais de 24 horas e que utilizaram pelo menos um medicamento durante a internação. Resultados: Foram observados 8060 pacientes e identificados 358 casos de Reações Adversas a Medicamentos (4,43%). O gráfico de rede mostra que a ocorrência de hipotensão induzida por furosemida, espironolactona e enalapril está relacionada a alterações séricas de potássio e à ocorrência de insuficiência renal. Em torno do nó de náusea e vômito, há uma grande variedade de medicamentos de diferentes classes envolvidos nessa Reação Adversa a Medicamentos, sem outras conexões. Conclusão: A análise de redes é uma estratégia promissora para identificar padrões que correlacionam Reações Adversas a Medicamentos administrados durante a hospitalização.

Descriptores: Efectos Secundarios y Reacciones Adversas Relacionados con Medicamentos; Pacientes Hospitalizados; Terapia Medicamentosa; Estudio Observacional.

RESUMEN

Objetivo: Nuestro objetivo fue investigar si el análisis de redes permite estimar patrones de Reacciones Adversas a Medicamentos y medicamentos involucrados. Métodos: Se incluyeron pacientes admitidos a partir de los 18 años o mayores, hospitalizados por más de 24 horas y que utilizaron al menos un medicamento durante la hospitalización. Resultados: Se observaron 8060 pacientes e identificaron 358 casos de Reacciones Adversas a Medicamentos (4,43%). El gráfico de red muestra que la aparición de hipotensión inducida por furosemida, espironolactona y enalapril está relacionada con cambios séricos en el potasio y la aparición de insuficiencia renal. Alrededor del nodo de náuseas y vómitos, hay una gran variedad de medicamentos de diferentes clases involucrados en esta Reacción Adversa a Medicamentos, sin otras conexiones. Conclusión: El análisis de redes es una estrategia prometedora para identificar patrones que correlacionen reacciones adversas a los medicamentos administrados durante la hospitalización.

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INTRODUCTION

Adverse drug reactions (ADRs) are a concern in clinical practice, especially considering the great inter-individual variability and the use of multiple medications in hospitalized patients[1]. With an estimate that 16.9% of patients have one or more ADRs during hospitalization,[2] these prolong the hospitalization time and increase hospital costs, in addition to the increase in morbidity and mortality[3,4]. The inappropriate management of adverse events, due to the negligence of these situations, exposes the patient to additional preventable risks[3].

The identification of ADRs is not a simple process, since signs or symptoms manifested by the patient can be confused with worsening of the clinical condition or related to medication errors[5]. In addition, a single medication can present different ADRs, from light reactions to others of greater severity[6]. Another factor that makes it difficult to establish the causality of an ADR is the administration of multiple medications, a common practice in the hospital environment.

Considering the clinical relevance and complexity of the variables involved with the occurrence of ADRs, the need for an approach that identifies patterns and facilitates their identification in professional practice is highlighted. In this context, network analysis is an important strategy for the interpretation of complex data, allowing for greater extraction of relevant information through the visualization of patterns[7]. Therefore, we aimed to investigate whether network analysis performs to estimate patterns of ADRs and drugs involved.

METHODS

Study design and population

This is an observational, analytical, longitudinal, and prospective study conducted at the University Hospital Onofre Lopes - HUOL, Brazil over eighteen months between June 2016 to December 2017. HUOL is a general teaching hospital with 245 beds and about 8,000 annual admissions. The study was approved by the Research Ethics Committee (CEP) of the Federal University of Rio Grande do Norte (UFRN) under the reference number CAAE 34282914.0.0000.5992.

All patients admitted from 18 years of age or older, hospitalized for more than 24 hours, and using at least one medication during hospitalization were included. Patients admitted for less than 24 hours, patients in intensive care (ICU), transplanted patients, patients using chemotherapy, and pregnant women were excluded. Informed consent was obtained from all individual participants enrolled in the study.

For the purposes of this study, we consider the WHO definition for ADR characterized as "any harmful or undesirable and unintended response that occurs with drugs in doses usually used in humans for prophylaxis, diagnosis, treatment of disease or for modification of physiological functions"[8].

Data collection

Patients admitted to the wards were identified daily by the healthcare team during the data collection period to identify suspected ADRs, considering the most common ADRs of the prescribed medicines. These professionals were not part of the research team. All included patients received guidance for reporting any discomfort related to the healthcare team to the use of medications administered during hospitalization.

Only ADRs that occurred during admission as a result of drugs initiated or continued in the hospital were included. When ADR was suspected, a pharmaceutical researcher (SIVCL) investigated the following four steps: active search in medical records, healthcare team interview, collection of patient information, and ADR causality assessment. These steps are described below:

1. Active search in medical records:

Clinical patients records and medical notes were reviewed for the investigation of an ADR, considering clinical parameters: vital signs, laboratory signs of hepatotoxicity (alanine transaminase - ALT and aspartate transaminase - AST), nephrotoxicity (serum creatinine), coagulation disorders (international normalized ratio - INR), and ADRs such as headache and nausea. When necessary, the healthcare team, including physicians and nurses, and the patient was consulted.

Investigation of the prescription orders in search of drugs that indicate ADRs was based on the list of recommendations of the triggers of the Medication module triggers of the IHI Global Triggers Tool[9], as well as changing the dosage, and replacement or suspension of drugs.

2. Healthcare team interview:

Clinical and laboratory changes detected in the previous step were investigated with the health team. Physicians and nurses in charge of the patient were asked about the existence of a temporal relationship between the occurrence of any sign or symptom seen in the medical record and the administration of a certain medication. In cases of dose changes, substitution, or suspension of the administration of a drug, the possibility of toxicity as a cause was questioned.

3. Collection of patient information:

In the face of a suspected ADR, a data collection form was applied to patients investigating clinical information. The data included were related to clinical variables (age, sex, admission diagnosis, comorbidity, Charlson's comorbidity index, blood pressure, and heart rate) and laboratory parameters.

4. ADR causality assessment:

The assessment of ADR causality was performed using the Naranjo questionnaire in the cases described in step 3, classifying it as definite, probable, possible and doubtful10. Only ADRs with defined, probable or possible causality were included in the study, excluding those classified as doubtful. This step was performed by two investigators (SIVCL and IBA). Any discrepancies were resolved by consensus with a third investigator (RRM) to minimize bias. All drugs were recorded for all patients with ADR.

In the design of this study, after identifying an ADR, the patient was withdrawn from the study, and therefore, only one suspect ADR was considered per patient.

Statistical and Network Analysis

Data were presented as mean and standard deviation or relative and absolute frequencies as appropriate in each case. The analysis was performed with the Stata version 15.1 program (Stata Corporation, CollegeStation, TX, USA). A network analysis was conducted to explore further ADRs, an advanced statistical analysis that can characterize interconnected structures in data[11,12].

Network analysis comprises nodes and edges, where nodes represent the ADRs involved and edges between two nodes represent drugs that caused the corresponding ADR. The size of a node is proportional to the number of times the ADR was reported, and the width of an edge is proportional to the number of times that specific connection occurs, representing its weight.

The network analysis of the drugs involved with adverse reactions was performed using Gephi version 0.9.2, an open-source program that allows for the visualization and quantification of complex data derived from previously treated banks[13]. The final visualization of the incompatible drug networks was made using the Yifan Hu algorithm to present intuitive clusters and connections dimensioned by distance centrality[14]. Simplified versions of the networks were obtained by filtering. The entire network was then exported for viewing on the web using Gephi®'s Sigmajs exporter plugin.

RESULTS

During the 18 months of the study, 8060 inpatients were observed, with 358 of these experiencing one or more ADRs. Overall, the mean age of the patients was 57.7 ± 17.2 years. The proportion of patients with at least one ADR occurred was 4.43% (95% CI 4.00 - 4.90%). A higher frequency of ADRs was experienced in female patients (58.9%). A total of 169 (47.1%) patients have had a clinical diagnosis of diabetes mellitus. Demographic and clinical characteristics required for investigating ADR are summarized in Table 1.

Table 01. Characterization of the population

Characteristics	Values	
ADR occurrence in the population of the period (n, %)	358	4.43
Female (n, %)	211	58.9
Age in years (m, year)	57.7	17.2
Clinical diagnosis (n, %)		
Diabetes mellitus	169	47.1
Renal disease	96	26.8
Congestive heart failure	76	21.2
Acute myocardial infarction	67	18.7
Oncologic disease	50	13.9
Stroke	34	9.5
Vascular disease	31	8,6
Hepatic disease	22	6.2
Clinical parameters (m, year)		
Heart Rate in BPM	80.5	16.6
Systolic blood pressure in mmHg	119.0	24.2
Diastolic blood pressure in mmHg	69.3	13.9
Laboratorial parameters (m, year)		
Albumin (g/dL)	3.1	0.9
Creatinine (mg/dL)	1.8	1.9
AST (U/L)	30.6	39.6
ALT (U/L)	28.7	70.4
Potassium (mEq/L)	4.5	0.8
Leukocytes / mm3	8876	5789
Platelets	283941	140786
INR	2	10.9
Charlson's Index (m, year)	4.1	2.6

Caption: BPM: beats per minute; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio; m: mean; sd: standard deviation; n: absolute frequency; %: relative frequency.

Regarding the causality established by the Naranjo questionnaire, there was a predominance of ADRs characterized as probable (236, 65.92%) followed by possible (120, 33.52%) and defined (2, 0.56%). The most frequent ADR in the study was hypoglycemia (24.82%), followed by hypotension (17.5%), hemorrhages or high INR (8.5%) and renal insufficiency (5.1%). All adverse reactions detected are shown in Table 2. Among the drugs involved in ADRs, insulin stood out and was responsible for 26.4% of the detected ADRs, followed by furosemide (12.56%), enalapril (8.62%) and then tramadol (4.43%) (Table 3).

Table 02. Adverse drug reactions detected in hospitalized patients

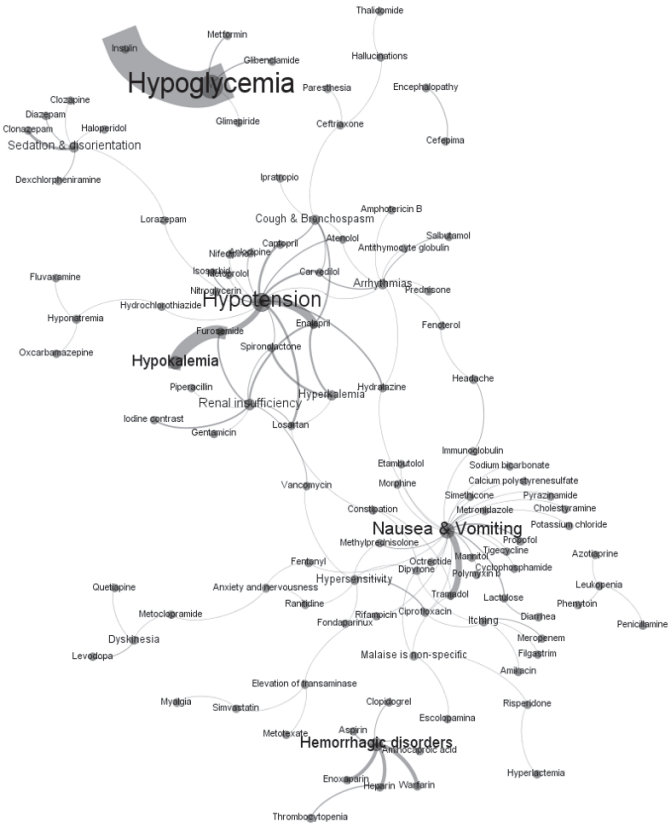
Adverse drug reaction	N	%
Hypoglycemia	102	24.82
Hypotension	72	17.52
Hemorrhages or high INR	35	8.51
Renal insufficiency	21	5.1
Nausea and Vomiting	46	11.2
Hypokalemia	33	8.03
Hyperkalemia	12	2.92
Sedation and disorientation	14	3.4
Cough and Bronchospasm	12	2.92
Arrhythmias	12	2.92
Constipation	3	0.73
Hypersensitivity	8	1.95
Itching	6	1.46
Headache	3	0.73
Non-specific malaise	4	0.97
Anxiety and nervousness	3	0.73
Thrombocytopenia	3	0.73
Leukopenia	3	0.73
Elevation of transaminases	3	0.73
Hallucinations	2	0.49
Encephalopathy	2	0.49
Diarrhea	2	0.49
Dyskinesia	4	0.97
Hyponatremia	3	0.73
Hyperlactemia	1	0.24
Paresthesia	1	0.24
Myalgia	1	0.24
Total	411	99.99

Table 03. Drugs involved in adverse drug reactions

Drug involved in ADR	N	%
Insulin	95	23.4
Furosemide	51	12.56
Enalapril	35	8.62
Tramadol	18	4.43
Heparin	12	2.95
Carvedilol	10	2.46
Losartan	10	2.46
Spironolactone	10	2.46
Warfarin	10	2.46
Enoxaparin	9	2.22
Captopril	9	2.22
Clonazepam	7	1.72
Atenolol	5	1.23
Ciprofloxacin	5	1.23
Dipyrone	5	1.23
Lactulose	5	1.23
Iodine contrast	4	0.98
Propofol	4	0.98
Aspirin	3	0.74
Ceftriaxone	3	0.74
Glibenclamide	3	0.74
Immunoglobulin	3	0.74
Isosorbid	3	0.74
Metformin	3	0.74
Methylprednisolone	3	0.74
Vancomycin	3	0.74
Anlodipine	2	0.49
Cefepima	2	0.49
Clopidogrel	2	0.49
Dexchlorpheniramine	2	0.49
Diazepam	2	0.49
Dobutamine	2	0.49
Fenoterol	2	0.49
Fentanyl	2	0.49
Hydralazine	2	0.49
Hydrochlorothiazide	2	0.49
Levodopa	2	0.49
Lorazepam	2	0.49
Meropenem	2	0.49
Metoclopramide	2	0.49
Metronidazole	2	0.49
Ranitidine	2	0.49
Rifampicin	2	0.49
Risperidone	2	0.49
Salbutamol	2	0.49
Simvastatin	2	0.49
Other drugs	38	9.4
Total	406	100

Figure 1 shows the network analysis of the main medicines involved in ADR. This figure contains nodes (representing ADRs) and edges (representing the main drugs involved). In the graph two clusters are presented, one centered around the occurrence of hypotension (cluster 1) and the other around ADR nausea and vomiting (cluster 2). Hypoglycemia and hemorrhagic changes were characterized as frequent ADRs, although they showed no connections with the others. The hypoglycemia node orbits around cluster 1 and is strongly related to the use of insulin. With greater proximity to cluster 2, hemorrhagic disorders are related to antithrombotic agents, with an emphasis on enoxaparin, heparin and warfarin.

Figure 01. Network analysis demonstrating the correlation between the adverse drug reaction and the respective drugs involved



The occurrence of hypotension induced by furosemide, spironolactone and enalapril is related to serum changes in potassium (hypo and hyperkalemia) and renal insufficiency. The hypotension induced by betablockers carvedilol and atenolol was related to the occurrence of arrhythmias and respiratory changes (cough and bronchospasm). However, compared to atenolol, carvedilol is more strongly related to the interaction between hypotension and arrhythmia, as shown in cluster 1.

Regarding cluster 2, centered around the nausea and vomiting node, there is a more significant variability of drugs of different classes involved. These drugs are not involved in others ADRs. In contrast, nausea and vomiting node is firmly connected by dipyrone (metamizole) and ciprofloxacin to most ADRs that are part of cluster 2, highlighting the correlation with reactions of hypersensitivity and pruritus. A strong connection is received with the main node of cluster 2, tramadol also connects with ADRs of constipation and nonspecific malaise.

DISCUSSION

Most studies on ADRs focus on their incidence and prevalence but fail to explore potential correlations between ADRs and medications. Despite identifying commonly expected ADRs in the hospital environment, our study reveals that network analysis can identify clusters that detail the correlation patterns between ADRs and drugs. Specifically, we found that hypotension caused by antihypertensive drugs, particularly Angiotensin Converting Enzyme Inhibitors (ACEIs), signals potential drug-induced electrolyte abnormalities and arrhythmias, making it a principal cluster of concern. Additionally, another relevant cluster highlighted the occurrence of nausea and vomiting induced by multiple medications, especially tramadol. Finally, patterns of lesser relevance were observed in relation to insulin-induced hypoglycemia and drug-induced bleeding caused by anticoagulants.

Network graphs are central elements in graph theory, characterized as visual elements where vertices (also called points or nodes) are connected by edges (lines), facilitating the understanding of complex patterns[13]. The use of network analysis in drug studies is commonly related to the prediction of the pharmacodynamic properties of a given molecule, an essential step in the development of drugs[15,16]. When we consider the occurrence of adverse events in hospitalized patients, the literature is scarce regarding the use of this approach. A rare example is the characterization of drug incompatibilities in neonates undergoing intensive care using a network graph[17]. Therefore, this method seems to facilitate the visualization of patterns of ADRs.

The ADRs that makeup cluster 1 refer to a typical profile of cardiac patients with a predominance of hypotension, hypoglycemia, electrolyte changes and arrhythmias. Hypotension is a common reaction to antihypertensive drugs and is considered to be less severe,

however, in the hospital environment, it is considered a risk factor for renal failure[18,19].

In this pattern observed in cluster 1, hypotension induced by furosemide, spironolactone and enalapril stands out as being more strongly related to renal failure and changes in potassium (hyperkalemia and hypokalemia). Among ACEIs, enalapril shows itself to be the most implicated in the occurrence of ADRs[20]. On the other hand, in the case of hypotension induced by beta-blockers (carvedilol, metoprolol and atenolol) there was a connection with the occurrence of arrhythmias[21]. As we can see, the ADRs identified by the network analysis are already expected in hospitalized patients with cardiovascular disorders. However, the observed pattern allows us to infer that the occurrence of hypotension in these patients should lead to the investigation of potential electrolytic alterations and arrhythmia since an important relationship was perceived in the network analysis.

The occurrence of nausea and vomiting is a common complaint among hospitalized patients. It is a nonspecific clinical complaint, and few cases allow for easy identification as an ADR, such as in situations of rapid infusion of tramadol[22]. However, the second cluster characterized by the network analysis indicates that nausea and vomiting as an ADR are associated with multiple medications. Therefore, their occurrence in hospitalized patients may indicate the need for investigation into the drug origin.

Hypoglycemia and hemorrhagic disorders were ADRs that had a distinct conformation in the graph structure, the drugs involved were not related to the occurrence of other ADRs, resulting in nodes independent from the others. Orbiting cluster 1, hypoglycemia caused by insulin was the most frequent ADR in our study, usually related to overdose and the need for constant dose adjustments[23]. Also showing a high occurrence, hemorrhagic disorders caused by different antithrombotic drugs were positioned close to cluster 2. Medicines such as heparin and warfarin can result in hemorrhages, even in situations of small dose adjustments, as they have narrow therapeutic ranges[24]. Therefore, the proximity to cluster 2 is in accordance with a profile of ADRs common to hospitalized patients in general, regardless of specialty.

Unlike the other clusters described, the occurrence of hypoglycemia and bleeding disorders is restricted to the use of hypoglycemic agents and anticoagulant agents. Therefore, its occurrence does not deserve further investigation of other drugs involved.

Finally, the network analysis presents a highly effective visualization of connections between the several ADRs and the associated drugs compared to a traditional descriptive statistic. Suggesting that the identification of a certain ADR, as in the case of hypoglycemia caused by ACEIs, leads to the investigation of other potentially correlated ADRs in these patients (electrolyte abnormalities and arrhythmias). On the other hand, the identification of ADRs caused by multiple medications, as in the case of nausea and vomiting, indicates that a drug-related etiology should be considered as a hypothesis.

This study has some limitations. The research was carried out in a single hospital, a medium-sized tertiary hospital, which may limit the generalization of the results. Despite the robust sample of patients, it still does not allow for the detection of low or rare-frequency reactions. Another limitation to the generalization of results may be that the hospital has a standardization of medications and, therefore, some existing medications have never been administered to patients. It is important to highlight that the potential correlations between the different ADRs identified were not submitted to a panel of experts to validate the results. The main strengths of this study are the prospective design, the large sample size, the long observation period, the active search for ADRs and the approach to adverse drug reactions through network analysis.

CONCLUSION

Network analysis is a promising strategy for identifying patterns that correlate ADRs and drugs in hospitalization. Among the common ADRs observed in hospitalized patients, the identification of hypotension caused by ACEIs indicates the potential occurrence of electrolyte abnormalities and arrhythmias induced by other cardiovascular drugs. Additionally, clinical manifestations such as nausea and vomiting due to the existence of multiple potential causative medications should be investigated for the possibility of ADRs. Therefore, these patterns can guide strategies aimed at identifying ADRs in the daily practice of healthcare professionals.

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