Evaluation of drug-drug interactions in hospitalized patients at Sociedad Española de Beneficencia

Susuki Castorena-Palacios¹, Eduardo Nieto-Ortega^{1,2}, Diana Ali Macedo-Falcon^{1,2}, Alberto N. Peón^{1,3,*}

1 Laboratorio Santiago Ramón y Cajal, Sociedad Española de Beneficencia, Av. Juárez #908, Col. La Villita, CP42060 Pachuca, Hidalgo, México.

2 Área Académica de Medicina, Universidad Autónoma del Estado de Hidalgo.

3 Escuela Superior de Apan, Universidad Autónoma del Estado de Hidalgo, Carretera Apan-Calpulalpan s/n, 43920 Chimalpa Tlalayote, Hgo, México.

Abstract

Background: drug-drug interactions are a frequent cause of adverse drug reactions, the use of more than 5 drugs is significantly related to serious interactions. Comorbidities in patients have precipitated the frequency of polypharmacy, which produces an enhanced incidence of morbidity and mortality, hospital stay and costs. **Materials and methods:** 50 records of hospitalized patients were analyzed in the period from May to July 2019, a search for drug interactions was carried out with the help of Medscape Drug-Interactions Checker and the Drugs Interactions Checker. **Results:** 68% of the records presented at least one pharmacological interaction, the majority associated with musculoskeletal pathology and abdominal pain syndrome (45 and 29%, respectively). On the other hand, 48% of the interactions were related to the use of non-steroidal anti-inflammatory drugs and the use of opioid pain relievers combined with sedatives or anesthetics. **Conclusions:** there is a significant incidence in drug interactions, most of them related to poor pain management, however, it is essential to know the pathophysiology of each patient's disease, and to understand that the benefit must be greater than the risk when indicating the best therapy for the patient.

Highlights

The most prevalent drug-drug interactions are related to analgesics and anesthetics.

Pain is the first cause for seeking medical advice, but pain management strategies seem rather dubious.

Keywords

Drug-drug interactions

Pain management

Analgesia

*Correspondence should be addressed to Alberto N. Peón at investigacion@benepachuca.com

INTRODUCTION

Drug-drug interactions are a common cause of adverse drug reactions, and are more serious in elderly patients, patients with multiple comorbidities, and patients subjected to polypharmacy. Multiple pathologies, such as diabetes, systemic arterial hypertension, obesity, heart disease, etc. have forced the use of multiple drugs for their treatment, increasing the possibility of drug-drug interactions (1).

Pharmacological interactions arise when a drug interacts with another, modifying its pharmacokinetics or pharmacodynamics, thus, a negative or positive effect may occur with the interaction of the drugs (2). Drug interactions can be classified depending on the mechanism of action of the interaction or based on its severity. Pharmacokinetic interactions occur when the ADME (absorption, distribution, enzymatic metabolism, and excretion) of one drug is affected by another drug. Pharmacodynamics are affected when drugs interact on the same receptor or physiological system, resulting in additive interactions or in antagonistic interactions when drugs have opposing effects (3).

The risk classification of drug-drug interactions is established as A, B, C, D and X. Risk category "A" without any evidence of drug interaction, category "B" with evidence of interaction, but without clinical relevance, in "A" and "B", no action is required, therefore the use of drugs is safe; for category "C", therapy monitoring is required, as there is clinically significant drug interaction but with greater benefit than risk. For category "D", there must be a modification of the therapy, which may imply dose adjustment, an alternative therapy and intensive control to minimize toxicity. In risk category "X", drug combinations should be avoided since there is a greater risk than benefit, thus drug combinations are contraindicated (4).

It has been observed that DDI could bring adverse drug reactions, increase morbidity and mortality, longer hospital stays and enhanced hospital costs. In a multicenter retrospective observational study, it was identified that up to 30% of patients in the intensive care units are exposed to DDI's, most frequently observed in drugs that increase the QT interval, digoxin and NSAIDs (non-steroidal anti-inflammatory drugs) (5).

In another study carried out in elderly patients, a total of 216 serious or very serious interactions were identified, 48.9% of the patients had the risk of at least one serious interaction, patients with more than 4 drugs had a risk for presenting interactions of 84% (AUC = 0.781, $p < 0.0001$) (6). In México, the Comisión Nacional de Arbitraje Médico (CONAMED) conducted a study of patients with diverse medical complaints finding that 48.5% of them presented moderate interactions and 43% were found to be subjected to serious interactions. 63.9% of them consumed more than 5 medications. Bezafibrate, pravastatin, captopril, metformin, acetylsalicylic acid, diclofenac, insulin and Enalapril were the drugs most involved (2).

In such context, a search for drug-drug interactions was carried out in patients of the Sociedad Española de Beneficencia hospital in Pachuca, Hidalgo, based on

clinical records in order to determine the incidence of such problem, and to identify the most common flawed prescriptions.

Materials and methods

A total of 50 clinical files belonging to patients attended at the Sociedad Española de Beneficencia, Pachuca, Hidalgo Hospital were analyzed, disregarding the diagnosis. All the clinical files were gathered between May and July of 2019, with the inclusion criteria of i) patients of both genders, ii) with ages between 14 and 60 years. Clinical files of i) pregnant women and ii) patients with hepatic and renal damage were excluded.

The clinical files were checked for drug-drug interactions in concomitantly administered medication by using the Medscape Drug Interactions Checker(7) and the Drugs Interactions Checker(8) and all interactions were plotted into Excel documents to quantify any typify their occurrence.

Results and discussion

Of the 50 clinical files that were analyzed we found 33 (68%) records with at least one drug-drug interaction and 16 (32%) that did not present any interactions (Fig. 1a). The diagnoses ranged within muscle-skeletal trauma (45%), acute abdomen-type pathologies (29%), gineco-obstetric phenomena (8%), surgery-related phenomena (6%), infectious diseases (4%) and other scattered phenomena (8%) (Fig. 1b). Most (48%) of these interactions were related to non-steroidal anti-inflammatory drugs (NSAIDs), followed by analgesic/anesthetic drugs (AA) (29%), and steroids (16%) (Fig. 1c). In fact, the five most commonly misprescribed drugs were found to be ketorolac (found in 39% of the files), followed by parecoxib (25%), dexamethasone (14%), enoxaparin (11%) and diclofenac (11%) (Fig. 1d).

We further characterized the specific incidence of drug-drug interactions, finding that the parecoxib-ketorolac interaction was the most common, occurring 25 times (48% of NSAID DDIs) (Fig. 2a, Table 1), followed by diclofenac-ketorolac, which occurred 10 times (19% of NSAID DDIs) (Fig. 2a, Table 1), then fentanyl-propofol, which occurred 9 times (29% of AA DDIs) (Fig. 2b, Table 2), ketorolac-enoxaparin (7 times, 13% of NSAID DDIs) (Fig. 2a, Table 1), dexamethasone-fentanyl and parecoxib-dexametasone, which occurred 6 times (35% of steroid DDIs) (Fig. 2c, Table 3). Although present in the study, other DDIs were not highly incident (Fig. 2d, Table 4), thus we observe a pattern of enhanced DDIs in the setting of pain management, as NSAIDs, AA and corticosteroids were the drug types that were most commonly misprescribed. It has been estimated that 42% of people experience pain before seeking medical advice (9), while this condition has been linked to at least 40% of the reasons for a patient to seek medical advice outside of the emergency department (10) and

to 70.7% of the reasons for patients to visit an emergency department (11). Moreover, the prevalence of chronic pain has been estimated between 11% and 40% of the population (12), and post-operative pain has been detected in 37.5% of patients (13), of whom 12% described a severe to extreme pain and 54% a moderate pain (14).

Table 1. NSAID interactions.

Interaction	Incidence
Parecoxib-Ketorolac	25
Ketorolac-Enoxaparin	7
Diclofenac-Ketorolac	10
Diclofenac-Enoxaparin	3
Ketorolac-Ciprofloxacin	2
Mefenamic acid-Ketorolac	2
Mefenamic acid-Enoxaparin	1
Celecoxib-Ephedrine	1
Ketoprofen-Ketorolac	1
Total	52

Table 2. Analgesics/anesthetics interactions.

Interaction	Incidence
Fentanyl-Propofol	9
Ondansetron-Tramadol	4
Fentanyl-Lidocaine	3
Fentanyl-Ondansetron	3
Fentanyl-Atracurium	2
Fentanyl-Tramadol	2
Tramadol-Buprenorphine	2
Ciclobenzaprine-Tramadol	1
Fentanyl-Ondansetron	1
Fentanyl-Vecuronium	1
Fentanyl-Rocuronium	1
Fentanyl-Atropine	1
Metoclopramide-Tramadol	1
Total	31

Table 3. Antinflammatory interactions.

Interaction	Incidence
Dexametasone-Fentanyl	6
Parecoxib-Dexametasone	6
Dexametasone-Ondansetron	2
Dexametasone-Tramadol	1
Dexametasone-Diazepam	1
Ketorolac-Dexametasone	1
Total	17

Table 4. Other interactions.

Interaction	Incidence
Ceftriaxone-Enoxaparin	4
Dapagliflozin-Insulin	1
Diazepam-Omeprazole	1
Levofloxacin-Ondansetron	1
Midazolam-Ephedrine	1
Total	8

On the other hand, our results show (Fig. 1b) that most of the prescriptions were related to muscle-skeletal trauma and acute abdomen-type pathologies, which tend to cause severe pain, and in some instances require surgery. As such it was expected to find an intense use of NSAIDs, analgesics/anesthetics and strong anti-inflammatory drugs that can also counteract pain, like corticosteroids.

DDIs are mostly predictable, and tend to occur as a sub-product of polypharmacy (15), but can also originate from the lack of knowledge about the pharmacokinetic and pharmacodynamics properties of each drug, as well as their metabolism (16). Moreover, we detected an ample incidence of DDIs related

to the prescription of two NSAIDs combined, two steroids, or two AAs, which reflects a strong intent to manage pain, but on a less efficient manner. Nalamachu (16) suggests that “Appropriate treatment of pain requires an understanding of the characteristics of pain, including the severity and the nature of the pain—for example, acute versus chronic pain or nociceptive versus neuropathic pain. Appropriate treatment requires an understanding of the efficacies of the available agents in different pain models, and their adverse events, to best match them to the type of pain.”, in regards to an efficient treatment of pain. We thus think that more knowledge about the pathophysiology of inflammation and pain, as well as the metabolic, pharmacodynamics and pharmacokinetic properties of steroids, NSAIDs and AAs may be able to transform this panorama.

One of the limitations of the study is that patients are not discriminated based on their diagnoses of hospital stay, relevant for the fact that multiple pathologies require the combination of drugs that in theory could present important pharmacological interactions. However, the benefit outweighs the risk, for example, patients with an acute coronary syndrome, who require a double anti-aggregation with aspirin and clopidogrel also combined with an anticoagulant such as enoxaparin or the new ones administered orally such as rivaroxaban (17). On the other hand, the combination of opioid analgesics together with sedatives such as Propofol, is necessary for the management of critical patients who are in intensive therapy under mechanical ventilation and who need to be under sedation and analgesia part of the time of their therapeutic stay (18).

Conclusions

We found that more than a half of the clinical files that were included in our study presented at least one DDI. The most commonly misprescribed drugs were NSAIDs, followed by analgesics/anesthetics, and finally steroids, all of which relate with the management of pain. We think that these results were to be expected as pain is a very common condition, especially among people that seek medical attention. Nonetheless, the fact that the most prescribed drugs for this situation are commonly misprescribed suggests that both the pathophysiology of pain and the properties of analgesics may not be soundly understood. We think that more awareness and knowledge may be key factors to put a halt to this phenomenon.

Acknowledgements

All the authors wish to thank Sociedad Española de Beneficencia for providing the technical and financial means for the publication of the present study. Eduardo Nieto-Ortega and Alí Macedo-Falcon receive a full scholarship from such institution, for which they are also thankful.

References

1. Lopez-Picazo JJ, Ruiz JC, Sanchez JF, Ariza A, Aguilera B, Lazaro D, et al. Prevalence and typology of potential drug interactions occurring in primary care patients. Eur J Gen Pract. 2010 Jun;16(2):92–9.

2. Hernández JLG. Interacciones farmacológicas potenciales en pacientes ambulatorios en expedientes de queja médica de la CONAMED. Rev CONAMED. 2020;25(3):115–22.
3. Brewer L, Williams D. Clinically relevant drug-drug and drug-food interactions. Pharmaceut Med. 2013;27(1):9–23.
4. Shetty V, Chowta MN, Chowta K N, Shenoy A, Kamath A, Kamath P. Evaluation of potential drug-drug interactions with medications prescribed to geriatric patients in a tertiary care hospital. J Aging Res. 2018;2018.
5. Bakker T, Abu-Hanna A, Dongelmans DA, Vermeijden WJ, Bosman RJ, de Lange DW, et al. Clinically relevant potential drug-drug interactions in intensive care patients: A large retrospective observational multicenter study. J Crit Care. 2021;62:124–30.
6. Petrini E, Caviglia GP, Pellicano R, Saracco GM, Morino M, Ribaldone DG. Risk of drug interactions and prescription appropriateness in elderly patients. Irish J Med Sci. 2020;189(3):953–9.
7. Medscape. Medscape Drug Interaction Checker [Internet]. 2020. Available from: <https://reference.medscape.com/drug-interactionchecker>
8. Drugs. Drug Interactions Checker – For Drugs, food and alcohol [Internet]. 2021 [cited 2021 Dec 31]. Available from: https://www.drugs.com/drug_interactions.html
9. Galinski M, Ruscev M, Gonzalez G, Kavas J, Ameur L, Biens D, et al. Prevalence and management of acute pain in prehospital emergency medicine. Prehospital Emerg care Off J Natl Assoc EMS Physicians Natl Assoc State EMS Dir. 2010;14(3):334–9.
10. Mäntyselkä P, Kumpusalo E, Ahonen R, Kumpusalo A, Kauhanen J, Viinamäki H, et al. Pain as a reason to visit the doctor: a study in Finnish primary health care. Pain. 2001 Jan;89(2–3):175–80.
11. Mura P, Serra E, Marinangeli F, Patti S, Musu M, Piras I, et al. Prospective study on prevalence, intensity, type, and therapy of acute pain in a second-level urban emergency department. J Pain Res. 2017;10:2781–8.
12. Kuehn B. Chronic Pain Prevalence. JAMA. 2018 Oct;320(16):1632.
13. Domínguez HJG, Sandoval LCG DC. Postoperative pain prevalence. Acta Med. 2016;14(2):84–9.
14. Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The Incidence and Severity of Postoperative Pain following Inpatient Surgery. Pain Med. 2015 Dec;16(12):2277–83.
15. Carpenter M, Berry H, Pelletier AL. Clinically Relevant Drug-Drug Interactions in Primary Care. Am Fam Physician. 2019 May;99(9):558–64.
16. Astrand B. Avoiding drug-drug interactions. Chemotherapy. 2009;55(4):215–20.
17. Ibáñez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. Guía ESC 2017 sobre el tratamiento del infarto agudo de miocardio en pacientes con elevación del segmento ST. Rev española Cardiol. 2017;70(12):1082–e1.
18. Celis-Rodríguez E, Díaz Cortés JC, Cárdenas Bolívar YR, Carrizosa González JA, Pinilla D-I, Ferrer Zaccaro LE, et al. Evidence-based clinical practice guidelines for the management of sedoanalgesia and delirium in critically ill adult patients. Med intensiva. 2020 Apr;44(3):171–84.