EVALUATION OF THE PROFILE OF ADVERSE EVENT NOTIFICATIONS FOR IVERMECTIN AND NITAZOXANIDE BEFORE AND DURING THE COVID-19 PANDEMIC

Amanda Fernandes Borges de Araújo[1]
Thalyta dos Santos Alencar[2]
Aline de Araújo Freitas[4]
Emerith Mayra Hungria Pinto[3]
Universidade Evangélica de Goiás – UniEVANGÉLICA[124]
Universidade Estadual de Goiás[3]

ABSTRACT

COVID-19, caused by the SARS-CoV-2 virus, was discovered in 2020, with the pandemic originating in Hubei, China, in December 2019, and spreading rapidly worldwide. Patients presented symptoms of acute respiratory infection, with some progressing to severe complications such as acute respiratory distress syndrome (ARDS) and respiratory failure. Fear and the rapid spread of the disease led to an increase in self-medication with drugs such as ivermectin, azithromycin, chloroquine, and nitazoxanide, whose efficacy against COVID-19 was unproven. This study aimed to analyze the profile of adverse event notifications associated with nitazoxanide and ivermectin before and during the pandemic, using data from the VigiMed platform. The comparative analysis of the periods revealed a significant increase in adverse event notifications during the pandemic, highlighting the expanded and unfounded use of these medications. Furthermore, notifications increased in number and severity, with an emphasis on self-medication and changes in the profile of notifiers. In conclusion, the findings underscore the need for clear, evidence-based communication by health authorities and continuous surveillance of the off-label use of medications, especially during public health crises, to prevent an increase in adverse events and the overload of health systems.

Keywords: COVID-19; Ivermectin; Nitazoxanide; adverse events.

INTRODUCTION

In December 2019, cases of pneumonia were reported in Wuhan, China, with patients showing signs of acute respiratory infection and, in some cases, progressing to acute respiratory distress syndrome (ARDS) and respiratory failure. In January 2020, a new coronavirus, SARS-CoV-2, was identified. With the rapid spread of the virus and the absence of effective treatments, medications without scientific proof, such as hydroxychloroquine, azithromycin, ivermectin, and nitazoxanide, began to be used for the treatment of COVID-19 (Chen et al., 2020; Lopes et al., 2022).

Ivermectin, an antiparasitic, is indicated for various parasitic infections and has an anti-inflammatory effect, but its use against COVID-19 is controversial due to the need for very high doses to achieve antiviral effects *in vitro*, which could lead to serious adverse effects such as neurotoxicity and hepatotoxicity (Heidary; Gharebaghi, 2020; Caly et al., 2020). Nitazoxanide, a broad-spectrum antiparasitic, was used in COVID-19 for its potential to regulate cytokines and inhibit viral replication, but there is a lack of robust clinical evidence for its safe and effective use against SARS-CoV-2 (Matuoka et al., 2020; Kuraishy-Al et al., 2022).

The indiscriminate use of these medications during the pandemic, driven by desperation and self-medication, may have increased the incidence of adverse

reactions and drug interactions (Baracaldo-Santamaría et al., 2022). Thus, this study seeks to evaluate the profile of notifications of events related to the use of ivermectin and nitazoxanide in the pre-pandemic and COVID-19 pandemic periods.

METHODOLOGY

This is a cross-sectional study with descriptive-exploratory and analytical stages. The study analyzed the profile of adverse events related to the drugs nitazoxanide and ivermectin, using data extracted from the VigiMed platform, provided by Anvisa (the Brazilian Health Regulatory Agency).

The study considered data on adverse events reported between January 1, 2018, and December 31, 2019 (pre-pandemic) and between March 1, 2020, and December 31, 2021 (pandemic), with notifications categorized by state, sex, age group, entry service, and type of notifier. The VigiMed system uses the Medical Dictionary for Regulatory Activities (MedDRA) as the standard for medical terms related to adverse drug reactions.

RESULTS AND DISCUSSION

During the pandemic period, the promotion of off-label use of medications such as nitazoxanide and ivermectin resulted in a significant increase in adverse event notifications. Even with little or no scientific evidence of efficacy, the increasing consumption of these medications also occurred in other Latin American countries and worldwide (Orjuela-Rodríguez et al., 2022).

The data show that nitazoxanide had a significant increase in the number of adverse event notifications during the pandemic, jumping from 9 notifications in 2019 to 27 notifications in 2020 (a 200% increase), and there were also notifications for Azox® and Nitazoxanid® (1 notification each), in addition to Annita (17 notifications), Tanisea (1 notification), and nitazoxanida (7 notifications). This increase may be associated with the expanded use of the drug as part of alternative therapies for COVID-19, reflecting the evidence-based promotion that occurred during this period. Although some *in vitro* studies since the early 2000s have correlated the use of anthelmintics as antivirals, this relationship cannot be transposed into *in vivo* therapeutic responses (Paumgartten e Xavier de Oliveira, 2020).

Even the pharmaceutical company responsible for producing ivermectin (Merck Sharp and Dohme -- MSD) advised against its use in COVID-19 due to the lack of evidence on its efficacy (Bezerra et al., 2022). Furthermore, the Cochrane systematic review also demonstrated the absence of a significant difference between the group that received ivermectin and the control group (Oliveira et al., 2023).

The diversification of suspect medications, including different brands and formulations, also suggests that the increased demand led to a greater number of patients using different versions of the medication, possibly with variations in quality and safety. As shown by the study proposed by Santos-Pinto, Miranda e Osorio-de-Castro (2021), the volume of prescriptions and demand opens the door for discussion about the quality of use, since it also involves the prescription and dispensing of

medications for unapproved use by the regulatory body, amplifying the health risks already established by the pandemic.

In the pandemic period, the most prevalent type of notifier profile (44.44%) was consumer or other non-health professional, with 12 records. This suggests an increase in self-medication, a potentially dangerous practice that may have contributed to the increase in adverse events, reflecting the lack of adequate medical guidance and trust in unproven treatments. In contrast, an analysis by Hentschke-Lopes et al. (2022) observed that pharmacists reported the majority of adverse reactions, while doctors and health professionals reported less, revealing underreporting and the importance of training health professionals in pharmacovigilance. Furthermore, the hypothesis of increased self-medication is emphasized, but this cannot be proven by this study, since VigiMed does not report whether the use was medically indicated or not (Melo et al., 2021; Hentschke-Lopes et al., 2022).

In the case of ivermectin, the increase was even more dramatic, as there were no notifications in 2018 and 2019, but from April 2020 onwards, 42 adverse event notifications were recorded. This scenario was also seen in a study that observed adverse reactions to drugs used for COVID-19 in Latin American countries, which reported that the drugs with the highest number of notifications were antimicrobials, including ivermectin (Orjuela-Rodríguez et al., 2022).

The profile of the reported adverse events is also concerning; while in the pre-pandemic period events were less frequent and less severe, in the pandemic period there was an increase in both number and severity (40.48% were considered severe for ivermectin), reflecting a possible inappropriate use in response to fear and misinformation. The most frequently described terms were pruritus (7 records - 16.67%), off-label use (4 records - 9.52%), headache, abdominal pain, nausea and vomiting, and problems regarding product dose omission (3 records - 7.14% each). This profile of worsening was also seen by Paumgartten and Xavier de Oliveira (2020), who stated that even effects that could be considered mild and tolerable for severely ill patients may not be acceptable for those who present only mild symptoms and have a high probability of cure, which corresponds to the majority (80%) of patients.

CONCLUSION

In summary, these findings highlight the importance of clear, evidence-based communication by health authorities, as well as the need for continuous surveillance of the off-label use of medications, especially in public health crisis situations. The promotion of treatments without scientific backing can lead to serious consequences, such as an increase in adverse events that can further overload already fragile health systems.

REFERENCES

Al-KURAISHY, H.M., *et al.* Nitazoxanide and COVID-19: A review. **Mol Biol Rep**, v. 49, p. 11169–11176, 2022.

BACARALDO-SANTAMARÍA, D. *et al,* Segurança medicamentosa de medicamentos e substâncias de uso frequente para automedicação na COVID-19. **Avanços Terapêuticos na Segurança de Medicamentos,** v. 13, p. -14, 2022.

BEZERRA, M.M.A. *et al.* Medicamentos na pandemia da COVID-19: Análise da comercialização de azitromicina, hidroxicloroquina, ivermectina e nitazoxanida no Brasil. **Research, Society and Development**, v. 11, n. 6, 2022.

CALY, L. *et al.* The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. **Antiviral Research**, v.178, 2020.

CHEN, N. *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. **Lancet**, v. 395, n. 10223, p. 507-513, 2020.

HEIDARY, F.; GHAREBAGHI, R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. **The Journal of Antibiotics**, v.73, p.593-602, 2020.

HENTSCHKE-LOPES, M. *et al.* Sales of “COVID kit” drugs and adverse drug reactions reported by the Brazilian Health Regulatory Agency. **Cad. Saúde Pública,** 2022, v. 38, n. 7.

LOPES, M.H. *et al.* Sales of “COVID kit” drugs and adverse drug reactions reported by the Brazilian Health Regulatory Agency. **Cad. Saúde Pública**, v. 38, n. 7, p. 1-10, 2022.

MATUOKA *et al.* Nitazoxanida no tratamento de COVID-19 revisão sistemática rápida. **Oxford Brazil EBM Alliance**, p.1-24, 2020.

MELO, J.R.R., *et al.* Automedicação e uso indiscriminado de medicamentos durante a pandemia da COVID-19. **Cad. Saúde Pública,** 2021; v. 37, n. 4.

OLIVEIRA, F.B.M. *et al.* Uso de ivermectina e atazanavir no tratamento da covid-19: uma revisão de escopo. **Arquivos de Ciências da Saúde da UNIPAR**, Umuarama, v.27, n.3, p. 1047-1128, 2023.

Orjuela-Rodríguez, T. *et al.* Reacciones adversas a medicamentos utilizados para la COVID-19 en cinco países de América Latina. **Rev Panam Salud Publica**, v. 46, 2022.

PAUMGARTTEN, F.J.R.; XAVIER DE OLIVEIRA, A.C.A. Off label, compassionate and irrational use of medicines in Covid-19 pandemic, health consequences and ethical issues. Ciência & Saúde Coletiva, v. 25, n. 9 p. 3413-3419, 2020.

SANTOS-PINTO, C.D.B.; MIRANDA, E.S.; e OSORIO-DE-CASTRO, C.G.S. O “kit-covid” e o Programa Farmácia Popular do Brasil. **Cad. Saúde Pública,** 2021; v. 37, n. 2.