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The role of pharmacovigilance in patient safety in the COVID-19 pandemic

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ABSTRACT

A pharmacovigilance system is essential to prevent or minimize the risk of adverse drug-related events. It is necessary that both health institutions and drug manufacturers and health surveillance have risk management guidelines. With the rapid spread and evolution of COVID-19, researchers have been looking for treatments capable of curing or delaying the disease. However, the time required for the development of new drugs is prolonged, so some existing drugs are emerging as alternatives. Due to the relevance of patient safety as a public health problem, health authorities have been demanding the monitoring of the risk-benefit associated with the use of each drug. Despite the limitations regarding the nature of information in pharmacovigilance studies, it is still possible to use it for health regulation and definition of strategic actions to reduce unwanted outcomes, such as adverse drug events and deaths. Thus, this literature review article aimed to present the relevance of pharmacovigilance related to patient safety in the period of the Covid-19 pandemic.

O papel da farmacovigilância na segurança do paciente na pandemia de COVID-19

RESUMO

Um sistema de farmacovigilância é essencial para prevenir ou minimizar o risco de eventos adversos relacionados ao uso de medicamentos. É necessário que tanto as instituições de saúde quanto os fabricantes de medicamentos e a vigilância sanitária tenham diretrizes de gestão de risco. Com a rápida disseminação e evolução do COVID-19, pesquisadores têm buscado tratamentos capazes de curar ou retardar a doença. No entanto, o tempo necessário para o desenvolvimento de novos medicamentos é prolongado, por isso alguns medicamentos existentes vêm surgindo como alternativas. Devido à relevância da segurança do paciente como problema de saúde pública, as autoridades de saúde vêm exigindo o monitoramento do risco-benefício associado ao uso de cada medicamento. Apesar das limitações quanto à natureza da informação em estudos de farmacovigilância, ainda é possível utilizá-la para regulação em saúde e definição de ações estratégicas para redução de desfechos indesejados, tais como eventos adversos a medicamentos e óbitos. Desta forma, este artigo de revisão de literatura teve como objetivo apresentar a relevância da farmacovigilância relacionada à segurança do paciente no período da pandemia de Covid-19.

1. Introduction

The search for healing and disease treatment with the use of drugs came with our most primitive ancestors (1). The technological development of the Second World War brought advances in the pharmaceutical industry due to the industrialization of the manufacturing process. The mass production and the increase of different types of drugs recognizes a big growth in the pharmaceutical industry and leads to an uncontrolled consumption by the population (2).

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Nowadays medication is the most used therapy. Although it is necessary to pay attention to health risks, considering both the occurrence of adverse reactions associated with the use of medicines and the low product quality (3, 4).

The health services must provide a special quality care for the population, in the process of providing health care (5). The Institute of Medicine (IOM), of the United States of America, defines the quality of assistance as the rate at which health services increase the probability to get the results desired with the current level of scientific knowledge. It is understood by the quality of assistance in the provision of care, such as the efficient use of physical and human resources, with the minimum of the risk to the client (6).

It can be affirmed that the quality and the risk are indissociably attributes, in relation to the patient's safety. For the World Health Organization (WHO), this should be treated as reducing the risk of unnecessary damage, related to health care, to an acceptable minimum level rate (7). This theme is a component in health care, because it deals with initiatives that aim to avoid, prevent and reduce adverse events (AE) in health care (8, 9).

Based on this, the primary challenges to ensure the quality excellence in the health sector are established, with the objective to reduce the risk associated with health care, in the context in which care was provided (10).

It is known that the systems of the health service are complex and have increasingly incorporated elaborate technologies and techniques, followed by additional risks in providing care to patients. In this way, can may appear undesirable health effects may appear, normally, caused by some failure in the quality arising from processes, products or from structures assistance (11).

The medicine treatment generates positive results to the patient, however, they can increase the costs of health care when used improperly (12). When new therapeutic classes, pharmaceutical forms and/or new technologies arise, the possibility of prevention, treatment and even the cure of diseases is increased, however there is also the possibility to appear reactions and/or unexpected adverse events (13).

The disease caused by the new coronavirus, discovered in December 2019 (Covid-19), identified in Wuhan, China, was declared a pandemic by the World Health Organization in March 2020, after affecting the world population in a few months (14), causing a series of symptoms related to pneumonia. In this scenario, the Covid-19 pandemic has been subjecting public health to significant and unprecedented challenges, representing a true global threat (15). Because of this, the need and exasperation for treatments that help to cope with this situation emerges (16).

As the global burden of the Covid-19 pandemic continues to grow, health systems have been preparing, concomitantly, with the significant increase in patients seeking medical care. And the severity of the disease can vary from mild to extremely critical (17). The use of drugs in patients with mild to medium conditions is similar to that of a common flu with monitoring of signs and treatment of symptoms. However, patients with the development of severe respiratory syndromes need greater support and the aid of pharmacological treatment for the serious outcomes of the virus (16).

With the high lethality observed worldwide and the rapid development of severe respiratory syndromes to a large portion of the affected, a positive result for COVID-19 becomes an emergency and requires quick and effective decisions by health professionals (18, 16). In these situations, the development of new drugs for the specific treatment of Covid-19 is a potential target for study, since the number of deaths increases exponentially every day, expressing the urgency of therapy (18, 16).

In the face of the pandemic, it has been possible to observe a proliferation of clinical trials designed to delay/prevent and/or treat Covid-19. However, the experimentation and the time required create a barrier to research and the efforts often turn to the reuse of drugs

already commercialized for other purposes (19). Among the studies that seek to treat the disease caused by the new coronavirus, research with antiviral drugs that have already been used for other severe respiratory syndromes, as well as studies involving the use of antiparasitic and antimicrobial agents (20, 21, 22).

However, the case reports of tests performed with such drugs often do not take into account the use of control groups, to prove their effectiveness, which becomes a risk in the use of treatments without specific evidence for Covid-19. Therefore, it is important to discuss patient safety, since certain drugs can cause AE when used incorrectly, without clinical evidence to support their use (23).

Precisely because of these facts, it is necessary to pay attention to the evaluation of possible AEs to medications, especially in moments of euphoria such as these that increase the patients' medication exposure (24).

Considering also the possibility of prevention of medication errors and the risk of injuries due to its occurrence, it becomes relevant to identify the nature and determinants of errors, as to take actions for prevention.

With the main objective to prevent or reduce the harmful effects presented by the patient and to improve public health actions, it is essential that both the health institutions, as well as drug manufacturers and health surveillance, have a work guideline and risk management, aiming at minimizing injuries and reducing patient risk.

Based on this scenario, the present study aimed to present the relevance of pharmacovigilance as a quality instrument to guarantee patient care and safety, especially in times of a global pandemic, but also to carry out a critical assessment of the evidence and status. current knowledge related to the researched topic, as well as the identification of gaps that may guide the development of future research.

2. Materials and methods

The research strategy, to achieve the objectives proposed for this study, was designed as a qualitative, exploratory-descriptive study, which uses literature review, document analysis and available quantitative data as research techniques.

Choosing the right source of information is essential for carrying out a scientific study. In view of this, a review of the bibliographic collection was carried out in the databases available in virtual libraries and sites of the world wide web, including the databases of the CAPES Portal, Latin American Literature in Health Science (LILACS), US National Library of Medicine (PubMed) and Scientific Electronic Library Online (SciELO), and in other data sources, such as regulatory authority portals.

The descriptors were selected from the definitions found in the Health Sciences Descriptors (DECs/BIREME) and the Medical Subject Headings (MeSH), namely: pharmacovigilance, patient safety, drug, adverse event, Covid-19. The search period was initially not limited, and the search was carried out covering all articles published until June 19, 2021.

The inclusion criteria for this review were: articles in Portuguese, Spanish and/or English without delimiting the year of publication, with full texts available; and the exclusion criteria: articles that were not related to the subject studied, articles in a foreign language different from those mentioned above, and articles in which the full text was not available.

For the selection of scientific articles, procedures were organized in stages: in the first stage, they were evaluated and selected by reading the titles and abstracts; in the second stage, the selected studies were then accessed in their full version for full reading. Two independent evaluators analyzed all studies found.

3. Patient safety

The subject of patient safety and the development of measures to reduce the risks of unnecessary injuries to the patient, during the health assistance, are growing especially in the scientific community where many research are directed to hospital assistance even though most of health care should be done in basic attention (8, 9).

The starting point of patient safety was the publication, in 1999, of the report "To Err is Human: Building a safer Health System". This document presented an estimated occurrence of 44,000 to 98,000 deaths by AE in the U.S. related to patient care and that 7,000 deaths were related to medication errors (25). This alarming data caused huge discussions in the scientific community (11).

The global mobilization is due to the occurrence of AE, which occurs in any area of healthcare and most of the time can be avoided (11).

The medication errors and the adverse events related to drugs are among the most frequent failures in health care (26). Therefore, it can be stated that the identification of these AE is an indispensable ally for a better knowledge of drug iatrogeny and the safety profile of medicines.

The patient safety became internationally recognized in 2000 as one of the factors in health quality. The U.S and many other countries with different health systems create initiatives like a creation of institutes, associations and organizations focused on patient safety issues (27).

The North-American organizations, as well as other countries, in this context, started to analyze with more attention the patient safety issues after finding that the occurrence of AE may involve economic and social costs and result in irreversible injuries to the patients and their families (28).

The injuries to the patients during the health care can result in high morbidity and mortality. In order to pay more attention to the problem, WHO launched strategies designed to reduce risks in patient assistance and in 2004 created the World Alliance for Patient Safety (WAPS) with international coverage and the mission to coordinate, disseminate and accelerate improvements for patient safety on a worldwide level (28).

Even with the huge technological and practice advances used in the therapeutic and diagnostic health field, it is still an observed scene of AE occurrence to worry about. In the midst of this problem, it appears as an improved strategy for hospitalized patient's safety, the inclusion in programs of quality monitoring of the offered health services of quality and safety indicators (29).

Despite the growing number of studies on the subject, there is still necessary a greater awareness in relation to patient safety, once this represents a bigger factor in quality of care during the treatment (30). However, for the full exercise of pharmacovigilance it is necessary the involvement of the various health professionals (5).

As previously mentioned, over the years, there has been a rise in concerns about AE related to care practices. In this context, medication mistakes are a target for studies with the purpose of evaluating and indicating means to avoid and/or reduce the AE, since these errors bring negative repercussions and damages to the life of the assisted individuals.

According to the Joint Commission Accreditation of Healthcare Organizations (JCAHO), the patient care process has five stages: medicine's selection and procurement, prescription, preparing and dispensation, medicine's administration and for last, patient monitoring. Studies demonstrate that over the years mistakes were evidenced during these stages (31).

It is important to highlight that many relevant AE are totally unexpected, not being identified for only one methodological approach in its totality. When analyzing the

literature, it is possible to observe a multiplicity of approaches having as a security patient theme, however, all the studies have in common questions related to the health quality politics.

In this sense, it has been identified that the evidence about the activity of possible treatments against COVID-19 is still very limited, being possible to observe different profiles of efficacy and safety, which demands a strict monitoring on the occurrence of AE (32, 16).

However, in times of urgency like this, the all-or-nothing relationship is imposed on both patients and health professionals, since, when in doubt between providing treatment to the patient and suffering from AE or leaving it to its own capacity, the first option is the one that has prevailed (33).

With this, the different regulatory agencies around the world have stimulated research in search of a cure for this disease. These actions are part of the strategies to offer immediate and aligned responses to the conduct of international health authorities in the identification of safe and effective therapeutic alternatives for the treatment of Covid-19. One of these strategies involves the development of studies on the use of drugs already known, but used for other therapeutic indications, in the fight against the disease. Since for such drugs, aspects of the safety profile and drug interactions are already known, among others. (34)

The limitations related to safety data resulting from clinical trials in the pre-marketing phase are well known. Studies report that around 50% of approved drugs can cause adverse reactions that were not detected before their registration (35).

In the face of the COVID-19 pandemic and the already mentioned off-label use of several drugs, the occurrence of AE can be a negative surprise with the development of new situations or with the enhancement of previously known effects (36). In view of this, obeying standards and protocols is of paramount importance to ensure the minimization of unexpected damage to patients seen (33, 36).

4. Pharmacovigilance

For a medicine to be registered, commercialized, and distributed to the population, it is necessary to comply with a series of legal requirements from the regulatory bodies responsible for the sanitary control and the public national health (37).

According to the rules, in the new medicine developing process, it must include human trials, which will be part of clinical trials (38, 39, 40). According to the concept adopted by the international conference about harmonization of technical requirements to register pharmaceutical products for human use, a clinical trial is a systematic study of medicines in human voluntaries whose purpose is to discover or confirm the effects and/or identify the AE of the investigated product, in order to determine their safety and efficacy (41, 42).

Due to the global pandemic, health professionals and regulatory bodies have been under pressure to act quickly to make medicines and/or vaccines available to patients. The search for treatment is testing countries' ability to develop, test and use drugs quickly, presenting both opportunities and challenges. Since the possibility for regulatory bodies to speed up the approval processes for new drugs and / or indications runs counter to the idea of evidence-based drugs and there is a risk of further undermining public understanding of drug review processes, which require substantial safety evidence based on adequate and well-controlled trials before it can be marketed (43).

While this unprecedented emergency can provide sufficiently compelling reasons for regulatory agencies to act as efficiently as possible, agencies and medical communities need to maintain the highest level of science and specific standards while acting quickly

to combat the pandemic (43).

The medicines' clinical trials are developed in four different phases, which varies according to the purpose of the research and the participating population. The studies of phases one, two and three are used to prove statistically the efficacy of the medicine in controlled conditions and their safety by means of AE observations. However, in these phases it is only possible to detect the most frequent AE. On this, it is essential to perform phase 4 studies (pharmacovigilance) to identify the AE not observed during the previous trials and evaluate the safety and the effectiveness of the medicine in the population (39).

Pharmacovigilance has been defined by WHO as "the science related to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". In 2002, WHO extended this concept, contemplating "any drug-related problems" such as technical complaints, medication errors and drug interactions (44).

The AE relates to medicines, whether in hospitals or in the community, compromising the patient's safety and this is the reason why it has become a subject of growing relevance in the literature. However, to obtain information about the subject is very difficult due to the scarcity of studies carried out with this population, which certainly compromises the safety of the patient and the society (45).

It is in this context that pharmacovigilance must be inserted, due to the need to identify and collect consistent evidence about the iatrogenic, the use of medicines and the occurrence of AE. These evidences can be used in the foundation of decision-making processes in sanitary regulation, since with the use of consistent evidence it will possible to carry out and elaborative inferences of causality, based in the etiological link between the exposure to the medicine and occurrence of an AE (40, 42, 46).

Due to the relevance of patients' safety as a public health problem, the sanitary authorities are demanding, over the years, the monitoring of risk-benefit associated with each medicine use, specialty in pos-commercialization.

Even with all mechanisms and regulations in place to reduce this risk, the occurrence of adverse reactions to severe and unexpected drugs still persists and with a high impact on the health of populations. This is because only after widespread use of the drug, in clinical practice, can you effectively know your safety profile.

During this pandemic that is causing an exponential increase in morbidity and mortality, there is an understandable temptation to make unproven therapies widely available and not to wait for accurate clinical trial data. However, well-conducted randomized, controlled clinical trials in these acute patients can really be performed quickly. Thousands of new patients with Covid-19 show up for care every day, and many can be (and are) being recruited quickly in pragmatic clinical trials. The most relevant clinical results for evaluating these drugs - including death, hospitalization, number of days spent in intensive care and need for a ventilator - are readily assessed and available in days or weeks (43).

There are already more than 1,400 clinical studies underway to investigate the effectiveness of new antiviral drugs, convalescent plasma transfusions and vaccines. However, only 50 of these are phase IV (pharmacovigilance), related to the use of drugs already known, but used for other therapeutic indications, in the fight against the disease.

All patients with severe respiratory syndromes and infected with COVID-19 received antibacterials, 90% received antiviral therapy and 45% received methylprednisolone. Most trials were started by researchers and the study period is from 1 to 11 months. Although the final results of these studies take a long time to complete, interim research data may provide some help for the current urgent demand for therapy (47, 48).

The COVID-19 pandemic is a public health emergency of international interest, and all countries need a coordinated international effort to combat COVID-19. However, the

clinical trials themselves and the pharmacovigilance systems have limitations that are inherent in the methodology used in their execution. This fact, which exemplifies the difficulty in guaranteeing a total absence of risk associated with the use of medications.

A constant challenge in pharmacovigilance is that the complete data, which allow the evaluation of the causality from the use of different methodologies, are not always available, representing a critical aspect for these monitoring systems. Moreover, even analyzing studies, although well designed, alone, can not be enough to refute a causal relationship in an individual (46).

In the current pandemic situation, there is still insufficient conclusive information to guide a standardized clinical conduct and, consequently, to conduct an effective and safe use of the highlighted drugs for COVID-19 (24). However, even in the face of the growth of research related to this theme, there is a need to strengthen policies aimed at planning actions that can implant a culture of patient safety among health professionals and the community itself, and also the promotion of rational use of medicines. It can be said that the rigorous pre-marketing assessment of the safety and efficacy of drugs in randomized controlled trials remains the main tool to protect the world population from ineffective, unsafe drugs or both (43).

It is necessary to strengthen monitoring and contribute to the development of drugs and / or vaccines against COVID-19 infection as soon as possible. However, it is a false dichotomy to suggest that we must choose between the rapid implantation of treatments and the appropriate scientific evaluation.

5. Conclusion

In recent years the recognition of patient safety as a priority element of health organizations has been identified, with a special interest for the scientific community and a great impact on the community, but it must be committed by professionals to achieve the changes expected in practice clinics.

The scope of patient safety is dependent on a set of individual, collective, and organizational attitudes. This is, therefore, the key word for incorporating a safety culture within organizations, although it is a recent one in health, it is not in other areas.

The clinical safety of the patient can be implemented, with strategies to reduce the probability of occurrence of AE, and act before they cause damages, thus minimizing their consequences.

Several aspects raise serious concerns, especially when the drug evaluation and approval processes (accelerated due to the pandemic) can go wrong during a public health crisis. Despite the limitations on the nature of the information from the pharmacovigilance studies, it is still possible to use them in favor of health regulation and actions that promote patient safety. Since decisions about the risks and benefits of medicines should always be made on the basis of technical and scientific evidence.

Through the elements presented and considering the impact that monitoring of drug iatrogeny and the quality of care offered by health services may represent in relation to patient safety, it is proposed to work towards the expansion of strategic discussions, in order to reduce unwanted outcomes.

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