PHARMACOKINETICS SURVEILLANCE ON DRUGS- A REVIEW

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ABSTRACT

All drugs can have negative effects. When they reach the market, there are reasonably safe, yet remain in surveillance by pharmacovigilance. Pharmacokinetics plays a very important role in this because we can have monitored the ranges of concentrations of pharmacologic active principles. With these results, we calculate pharmacokinetic parameters and ranges of concentrations and with this information, we can determinate if the treatment is ineffective and above. It is frequent that toxic effects are observed. However, there are patients who respond to levels below this range and others need levels above this. For the determination of serum levels of a drug is justified it is necessary that there is a reliable analytical method that allows its determination, that there is a poor relationship between administered doses and levels and that there is a good relationship between the serum levels of the drug and its therapeutic or toxic effects i.e., an optimal interval. Variability in the response to drugs depends on multiple pharmacokinetic factors, which modify the plasma levels, and pharmacodynamic factors that alter the sensitivity to a certain level. In addition, the prescribed dose may be different from the taken by the patient by errors in the administration or therapeutic non-compliance.

KEYWORDS: toxic, serum, factor pharmacokinetic.

INTRODUCTION

The determination of serum levels of drugs allows you to differentiate the causes due to breach of the pharmacokinetic and the pharmacodynamic and take appropriate action: If the cause of a failure is that levels are low the dose should be increased, but if resistance is because you need to change medication.[1,2,3]
Pharmacogenetics studies how the genetic profile of an individual affects the response to drugs and aims to adjust the doses and predict, through the partnership between the pharmacological response and genetic variants, which patients will be benefited and which not, with the use of a drug, since genetic differences affect the pharmacodynamics and pharmacokinetics of the same, your metabolism, excretion and therefore, their blood levels.\[^4\] How much worse is the relationship between dose and serum level and better the relationship between the serum level and effect, much more useful will be the determination of the levels in the control treatment.

The relationship between serum levels and therapeutic or toxic effects is a sigmoid curve: from a certain level begin to observe the effects, thereby increasing the levels until you reach a limit above which gets out more effectively, or may even decrease.

One of the major difficulties of treatment in clinical practice is the individual response to drugs. Thus, not only vary in their effectiveness, which in general is around 50%, but it, also, while in some individuals, they are safe, others may cause adverse reactions of different magnitudes.

One of the major difficulties of treatment in clinical practice is the individual response to drugs.\[^5\] Thus, not only vary in their effectiveness, which in general is around 50%, but it, also, while in some individuals, they are safe, others may cause adverse reactions of different magnitudes. desired, which is presented to the doses used in man for prophylaxis, diagnosis, Therapeutics, or modification of a function. Adverse reactions include:

a.) exaggerations of the therapeutic effect, as by oral hypoglycemic hypoglycemia.
b.) are due to the pharmacological action giving rise to the therapeutic effect at a site different from the site of action, such as carcinogenesis by estrogen.
c.) may occur due to the nature of non-selective drugs, as with NSAIDs, causing irritation of the gastrointestinal tract.
d.) the specter of its pharmacological action, such as antidepressants which produce anticholinergic effects.

Characterized by being generally dependent on the dose, be predictable based on the pharmacological actions of the drug, have high morbidity rates and low mortality rates.\[^6\] Since 1950 referred to the existence of "quick metabolizers" and "slow metabolizers" in response to a drug, causing respectively that the drug is ineffective or result in an exaggerated
accumulation in the body.\textsuperscript{[7]} The transport of drugs represents a fundamental role, since drugs move a compartment of the body to another through a specialized range of conveyors. To modulate their effect, the drugs must unite physically to their targets of action: either their receptors and proteins involved in drug responses (transduction of signals, etc.).\textsuperscript{[8]} Genes involved in this process also determines individual differences in drug response.\textsuperscript{[9-10]}

As a result, candidate genes that could be involved in the response to drugs could be grouped into those that control:

1) Pharmacokinetic properties of drugs (including the availability of the same) and
2) The Pharmacodynamics (using the genes that encode the action targets and intermediate elements of the mechanism of action). However, it may occur a therapeutic ineffectiveness that is defined as absence, decrease or changes of the effect that appear unexpectedly, i.e. answers weak or absent, delayed start, of short duration, decrease or disappear after a period of satisfactory use.

Therapeutic responses depend in some measure of the usefulness of the program of pharmacovigilance.\textsuperscript{[9,10]}

\textbf{Pharmacovigilance}

All drugs can have negative effects. When reach the market are reasonably safe, yet remain a permanent surveillance, pharmacovigilance.\textsuperscript{[7]} Pharmacovigilance describes the activities for the detection, assessment, understanding and prevention of adverse reactions to drugs (RAM), which are harmful and unintended, answers that can produce the drugs normally prescribed dose.\textsuperscript{[6]}

The impact of adverse reactions to drugs (RAM) on health costs is evident, since about 5% of hospital admissions are the result of adverse reactions to drugs (RAM). The most common medications causing adverse reactions to drugs (RAM) are: antibiotics, anticoagulants, anticonvulsants, agents cardiovascular, respiratory and the analgesic.\textsuperscript{[6,8]}

Understand the risk associated with the use of medications, measure and weigh its consequences, can be a catalyst for the pharmaceutical industry, paraphrasing to Bernstein. Attention is directed to observe the impact of drugs and vaccines in the population, with the aim of undertaking actions that allow to maintain the ratio of risk-benefit It is a favorable
situation, i.e., must adjust the prescription and write contraindications to use in special populations, or to suspend use where this is not possible.[5]

Figure 1 shows the global pharmacovigilance market in USD Millions.

**Figure 1**

![Graph showing global pharmacovigilance market by clinical trials from 2012 to 2020](image)

**Figure 1. Global pharmacovigilance market, by clinical trials, 2012-2020**

**Monitored drugs**

Are some commonly monitored drugs: digoxin, antiepileptic (carbamazepine, valproic acid, phenytoin, phenobarbital); antiretroviral drugs (indavir, nefinavir, ritonavir, saquinavir); Cyclosporine, Tacrolimus, imipramine, lithium, haloperidol, theophylline, Vancomycin, lidocaine, among others. In addition to the monitoring of drugs for the purpose of optimizing therapy in a patient, the monitoring also applies to samples of forensic toxicology and in the case of substances of abuse, as well as on the assessment of bioavailability and bioequivalence of drugs.

In the latter case, studies ensure that the bioavailability of drugs marketed under the generic name and the innovators is equivalent, providing safety to the patient. A critical point to be considered to monitor the drug is the knowledge of pharmacokinetics and its pharmacodynamics.[7,11]

The information gathered in the previous registration phases is not enough to contour the safety of medicines and vaccines, as it is obtained on samples relatively small and a selective collection of data in a limited time and out of routine clinical practice.

The biography of the product starts with registration and concrete in phase IV of the development of the drug, which is detect rare adverse events and the effect of interactions or
co-occurring clinical conditions. The field of competence of the pharmacovigilance included: blood, biological products, medical devices, vaccines, cosmetics, food additive, counterfeit medicines, health food, medication, among other errors.[5,12]

View from the pharmaceutical industry this activity allows to comply with the principle of bioethics: "primum non nocere". Just so you can protect users of its products through the early identification of risks inherent in medication, detection of predisposing factors, discover programmatic errors, rule out false signals, estimate the causality by means of algorithms and quantify the magnitude of the risk in relation to the benefit.[5,8,13]

Order to establish a program of pharmacovigilance hospital[14,15], is to ensure the greatest possible safety in the use of drugs, and therefore its fundamental objectives are:
1. Achieve more timely detection of adverse reactions to drugs (RAM) and as a priority those which are of greater gravity. Pay particular attention to recently introduced therapeutic drugs.
2. Describe the new adverse drug reactions (RAM) that can detect it and assess its severity and clinical significance.
3. Confirm causality between adverse reactions to drugs (RAM) and medication.
4. Establish incidence of adverse reactions to drugs (RAM).
5. Identify and assess factors predisposing to the emergence of adverse reactions to drugs (RAM), such as age, sex, disease, genetic factors, etc.
6. To promote training and information in the field of adverse reactions to drugs (RAM), aimed at health professionals, in general. Thus, also to patients.
7. Take measures aimed at the effective pharmacological treatment and possible prevention of adverse reactions to drugs (RAM), which ultimately is the goal they go directed all the above.

A pharmacovigilance program, may be justified based on improving the care present and future of the patient. It has shown that the monitoring of adverse reactions to drugs (RAM), decreases its incidence and severity, as well as the length of hospital stay. As a result, it improves the individual care of the patient. Pharmacovigilance systems, must adapt to the characteristics of each hospital and the available media.[8,16]

In Mexican hospitals all General pharmacovigilance methods, can be provided effectively adapt to the characteristics of the hospital units. It is important to consider, that when pharmacovigilance activities are initiated or monitors drugs[17], it is utopian to find an
excellent acceptance of the program and that this will arouse, a general and immediate interest for working on them. For this reason, it is advisable to introduce programs gradually, acting on stage and if necessary, establishing pilot programs that ensure the viability of a methodology of work prior to generalize to all hospital.

Before starting to develop any specific program two previous actions are necessary:
(a) from if possible, create a group of pharmacovigilance, who will be responsible for promoting and coordinating all control reactions adverse drugs (RAM) that occur at the hospital, otherwise appoint a manager that coordinates the activities.
(b) conduct an information campaign aimed at health personnel, about the need and importance pharmacovigilance programs in hospitals, with the aim of promoting, from the beginning, the collaboration of the doctors and nurses of the hospital, since they depend on obtaining the resources necessary to implement correct programs.

The development of these activities in Mexican hospitals, will allow to have data of incidence and frequency of adverse drug reactions (RAM) in Mexican patients, to prevent them and if possible, minimize them and they will help support the rational use of medicines.\textsuperscript{[18]} The success of the program depends largely on the degree of awareness of the health authorities, professionals of the health and the patients themselves, about the importance of getting timely detection of adverse reactions and exercise on them a rational and systematized, surveillance enabling act effectively when necessary.\textsuperscript{[5, 6, 8]}

In figure 2 we present an example of monitoring drugs.

Figure 2

![Monitoring Requirements for Disease Modifying Antirheumatic Drugs](image-url)

Figure 2: Monitoring Requirements for disease.
Individualized Therapies
Now a day the accelerated lifestyle of the population, its form of unbalanced power that leads to malnutrition and the range of diseases directly affect the interaction of drugs in the body, but this should be in mind affecting both external factors as inmates in the same way as in the case of genes. The combination of drugs can bring both benefits and risks, drugs that are more prone to. The degree of present an adverse effect as it is the toxicity or a pharmacological therapeutic inefficiency is the result of the action between the genes of every human being and to environmental factors such as diet, age, tobacco addiction, alcohol intake, as well as other medicines you consume.\textsuperscript{[19,20]}

In general, the effectiveness of pharmacological therapy is far from optimal; Indeed, it has been estimated that the response to the drugs of current clinical practice, varies from 30 to 60\%.\textsuperscript{[9]}

Drug metabolizing enzymes play a very important role in the biotransformation of drugs or Xenobiotics. In the population, cytochromes P450 are a super family of enzymes implicated in more than 90\% of the metabolism of the drugs CYP2C9, CYP2C19 and CYP2D6 are more polymorphic enzymes and metabolize about 40\% of the drugs that are currently on the market.

The CYP2D6 gene is located on chromosome 22 and has more than 70 polymorphisms, this gene depends on population variants, as well as demographic, this can be divided into four main groups:

a. ultra rapid metabolizer (MU)

b. quick (MR)

c. intermediate (MI)

d. slow (ML)

It has been found that people with a ML have a low or no CYP2D6 enzyme activity, which gives as a result an alteration of metabolism and elimination of many drugs, so are more likely to show RAF to these drugs. In comparison, subjects presenting MU are more likely to introduce inefficiency to drug treatment, are therefore needed higher doses than those normally prescribed for therapeutic concentrations.\textsuperscript{[20,21]} According to these studies have been conducted to assess the frequency of these walls in the world's population that has been found that the frequency of individuals ML is 1-2\% in Asian, 5\% African American and 6-10\% in
Caucasian populations. The Ethiopians have 29% individuals MU, 20% Saudi Arabs, Caucasians of 1-2%, except for the Spaniards (7-10%).

In certain pathologies has resorted to Pharmacogenomics to identifies it genes for susceptibility to diseases that represent potential therapeutic targets. From the therapeutic target, clinical trials are designed to sift possible chemical compounds and determine its value.[9,20,22,23]

DISCUSSION
Clinical pharmacokinetics is responsible for the implementation of pharmacokinetic parameters, individualized therapeutic control and optimization of pharmacological treatments dosing regimens. Response to pharmacological treatment depends in great part of the dosing regimen is used, which can be influenced by variations in profile pharmacokinetic and/or pharmacodynamic, of the drug. The interactions that occur when there is concurrent administration of various drugs, may be due to genetic variations that affect your metabolism and produce significant differences in drug response of patients.

CONCLUSION
To understand the interactions between the Pharmacology and health care, it is necessary to implement education programs to the health professional, since they are primarily responsible for the care of patients. In clinical practice, all staff who work in a hospital or in private clinics, you must have adequate knowledge to implement combination therapies in which pharmacological interactions are not a limiting factor to the characteristics of each patient.

By which the challenges of new diseases and the re-emergence of the old, the strengthening of pharmacovigilance allows the health authorities to shorten the registration approval plans medical health for new drugs, security that provide post commercialization monitoring systems. All this is thanks to advances in pharmacokinetics that greatly influence efficiency in drug treatment.

BIBLIOGRAPHY


