PHARMACOEPIDEMIOLOGY AND BIOINFORMATICS: EVOLUTION AND INTEGRATION OF ANALYTICAL WAYS ON PRECISION THERAPEUTICS ON CARDIOVASCULAR RISK

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Annotation

The pharmacological intervention is positioned as a common element in the process of approaching patients at different levels of care, with the aim of limiting the natural evolution of various pathological conditions, generating symptomatic relief, preventing and in some circumstances, diagnosing. The use of therapeutic molecules within the framework of clinical decisions requires the conjunction and analysis of elements such as pharmacological, regulatory, epidemiological knowledge and individual characterization of the patient. This complex and multivariate scenario implies an important effort of the health professional, who will also find himself with a systematic element in front of the exposure to drugs: the adverse drug reactions, unwanted and within the therapeutic spectrum. To support the professional in the area of health sciences, bioinformatics and biostatistical information analysis processes arise, techniques that together with the advance in omics sciences, allow to describe, generate inference, explain, predict and apply knowledge of the science of data, at the bedside of the patient. The incorporation of bioinformatics and pharmacological analysis in complex levels of health care, with special reference to cardiovascular drugs, would allow to anticipate problems derived from interactions, indications, use, compliance, and clinical impact.

Keywords: Cardiovascular drugs, database, computational biology, medical informatics, analytical epidemiology, pharmacogenomics

INTRODUCTION

The use of drugs has become the tool of intervention that is most used in public health, establishing itself as a central determinant in the modification of the natural evolution of the disease, whether from the field of prevention, mitigation, palliation, or even diagnosis. The use of this resource is converted, so contemporary, in an indicator of the state of health or disease of the population. In the field of health care, there is a massive exposure of the population to drugs; in fact, the prescription of drugs, it is the health intervention more widespread and accepted, representing the diverse health systems of developing countries, an expense representative of up to 66% of the health budget.

Despite all the advantages of the mode of intervention with drugs, there is more evidence that medication errors (MS) coupled to Adverse drug Reactions (ADRS) are a common cause, although preventable disease, disability, persistent, and death. The coordinating council american for the reporting and prevention of errors related to drugs, defines MS as any event preventable that may cause or lead to inappropriate use of medications or cause damage to the patient while the medication is under the control of the healthcare professional, patient or consumer. The RAM is defined by the World Health Organization as the response which is noxious and unintended, which appears in the context of drug use within your handling normalized ratio; not only is included in the definition to the harmful effects and involuntary arising out of your authorized use, but also those associated with MS and uses outside the terms of the marketing authorisation (drugs off-label), including misuse, overdose and abuse of the drug. These problems occur with high proportion in the process of clinical care, and frequently are subregistrados or attributed to the pathological condition patient's own, it is considered that they are able to detect and notify on the part of the doctor only between 5 and 10% of RAM .

In some countries, adrs represent an important cause of hospital admission, increase in the period of hospitalization and mortality global estimates show that 40% of patients in ambulatory care are exposed to the RAM and a minimum of 1 patient per day in inpatient services is subject to medication errors (in addition, several investigations show that about 30% of these situations can be anticipated, thereby improving the quality of care and reducing the cost at the hospital level. The percentage of admissions to the emergency centres for RAM is located close to the 5% and 10% of the patients presented a RAM during their hospital stay. These events diminish the quality of life of the patient, prolonged hospital stay, increased morbidity and mortality, induces loss of confidence in the personal care and increases the cost of clinical care.

Individual variability is presented as a key element to determine the response of each patient and their predisposition to adverse events associated with drugs, so that, the evaluation of both the characteristics of the patient, the medication, and the context

of care, become the determinants of the process of medication use and presentation of adverse events.

The safe use of medicines comprises the prevention of the MS that affect patients in different levels of care, which have been associated to the ignorance or total or partial breach of the correct sequence of the rational use of the same, arising from the interaction of variables corresponding to the drug (aspects pharmacokinetic, pharmacodynamic, dosage, indication, interactions, precautions), the patient (characterization of individual socio-economic, clinical, paraclínica and genetics), to the regulation in force (molecules approved, available, pharmaceutical policies) and the epidemiology (incidence, prevalence, demographics, clinical trials, evidence, meta-analysis); this confluence of factors in the framework of a system of health care in limited periods of time, ends in a major way in adverse events arising from improper use and non-rational drug.

Inside of the drugs frequently used in the clinical field, highlights the group of cardiovascular drugs, taking between 20 and 50% of the prescription global. This type of modality pharmacotherapeutic tends to be associative (polypharmacology), so that a patient with a history of cardiovascular disease receives an average of four different drugs, determining a widespread practice based on the combination and synergism, which initially posed a better control of the pathology, however, so frequent and negative can lead to the presentation of RAM. Is set so that one of the areas of more frequent occurrence of adverse events related to drugs is the area of cardiovascular condition which has allowed the development of activities for the evaluation of factors and variables associated critical to this situation of global impact.

The situation multivariate structure of the adverse events associated with drugs, is an analytical effort important part of the treating physician, stage derivative of the amount of information that should be available at the time of the clinical decision-making; this situation, which ends up frequently in MS. These variables occupy a central place within the chain of analysis of the negative events are not intentional use of drugs, so that, in an attempt to sort out the massive amount of information that occurs in the clinical care, is the systematization of data; trend in the last 10 years has been enabled by the electronic formats, to develop and manage large databases, which are evaluated by the administrators of the health care system for purposes such as the evaluation of trends, prevalence of conditions, times for the provision of the service and, above all, to manage the spending on health.

EMERGENCE OF BIOINFORMATICS AND THEIR INTEGRATION INTO THE MEDICAL FIELD

In parallel to the capture of clinical data in the process of care, the data derived from the field of the sciences omics and that, by its exponential growth, have allowed

the way for the creation of a new paradigm in the analytical life sciences, bioinformatics, and computational biology.

This utility of the clinical information, although practical, can be integrated into planning strategies of the same activity of care, rising within the process to quantify, reason, and generate answers to the problems arising from the intervention, pharmacological, epidemiological analysis, allowing the exploration of techniques for assessing the RAM, and its likely impact on public health. Tools developed in the field of pharmacoepidemiology and, more specifically, pharmacovigilance, establish your purpose through the articulation of information, with fields in the data analysis as biostatistics. Such procedures have the clear intention to bring the professional of the health sciences, criteria that allow you to make vital decisions, based on evidence, trends and probabilities.

The routes analytical explored are the multivariate, mainly due to the increasing number of variables that are difficult to manage with descriptive procedures or basic analytical general. The data in health require the establishment of cost-effective ways and innovative to the processing of data in such a way as to enable the generation of new approaches, decision making, and prediction.

The collection and evaluation of data and pharmacology in the field of health, in a higher scale, starts at the end of the TWENTIETH century, primarily due to the global implementation of the Electronic Health Records (BEEF or EHR for its acronym in English), the database of genomic medicine and precision, including in addition to the administrative data. The use of analytical multivariate have received great attention in recent years on the part of the health sciences. The information derived from the care of patients presents a significant opportunity for the improvement of diagnostic procedures, treatment, and prevention of diseases and to achieve interventions that improve health outcomes. Applications of these technologies of analysis have been implemented in various fields, which constitute the central axis of the analysis of prescribing information and pharmacovigilance.

In the field of analysis pharmacotherapeutic with an impact on health care and the data analysis have focused on two main fields: interactions drug-drug and pharmacovigilance. Approaches to the problems arising from the use of drugs related to or in interaction with variables in the clinical field and paraclínico, have been reviewed loosely, focusing on elements of biological and chemical as determinants of the interactions drug-drug, or in situations arising from specific drugs. This global framework, proposes the implementation of initiatives in data analytics for the understanding of the phenomenon of error in medication and RAM, from the integration of the information resulting from the process of patient care in complex levels of care, and that prior have been involved only for the management of administrative processes, which constitutes a valuable opportunity for the integration

of the information management for the improvement of the prescription and use of the valued resource, medication.

PROCESSES ASSOCIATED WITH HEALTH CARE: FROM THE PAST TO THE CONTEXT

The model of care classic in health for Colombia, it operates under the features of physical infrastructure, fixed administration/audit, professionals, patients, unidirectionality, interventionism, palliation, heterogeneity of sources and information, disaggregation causal and high costs; this paradigm contrasts with the current availability of procedures for systematic for the organization and management, based on the extensive development and computational particularly in the approaches of data analytics that are based on epidemiological tools and biostatistics.

The clinical care results in the generation of significant volumes of data, coming from the characterization of the same process of care and, more recently, sensors and new types of devices for hospital and outpatient connected to information networks and databases. It is estimated that between 2010 and 2013, was developed about 90% of the world's information available to analytical processes, playing an important role in this load of data, the processes of health care. In consideration of the magnitude of information originating from sanitary processes, are presented in parallel, strategies for its use and management, and emerging analytical processes applied to the life sciences, because the data in a generic way, represent a significant opportunity for improving diagnosis, treatment, prevention, and changes in health outcomes.

The evaluation of data mediated by the statistics used in biomedical sciences for the description and inference. Inferential statistics is used to answer questions about the data, to test hypotheses, generate measures of effect, rates or risks, to describe associations or patterns of relationships within the data and, in many other functions. Although the assessment of epidemiological data tends to focus on an event or exposure of interest, the characteristic multivariate events present in health, should be considered as possible modifiers in the approach of causality. The tools of analysis stratified and multivariable, minimize distortion that induce spurious associations or confuse the objectives for which it used the efforts evaluative information originated in the health care. The multivariate analysis plays a crucial role by acting as a mechanism of control by the simultaneous consideration of independent variables or predictor; in this way, it generates a greater economy in the analytical data, with the potential to make predictions and to obtain a greater consistency in statistical inference.

Examples of international initiatives in the field of multivariate analysis with the purpose of association and prediction of events in health, have been implemented in the surgical areas, oncology, psychiatric, infectious diseases, quality of care, basic care and specialized, highlighting in a notorious way, the amp powers to processes of analysis in the field of drug.

In the past five years, the British Pharmacological Society through its publications, warns of the relevant role of multivariate analysis in the detection of problems associated with drugs, highlighting the application of the analytical processes with emphasis predictive, on the data from the medical care in regions development pathway.

The pharmacological intervention, in fact, constitutes one of the elements of increased production of information, in consideration of the many variables involved in your employment generally, and to the overall risk of the generation of inappropriate prescribing in about 60% of the cases. Since 1995, there have been strong efforts to promote the phenomenon of association of variables and events from the in silico analysis for the discovery of molecules with therapeutic potential to innovative initiatives such as the systematic pharmacological and pharmacovigilance.

The systematic evaluations of data in intervention with drugs, have gained ground in the determination of patterns and relationships of adverse events in the geriatric population. In this group has focused much of the attention of the multivariate analyses, in function of polypharmacy and comorbidity. As part of the developments in analytical for this population models are proposed for prediction of risk based on various associative processes of clinical variables, pharmacological and paraclinical. Systematic reviews of models of analysis in prediction of risk for adverse events associated with medications in hospitalized patients, highlight the model BADRI (Brighton Adverse Drug Reactions Risk) as a process with appropriate validation, and performance, allowing their integration into processes of research in the field. The model BADRI used a combination of univariate and multivariate analysis (binary logistic regression) to identify the risk factors, clinical symptoms that characterize the RAM; five variables are considered within the prediction: number of medications, dyslipidemia, white cell count, use of anti-diabetic drugs and hospitalization time.

In the field of the monitoring of events associated with the use of drugs, since 2010 in Colombia, we have explored routes that determine approximations to the patterns or behaviors characteristic on the use of drugs. These research efforts have been based on the presentation of interactions both in hospital care as an outpatient, situations anticipables in a high proportion through the proper management of automated prescription data.

The analytical pathway, as a holistic concept, requires a multidisciplinary approach, a condition that makes it more attractive after the current concept of collaborative development in the field of innovation in health. Various authors hold and position the multivariate analyses as the genesis of the change in the organization of clinical care with improved decision-making and access to new possibilities of development, including innovation, research, economics, unification of criteria and

standardization of care processes. These changes would lead to a reduction in the gaps of the process of health care from a greater clarity of the data and its central role in the improvement of the conditions of life of the users and the system itself.

THE INTERINDIVIDUAL VARIABILITY AS AN ADDITIONAL ELEMENT TO THE SCENE OF THE PRESCRIPTION: THE CASE OF CLOPIDOGREL

When a xenobiotic (in this case a drug) has contact with the body, in most cases, it is transformed wholly or partly in another, or other substances. The scaffolding enzyme to perform these transformations is located mainly in the liver, but are also found in lesser extent in other organs such as the kidney, lung, intestine, adrenal glands, and other tissues, as well as the intestinal lumen. The drugs did not innovate the material enzyme of an organism, but are transformed by enzymatic systems already existing. The reactions involved in the process of metabolism are multiple and diverse, and, in general, can be considered as taking place in two phases: The reactions of phase I and / or activation, consist of oxidation and reduction reactions, which alter or create new functional groups, as well as reactions of hydrolysis, which broken links, esters and amides releasing new functional groups; and the reactions of phase II which tend to convert the intermediate metabolites from phase I into final products polar character of water-soluble.

The oxidative system of the liver microsome system (monooxygenases or mixed function oxidases), it is, by far, the most used in the metabolism of drugs, both for the variety of oxidative reactions gives rise as the number of drugs that use it. The enzymes involved are monooxygenases cytochrome P450 (CYP), which are attached to the structure membranous reticulum. Use an O2 molecule, but only used one atom to the oxidation of the substrate, while the other will be reduced to form water, thanks to the presence of an external donor of electrons.

The cytochromes P-450 (CYP450) are heme proteins that, when combined with the carbon monoxide in their reduced state, form a complex that absorbs light at 450 nm, situations these that determined its current nomenclature. The first knowledge of CYP450 be traced back to studies conducted by various groups in the decade of 50 from samples of liver tissue of mammals. Omura and Sato in 1964, identified the nature hemoprotéica of a pigment present in the liver microsomes of different species, which was able to bind to carbon monoxide (CO) after being reduced by NADPH. This discovery to be extrapolated by other researchers presented the problem of the non-coincidence with the descriptions of the different groups, which raised the theory of the existence of several families enzyme related. Have been described to date, around 200 families of CYP450 (described over 2000 individually), of which around 50 are present in the human species.

In our species, we have sequenced more than 57 genes and 47 pseudogenes, which determine 18 families of interest, of which the first 3 (CYP1, CYP2 and CYP3) are considered to have the greatest relevance in the field of metabolism of drugs. Specifically subfamilies have been identified as participants in the metabolism of xenobiotics in the human species are: CYP1, 2A, 2B, 2C, 2D, 2E and 3.

La oxidasa mixta CYP2C19, que metaboliza múltiples medicamentos de interés, entre ellos tienopiridinas, es codificada por un gen localizado en el cromosoma 10 (10q24.1-q24.3) y consiste de 490 aminoácidos. CYP2C19 es uno de los genes más polimórficos entre diferentes grupos étnicos (61).

Have been detected at least 30 allelic variants, highlighting 2 of them: CYP2C19*2 and CYP2C19*3 encoding loss of enzymatic function. CYP2C19*2 (rs4244285) corresponds to the change 681G>A in exon 5, which results in a site altered splicing generating a non-functional protein. CYP2C19*3 (rs4986893) results in a change 636G>A in exon 4, which generates a premature codon stop. Based on the alleles present in CYP2C19, individuals can be grouped into different phenotypes: *1/*1, metabolizers, extensive (EM, extensive metabolizers); *1/*2 - *1/*3, intermediate metabolizers (IM, Intermediate Metabolizers) and *2*/*2 - *2/*3, poor metabolizers (PM, Poor Metabolizers).

Multiple medications act as substrates, inhibitors or inducers of CYP2C19, which shows a complex picture in front of the use of schemas polifarmacológicos.

Hepatic expression of P-450 varies remarkably between different individuals as a result of genetic factors, pathophysiological and environmental. Some P-450 polymorphic expression which leads to variants enzyme that may have altered its catalytic activity.

Numerous in vitro studies have shown that the individual response to clopidogrel is not uniform in all patients and is subject to inter-and intrasubject variability. In particular, there is a growing degree of evidence that recurrence of ischemic complications may be attributed to poor response to clopidogrel. Research farmacogenéticas have shown features clear susceptibility interindividual front of the answer pharmacotherapeutic and in the outcomes of cardiovascular behind the usage of this and other medications substrate of metabolic pathways with genetic polymorphism.

The allele *2 is the variant is more frequent in Caucasians, african Americans, and asian populations. However, the allelic frequency is significantly higher in asian than in other populations. The allele *3 also occurs more frequently in Asian populations (approximately 10% greater) compared with other racial groups. The studies conducted to date, have found a higher prevalence of genotypes associated with PM in asians (10 – 30%) than in Caucasians (2 – 3%) and African. Work developed in relation to different genotypes of CYP2C19 have shown alteration in the

pharmacokinetics and pharmacodynamics of clopidogrel. The various investigations have found as an element homologous to the presence of the alleles *2 and *3 as predictors of resistance to clopidogrel in the clinical setting. It has been associated directly the presence of CYP2C19*2 and *3 with reduced levels of the active metabolite of clopidogrel, which is reflected in a response pharmacodynamic decreased. The research related to polymorphisms of CYP2C19 in Latin american populations are still scarce despite the relevance of the topic at the global level and of the possible genetic variability-related influences colonial and migratory.

The pharmacogenetics of cytochrome raised with great care in the development of medicines and such is its importance, the FDA indicated by specific guidelines for the pharmaceutical industry, the testing of genotyping in the various stages of drug development; these guidelines were recently updated to include recommendations on the labels of different drugs of interest and are intended to be international in scope.

It should be noted that the information of the variability of therapeutic response has been achieved to the population in general and to such a degree has reached the level of participation and understanding of the subject, which appear initiatives, such as those promulgated by the american association "Public Citizen", where, in the document entitled "Petition for Black-Box Warning for Clopidogrel", sent to the FDA on August 21, 2013, request to add a boxed warning to the technical data sheet of clopidogrel to alert patients of the risk of bleeding that supposed to take it to HANDLE more than 12 months after the implantation of a stent farmacoactivo. The group requested to distribute a "guide treatment" updated to the patients with respect to the above-mentioned adverse effects avoidable that occur with the use of more than 12 months of clopidogrel. This letter covers the relevant aspects of the therapy with the drug as the reference of more than 2 million prescriptions in 2012 alone, and the emergence of increasingly adverse reactions associated with the consumption of the same; specifically referred to the risk of bleeding.

CONCLUSION

The feasibility of the integration of clinical data, biological databases, knowledge of omics and decision making in public health is subject to the transformations communication and information that promotes the adaptation of digital, technological convergence, the adaptation to the patient care scenarios and ubiquitous, leading to the availability of information for decision making, which allows use of the times of care remain critical in the various contexts of health care. The integration of the analytical procedures in the field of health care in colombia, has allowed the generation of data of care, both clinical as paraclínico, parameterized and non-parameterized, with opportunity to be monitored in complex conditions and for complex decisions. There appears an opportunity for the research and application of

the techniques of analysis of data from the establishment of patterns, relations, and routes associative variables, clinical, paraclinical and genetic-molecular.

It is clear that we face a global level to the challenge of the individualization of the medical act and the opportunities that presents us with a new knowledge that is accompanied with the right technology will enable them to design and implement interventions for the prevention, diagnosis and treatment tailored to the genetic substratum of each patient and the molecular profile of each disease; personalized medicine involves a change of paradigm in the health care system so that it is essential that it is in the agenda of those responsible for defining the policies for national health. The genotyping soon it will become as part of the data that are evaluated routinely within the control of the patient, a situation that implies a challenge related to the upgrade of practising physicians and as training of future professionals in medicine. The evidence that exists in the time since the clinical and cost-effectiveness can not be simply ignored, and a basic concept of current should not be under-appreciated: the integration of data based from the analytical bioinformatics and epidemiology, cover the gap between the knowledge, clinical pharmacological and molecular applications, to get to realize the true individualized medicine.

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