Interest of pharmacoepidemiology for pharmacodynamics and analysis of the mechanism of action of drugs

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Pharmacoepidemiology for pharmacodynamics

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Summary

Pharmacology is often divided in separate branches, such as molecular and cellular pharmacology, pharmacokinetics, pharmacodynamics, experimental and/or preclinical pharmacology, clinical pharmacology (and therapeutics), pharmacogenetics, pharmacogenomics, pharmacovigilance, pharmacoepidemiology, pharmacoeconomics... This enumeration gives a global picture of different scientific areas, which are however dealing with the same question. Another mindset should be a global interactive and continuous approach, which could be designed as “human pharmacology”.

An original and attractive way to illustrate this continuous approach is to combine pharmacodynamics and pharmacovigilance and/or pharmacoepidemiologic data. Coupling disproportionality analyses in pharmacovigilance databases or computerized health databases, with pharmacological characteristics of drugs (receptor affinity, for example) allows to investigate in humans, the mechanism of adverse drug reactions. Examples of such analyses investigating the risk of movement disorders, diabetes related to psychoactive drugs, or the risk of adverse cardiac outcomes with different drugs (classical drugs or protein kinase inhibitors) are given. The increasing number of research works investigating this topic underlines the importance of this relatively new approach, which gives significant inputs for the better knowledge of drug safety.

KEYWORDS

Pharmacodynamics; Pharmacovigilance; Pharmacoepidemiology; Affinity; Efficacy; Disproportionality

Abbreviations

ADR: adverse drug reaction

AP: antipsychotic drugs

aROR: adjusted reporting odds ratio

CF: cardiac failure

EMA: European medicines agency

FAERS: Food and drug administration adverse event reporting system

FDA: Food and drug administration

hERG: human ether a go-go related gene

IUPHAR/BPS: Union of basic and clinical pharmacology/British pharmacological society

PE-PD: pharmacoepidemiologic-pharmacodynamic

PKI: protein kinase inhibitors

PRR: proportional ADR reporting ratio

ROR: reporting odds ratio

UMC: Uppsala monitoring center

WHO: World health organization

Introduction

According to the famous Goodman and Gilman manual of pharmacology and therapeutics, “the subject of pharmacology is a broad one and embraces the knowledge of the source, physical and chemical properties, compounding, physiological actions, absorption, fate, and excretion, and therapeutic uses of drugs.” [1].

Pharmacology can be defined as the study of effects of drugs on the function of living systems. This science born during the 19th century was one of the first representative of new biomedical sciences based on principles of experimentation rather than dogma. The boundaries of pharmacology today are shifting, with interface with other biomedical fields. Classically, pharmacology is often divided in separate branches, such as molecular and cellular pharmacology, pharmacokinetics, pharmacodynamics, experimental and/or preclinical pharmacology, clinical pharmacology (and therapeutics), pharmacogenetics, pharmacogenomics, pharmacovigilance, pharmacoepidemiology, pharmacoeconomics. This enumeration gives a global picture of different scientific areas, which are however dealing with the same question. Another mindset should be a global interactive and continuous approach, which could be designed as “human pharmacology” (Fig. 1).

The mechanisms by which the association of a drug with its target leads to a physiological response constitute a major thrust in pharmacological research. Drugs act on target proteins, represented by receptors, enzymes, transporters and ion channels [2]. In pharmacology, the term “receptor” describes proteins whose function is to recognize and respond to endogenous chemical signals. Specificity is reciprocal: individual classes of drug bind only to certain targets, and individual targets recognize only certain classes of drug, but no drug is completely specific in its actions. In many cases, increasing the dose of a drug will cause it to affect targets other than the principal one, and this can lead to adverse events, which are often named “off-target”. In most cases, mechanisms of action are studied with methods of preclinical pharmacology which use molecular and cellular models to evaluate the receptor binding profile of drug candidates. After these preclinical development phases, pharmacodynamics data predicting the occurrence of drug effect (harms and benefits) are often limited. In clinical and post-marketing phases, very few methods besides the clinical molecular imaging have

been proposed to better understand the pharmacodynamics, especially mechanism of adverse drug reactions.

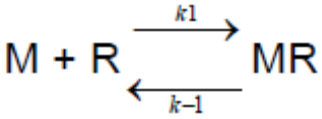
Brief overview of pharmacodynamics' principles

Pharmacodynamics aims at characterizing the nature of the pharmacological response underpinned by drug-targets interactions and measuring the intensity of drug response. To study drug pharmacodynamic properties, different concepts are used. A drug binding to a receptor is defined as a *ligand*. The tendency of a drug to bind to a receptor depends on its *affinity*, corresponding to the propensity of this drug to closely associate with a given receptor. *Efficacy* characterizes the change in state (activation or inhibition) of the receptor upon binding of a drug, while *potency* is related to the molar concentration of drug needed to produce a defined response or effect. *Occupation* of a receptor by a drug may or may not result in *activation* of this receptor. By *activation*, it means that the receptor is affected by the bound drug. In other words, *occupation* is governed by *affinity*, and *activation* by *efficacy*.

A receptor can be activated by endogenous agonists (hormones, neurotransmitters) or exogenous agonists such as drugs. *A full agonist* produces the maximal response that the physiological system can produce whereas *a drug antagonist* may not produce a direct effect, but does interfere with the production of cellular response to an *agonist*.

The pharmacodynamic response related to binding is often plotted as a *concentration–effect curve* for *in vitro* experiment or a *dose–response curve* for *in vivo* experiment. These curves allow to estimate the maximal response that the drug can produce, *Emax*, and the concentration or dose of agonist needed to produce half of the maximal response, EC_{50}. This concentration is usually expressed for statistical manipulation as the pEC_{50}, the negative logarithm of the molar concentration producing 50% response. For antagonist, IC_{50} (*inhibition concentration*) is defined by the concentration or dose needed to produce half inhibition of a defined agonist effect, and pIC_{50} is the minus logarithm pf the IC_{50} [3].

Ligand binding is a dynamic equilibrium process. Ligands bind to receptors and dissociate from them according to the law of mass action.



In this formula, M represents the molar concentration of unbound drug, R the molar concentration of unbound receptor, MR the molar concentration of the complex drug-receptor, K1 the association constant, expressed in M^{-1}x min^{-1}, K-1 the dissociation constant, expressed in min^{-1}

According to the law of mass action, the dissociation constant $K_{D,}$ expressed in molar concentration may be calculated

$$K_D = \frac{M \times R}{MR} = \frac{K-1}{K1}$$

K_D characterizes the *affinity* of the drug for one receptor. A low K_D indicates a *high affinity*. Similarly, the inhibition constant K_i is used to define the affinity of antagonists. K_D and K_i are usually expressed for statistical manipulation as pK_D and pK_i, negative logarithm of the K_D and K_i, respectively. For an antagonist, higher is the pKi, higher is the *affinity*.

The degree of receptor occupancy may be also used instead of the affinity constants, through the calculation of an equation derived from the pharmacological receptor theory's model [3]. This model is useful for predicting receptor-mediated pharmacological actions on a quantitative basis. The equation is the following:

$$Degree\ of\ receptor\ occupancy\ (\%) = \frac{[C_r]}{(K_i + [C_r])} \times 100$$

,

where $[C_r]$ represents the concentration of unbound drug and K_i is a constant which characterizes, for antagonist drugs the affinity for a given receptor.

Brief overview of disproportionality analyses in large pharmacovigilance databases

During the last decades, the databases collecting suspected adverse drug reaction (ADR) reports had grown, reaching sizes of more than several thousands or millions, thus making routine and regular quantitative screening a necessity. Data mining in these large databases has become a necessity in order to help pharmacovigilance systems to identify early signals for specific ADRs. Various statistical measures have been proposed for the application of computer-assisted quantitative signal detection procedures. Data mining encompasses a number of statistical techniques, including cluster analysis, link analysis, deviation detection and disproportionality assessment, which can be used to determine the presence of and to assess the strength of ADR signals. Disproportionality in large pharmacovigilance databases is often investigated under the scope of a case-non case method, in which cases of a given ADR are compared to non-cases (other spontaneous reports except this given ADR) regarding prevalence of exposure to specific drugs and/or classes of drugs. Results are presented in the form of a reporting odds ratio (ROR) or a proportional ADR reporting ratio (PRR), the interpretation of which makes it possible to identify drug safety signals [4, 5], or to rank different drugs for a specific ADR risk.

Many studies have been conducted at the international level, with data from the World health organization (WHO) database [6], the Food and drug administration (FDA) adverse event reporting system (FAERS), the European medicines agency (EMA) Eudravigilance database, or national pharmacovigilance databases [7, 8]. A further step forward has been taken by combining results obtained in these pharmacovigilance databases and pharmacological data related to drug targets and binding [9].

Some examples of combining pharmacodynamics and data at the population level from pharmacovigilance or pharmacoepidemiology points of view

We identified in the scientific literature several examples of such approaches in various contexts. The following presentation is not exhaustive but gives an overview about the possibilities of combining pharmacodynamics data, and pharmacovigilance or pharmacoepidemiological data, and the mutual inputs of these confrontation to enrich the research field in drug safety.

Exploring the implication of neurotransmitter receptors in adverse drug reactions of psychoactive drugs

Sekine in 1999 investigated the correlations between *in vitro* affinity of antipsychotic drugs (AP) to various receptors and clinical incidence of their adverse drug reactions [10]. For that purpose, they analyzed safety data of 17 AP available in Japan. From both post-marketing ADR databases and the investigational clinical trials of eight pharmaceutical companies with data collected from 1960 to 1995, they estimated the frequency of 7 different ADR (akathisia, dyskinesia, tremor, rigidity, drowsiness, hypotension and dry mouth). Affinity constants (K_i) of the respective drugs toward dopamine D1 and D2 receptors, alpha1-adrenoceptors, histamine H1 receptors, serotonin 5HT2 receptors and muscarinic receptors were obtained from the literature, among studies determining these K_i using rat brain synaptosomes. Relationships between *in vitro* receptor-binding properties and *in vivo* incidences of the respective types of antipsychotic-related ADRs were analyzed using Spearman's rank correlation. They found statistically significant correlations between Ki values for dopamine D2 receptor and akathisia and dyskinesia as well as between the Ki values for alpha1-adrenoceptor and histamine H1 receptor and drowsiness and dry mouth. According to these results, the authors concluded that preclinical receptor-binding data might be useful for predicting not only *in vivo* antipsychotic potency but also clinical incidence of some ADRs. According to the results regarding D2-receptors affinities, they suggested that newly developed antipsychotic drugs with more potent and selective antagonist activity against the dopamine D2 receptor might not necessarily be associated with a lower incidence of extrapyramidal ADR, which was confirmed later by a study conducted on the WHO international pharmacovigilance database, Vigibase® [11].

In this more recent study, the authors performed a case–non case analysis using spontaneous reports collected in Vigibase® from 1972 to 2015 [11]. They measured the risk of reporting movement disorders compared with all other ADR by the calculation of a reporting odds ratio (ROR) for 53 antipsychotic drugs (AP), 32 first generation AP, and 17 second generation APs. The authors secondly performed a linear regression analysis to explore the association between the specific value of ROR for each individual drug and its degree of receptor occupancy, for D2, 5HT2A and M1 receptors. In this

approach, computation of the degree of receptor occupancy was based on the pharmacological receptor theory. This study allowed to underline that the greater was the degree of 5HT2A or M1 receptor occupancy, the fewer movement disorders were reported, as presented in Fig. 2. This was not the case for D2 receptors, reinforcing conclusions of the previous study [10]. Finally, this study by using the example of AP-induced movement disorders, an adverse drug reaction with a well-established mechanism, supported the interest of this approach. Authors proposed to term this method "*the pharmacoepidemiologic-pharmacodynamic approach*", i.e. the PE-PD approach.

Another similar study was conducted on Vigibase® to investigate the risk of diabetes related to the use of APs, with a focus on 5HT receptors [12]. Using the same methodology than in the study having investigated movement disorders, the authors analyzed data related to AP and the degree of occupancy to the serotonin receptors (5HT1A, 5HT2A, 5HT2C), histamine H1 receptor, muscarinic M3 receptor, adrenergic α1 and α2 receptors and dopaminergic D2 and D3 receptors. The findings of this study supported that AP blocking both histamine H1 receptors and 5HT2C receptors are more frequently involved in drug-induced diabetes than that observed with other APs, and therefore that the role of these properties must be specifically anticipated when predicting the risk of glycemic and metabolic effects of candidate APs.

More recently, researchers have investigated the possible receptor/transporter mechanisms involved in the risk of diabetes related to antidepressant drug use, through a disproportionality analysis of the FDA adverse events spontaneous reporting system database [13] and in Vigibase® (14). In the FDA database, authors extracted data from 2004 to 2017 using OpenVigil2 and calculated adjusted reporting odds ratio (aROR) for reporting diabetes for 22 antidepressant drugs. The pharmacodynamic profile was extracted using the PDSP and Union of basic and clinical pharmacology / British pharmacological society (IUPHAR/BPS) databases and the occupancy to receptors (serotonin, α adrenergic receptors, dopaminergic, muscarinic, histamine) and transporters (SERT, NET, DAT) was estimated similarly to previous studies [11, 12]. The relationship between aROR for diabetes and receptor occupancy investigated with Pearson's correlation coefficient and univariate linear regression suggested that higher degrees of occupancy to muscarinic receptors and H1 receptors might be a plausible pharmacological mechanism for antidepressant-induced diabetes. In this study, six imipraminic antidepressants were found associated with type 2 diabetes: nortriptyline, doxepin, imipramine, sertraline, mirtazapine and amitriptyline [13]. The study performed in Vigibase®

concluded also to the probable implication of serotonin transporter in antidepressant-induced type 2 diabetes [14].

Exploring the role of specific targets on the occurrence of cardiovascular adverse reactions

To the best of our knowledge, one of the first application of the combination of pharmacodynamics data and disproportionality analysis in the WHO international pharmacovigilance database was performed by De Bruin et al in 2005 [15]. Drug-induced prolongation of the QTc-interval usually results from concentration-dependent blocking of cardiac human ether a go-go-related gene (hERG) potassium channels. The authors were interested in how inhibition of hERG potassium channels may lead to serious ventricular arrhythmias and sudden death observed in the real life context. For this purpose, they studied the quantitative anti-hERG activity of pro-arrhythmic drugs as a risk factor for this outcome, with a two-step analysis. In the first step, they identified all case reports of suspected adverse drug reactions with known anti-HERG activity received by the International drug monitoring program of the World health organization-Uppsala monitoring center (WHO-UMC) up to the first quarter of 2003 and recorded in the international pharmacovigilance database (which was not yet called "Vigibase®"). Cases of interest were all reports of cardiac arrest, sudden death, torsade de pointes, ventricular fibrillation, and ventricular tachycardia, which were designed as "cases" and compared to all other cases (as non-cases), to calculate reporting odds ratios (ROR). The anti-hERG activity of the study drugs was regarded as the exposure. Anti-HERG activity was defined as the free plasma concentrations attained during clinical use (ETCP unbound) divided by the concentration which inhibits 50% of the potassium channels (IC50). Anti-hERG activities of all study drugs which were assigned as 'suspect' were assessed. The authors hypothesized that increasing ETCP unbound/IC50 ratio led to an increased risk of an adverse event of interest. To control for potential confounding factors, the estimation of ROR was done by adjusting on several secondary factors including age, sex, several concomitant diseases (heart disease, pulmonary disease, and diabetes mellitus), pharmacokinetic drug–drug interactions, concomitant use of drugs which may lower blood potassium levels, year of reporting, and time since first marketing for each respective drug. Results highlighted a significant association between the anti-hERG activity of drugs (with an ROR of 2), measured as log10

(ETCP unbound/IC50), and reporting of serious ventricular arrhythmias and sudden death to the WHO-international pharmacovigilance database. These findings confirmed the value of pre-clinical hERG testing to predict pro-arrhythmic effects of drugs.

Other authors investigated the same question whether non-cardiovascular hERG channel blockers were associated with an increased risk of sudden cardiac death and whether hERG-channel-inhibiting capacity should be an indicator for this risk [16], not investigated through a pharmacovigilance database. Indeed, the originality of this study was that it was performed in the Integrated Primary Care Information database, a longitudinal general practice research database in Netherlands. A case-control study was performed, matched for age, gender and calendar time. Odds ratios were calculated with conditional logistic regression. The hERG-channel-inhibiting capacity of the different drugs, defined as the effective free therapeutic plasma concentration ($ETCP_{unbound}$) divided by the concentration that inhibits 50% of the potassium channels (IC50) and computed in the same way that in the De Bruin ‘s study [15] and was compared according to the risk of sudden cardiac death among 1424 cases and 14 443 controls. Current use of hERG channel blockers was found associated with an increased risk of sudden cardiac death, specifically in users of antipsychotics. Patients using hERG channel blockers with a high $ETCP_{unbound}$/IC50 ratio presented a higher risk than patients using drugs with a low ETCP $_{unbound}$/IC50 ratio, and this was confirmed at the population level.

The most recent example illustrating the interest of combining pharmacodynamics and pharmacovigilance concerns the implication of cellular targets involved in the development of cardiac failure in patients treated with protein kinase inhibitors (PKI) in oncology [17]. The human protein kinase (PK) gene family targeted by PKIs consists of 518 members. Although PKIs share a common mechanism of action when acting on protein kinases, there are different classes and subclasses. First, the PK targeted by a PKI could be a receptor or a non-receptor PK. The PK target could belong to one of the three large families of PKs: the tyrosine kinase family, the serine/threonine kinase family (the most abundant) and the atypical protein kinase family. PKIs are specific for an inhibitory binding site: type I PKIs bind to the ATP binding site of the PK, which is a very conservative site that leads to poor drug selectivity; type II PKIs bind to the hydrophobic pocket adjacent to the ATP-binding site, and are more selective; type III PKIs bind to a cysteine residue that can be variably located in the kinase domain, and is very selective for a single PK. In summary, the selectivity of PKI is a relative issue in the development of these drugs. Ideally, a drug should be able to bind only to the on-target site with

high affinity, to avoid “off target” toxicity [18]. Some ADRs can be considered as “on-target”, because they are induced by inhibition of the PKI’s target of interest, or as “off-target”, because they are related to the inhibition of a secondary or unexpected target(s) of the drug. Because some PKIs have been identified as inducing cardiac failure, Patras de Campaigno’s group aimed to evaluate the risk of cardiac failure (CF) associated with 15 anticancer PKI through a case-non case analysis among Vigibase® and to identify which PK(s) and pathways were preferentially involved in PKI-induced CF [17]. The analysis identified a significantly higher disproportionality for CF for dasatinib, imatinib, bosutinib, sunitinib and nilotinib compared with other PKIs. Pearson’s correlation regression models between reporting odds ratio and affinity data (product of dissociation constant [pKd]) of 15 different PKIs for 21 PKs were statistically significant for two non-receptor protein kinases: ABL1 (non-phosphorylated and phosphorylated forms) and ABL2 protein kinases, with values of Pearson’s correlation coefficients respectively equal to 0.83 (P = 0.0001), 0.75 (P = 0.0014) and 0.78 (P = 0.0006), respectively. This novel approach in this field, based on pharmacovigilance and pharmacodynamics data, was demonstrated as useful to identify cellular pathways involved in ADRs. For cardiac failure in cancer patients treated with PKI, ABL1 and ABL2 tyrosine kinases (Abelson murine leukemia viral oncogene homolog) are cellular targets likely to be involved in this ADR.

Conclusion

These different examples underline the importance of coupling disproportionality analyses in pharmacovigilance databases or pharmacoepidemiologic studies in large health care databases, with pharmacological characteristics of drugs (receptor affinity, for example); The PE-PD method could be interesting not only to better understand the mechanisms of adverse drug reactions but also to prevent the use or the development of drugs susceptible of inducing a given adverse drug reaction. The increasing number of research works investigating this topic underlines the importance of this relatively novel approach, which gives significant inputs for the better appraisal of drug safety.

Disclosure of interest

Authors have no competing interest to declare

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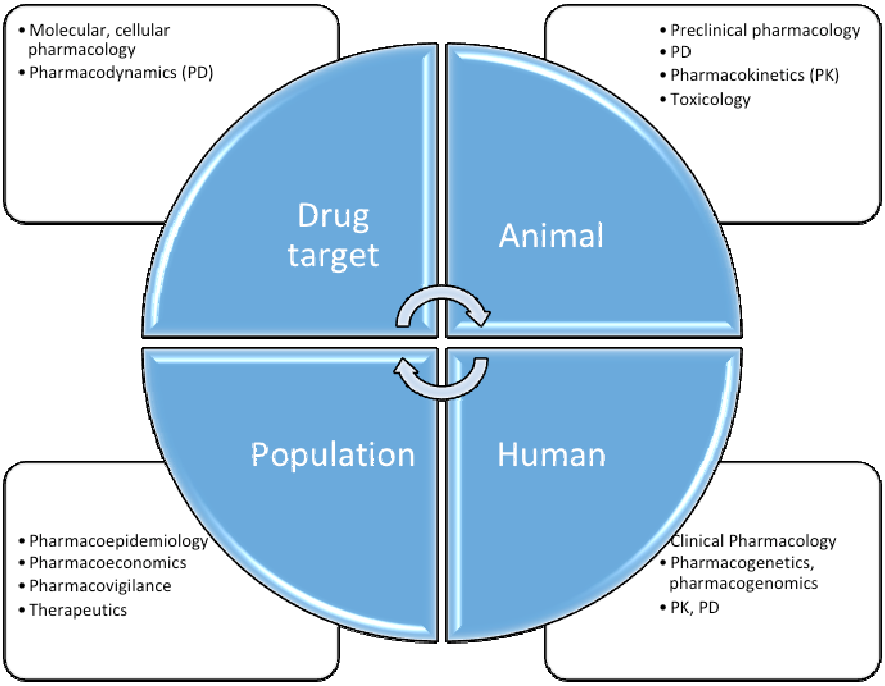

Figure 1. Pharmacology is the study of effects of drugs in living systems. It could be seen as a continuum from the identification and explanation of interactions between a drug and cellular and molecular targets, to preclinical pharmacology in animal models to investigate the pharmacological properties of the drug, then to clinical pharmacology by testing these previous hypotheses, and then to pharmacoepidemiology (and pharmacovigilance and/or pharmacoeconomics) to investigate the real impact of the drug at the population level. Because these relationships are not linear but circular, mutual inputs of pharmacodynamics and pharmacoepidemiology are evident.

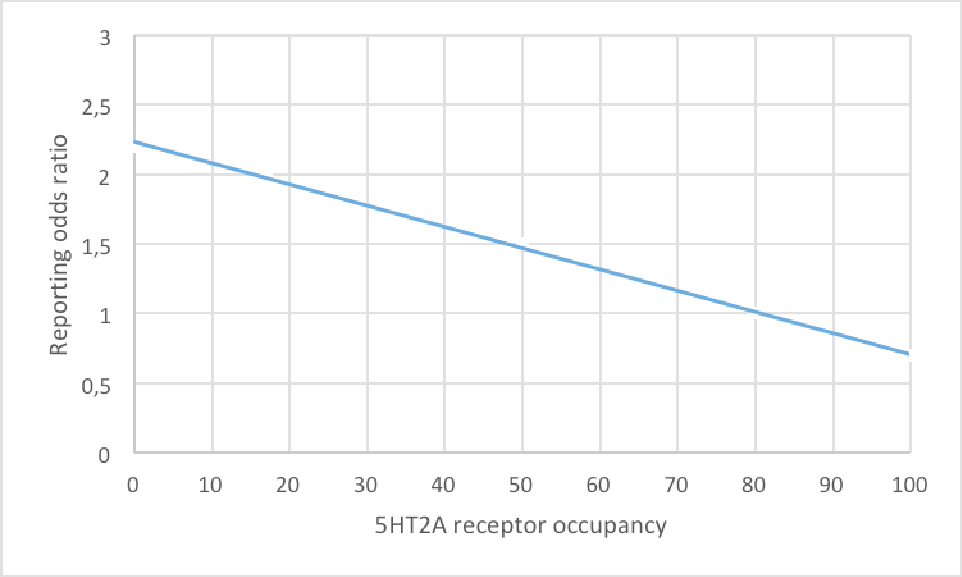

Figure 2. Association between serotonin 5HT2A receptor occupancy and reporting odds ratio (ROR) for movement disorders.

*Figure based on the paper by Nguyen TTT et al [11].