Advances in Biochemistry & Applications in Medicine

Chapter 4

Some Pharmacological Effects of Drugs

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Abstract

Pharmacology is the study of the properties of drugs and their interaction with living organisms, including viruses. These drugs exert pharmacologically some effects in a biological system called an effector. Such effects are pharmacodynamic, therapeutic, harmful, idiosyncratic or iatrogenic. The pharmacodynamic effect is a measurable, reproducible, functional or organic change. It concerns the action of the drug at elemental levels, such as molecules or cells. The biological effects of drugs lead to clinical effects that are observed in patients known as therapeutic. This therapeutic effect refers to the response(s) after a treatment of any kind, the results of which are judged to be useful or favorable. Exposure to drugs can be hazardous and results to harmful effects such as adverse and toxic effect on human being. Adverse effects occur in the actions of the body on the drug and the actions of the drug on the body. Carcinogenic, mutagenic and teratogenic effects can occur and much lower exposure levels than those required exhibit toxic effects. Toxic effects are the harmful manifestations resulting from an excess of medication. The evaluation typically includes acute, sub-chronic, chronic, carcinogenic and reproductive effects. Idiosyncratic effects are manifestations that occur only in subjects with a particularity, which are essentially genetics.

Keys words: Drug; Pharmacologic effects; Therapeutic effects; Harmful effects; Idiosyncratic effects

1. Introduction

Pharmacology is the science that deals with drugs, their properties, actions and fate in the body. It embraces the sciences of pharmaceutics (preparation of drugs), therapeutics (treatment of diseases by use of drugs) and toxicosis or adverse side-effects that arise from the therapeutic interventions [1]. Any pharmacological or non-pharmacological treatment has two components, one related to the specific effects of the treatment itself and the other, non-specific, related to the perception that the therapy is being administered [2]. During the journey, after its absorption and distribution, the drug reaches its specific sites where it interacts with its receptors, usually proteins and enzymes, and produces its biological effects; this is known as “pharmacodynamics.” The biological effects lead to clinical effects that are observed in patients known as therapeutics or pharmacotherapeutics. However, many people underestimate the toxicity of natural products and synthetic drugs [3] which may enter human body and exert their toxic effects. The toxic effects may take place prior to the binding of the toxicants to the vital organs such as liver and kidneys. Hence, evaluation of toxic properties of a substance is crucial when considering for public health protection because of the exposure to chemicals which can be hazardous and results to adverse effects on human being [4]**.** Adverse effects occur when the actions of the body on a drug and the actions of the drug on the body are reviewed in each stage. In doing so, the mechanisms and risk factors of adverse effects will be addressed [5]. Adverse drug reactions are unwanted pharmacologic effects associated with medications (e.g: constipation from codeine-containing medications). To avoid adverse effects of the drug or substance, the dose, frequency and duration of the treatment should be carefully defined [3]. In practice, the evaluation typically includes acute, sub-chronic, chronic, carcinogenic and reproductive effects [6].

2. Pharmacodynamic Effects

The pharmacodynamic effect is a measurable, reproducible, functional or organic change caused by a drug in a biological system called an effector. This term "pharmacodynamic effect" should be reserved for the action of the drug at elemental levels, such as molecules or cells. It is the support of the mechanism of action of the active ingredient. It is the basis of the pharmacological classification of drugs which is a classification by elemental effects and mechanisms of action [7]. The main pharmacodynamic effect is responsible for the response as far as it constitutes the mechanism of action that leads to the modifications of the organism that interest us. What we find in the patient is not only the result of these changes, but also those resulting from other pharmacodynamic effects of the active ingredient (side effects), as well as reactions of the body to these changes. These changes are the harmful consequences of the specific pharmacodynamic effects of the molecule. They are therefore constant at a given dose: those due to the main effect are inevitable and those due to side effects can be minimized by

changing the dosage form or by modifying the molecule [7]. The answer is the result of their integration. The relationships between pharmacodynamic effect and response are comparable to those that exist in genetics between genotype and phenotype.

3. Therapeutic Effects

Therapeutic effect or clinical effect refers to the response(s) after a treatment of any kind, the results of which are judged to be useful or favorable. This is true whether the result was expected, unexpected, or even an unintended consequence of the treatment. It is the impact of a drug on a pathological condition [8]. The therapeutic effect obviously stems from the main pharmacodynamic effect and the response of the organism, but also from the placebo effect. It is a consequence of a medical treatment of any kind, the results of which are judged to be desirable and beneficial. The therapeutic effects are the intended beneficial effects of the drug while the negative side effects are the unwanted effects of the drug. For example, non-steroidal anti-inflammatory drugs, like Advil, can help ease minor aches and pains resulting from running around too much. That's their therapeutic effect. A potential negative side effect is gastrointestinal ulceration. Gastrointestinal ulceration is a term that describes the formation of deep defects (like sores) in the digestive system. The pharmacodynamic effect does not constitute a therapeutic effect.

Margin of safety **(therapeutic index):** The dose-dependence of both effects can be graphed in the form of dose–response curves (DRCs). The distance between the two DRCs indicates the difference between the therapeutic and toxic doses. This margin of safety indicates the risk of toxicity when standard doses are exceeded [9].

4. Harmful Effects

a. *Toxic effects*

Toxicity is an expression of being poisonous, indicating the state of adverse effects led by the interaction between toxicants and cells [4]. Toxic effects are the harmful manifestations resulting from an excess of medication [7]. The toxic effect occurs as a result of taking excessive doses of medication on a voluntary or accidental basis. The mechanism of action from which the effect arises is in the prolongation of mechanism which is at the basis of the pharmacological effects of the substance. Toxic effects are predictable and preventable effects based on animal or clinical experimentation. They are systematically researched and quantified experimentally (i.e on the animal) during the toxicological phase of the preclinical study of the drugs, with a different difficulty and efficiency according to whether it is acute toxicity or chronic. We talk about absolute overdose if it involves abnormally high doses, and relative for an abnormally large reactivity of the patient at correct doses. Toxicological investigations serve to evaluate the potential for: (1) toxicity associated with acute or chronic administration;

(2) genetic damage (genotoxicity, mutagenicity); (3) production of tumors (oncogenicity or carcinogenicity); and (4) causation of birth defects (teratogenicity) [9]. According to [1], the main types of evaluation needed from safety and toxicity studies include: Acute toxicity, Sub-acute toxicity, Chronic toxicity testing, The reproductive performance, Carcinogenicity studies, Mutagenicity studies and Investigative toxicology.

Overdosage: It is defined as the repetition of administrations that results in the presence in the body of sufficient quantities of drugs to cause toxic effects, which are similar to those of acute intoxication [7]. The drug is administered in a higher dose than is required for the principal effect; this directly or indirectly affects other body functions [9]. The dose alone makes the poison. This holds true for both medicines and environmental poisons. In order to assess the risk of toxicity, knowledge is required for: (1) the effective dose during exposure; (2) the dose level at which damage is likely to occur [9]. The processes leading to this are multiples: relative intolerance, accumulation, poorly adapted and excessive dosage; and in some patients, the overdose comes from a lack of elimination or transformation of the active principle, either as a result of pathological disorders (renal insufficiency), individual innate or acquired (age) characteristics (pharmacogenetic), or interaction [7].

Acute toxicity: The acute toxicity of drugs is often known, predictable and extrapolable from the experimental animal to humans. Also called short-term toxicity, it results from the absorption at one time, an excessive amount of toxic [7]. It involves looking at the effects of large single doses of therapeutic agent [1]. The characteristic of being dose-dependent (their intensity increases with the dose) differentiates in particular the toxic effects of allergic or immune reactions for which it is impossible to establish such a relationship, and even it is very difficult to determine a "dose- threshold. "It occurs immediately after or within hours of the drug intake. Acute toxicity studies are usually performed in animal models such as mice and rats. These studies enable investigators to correlate any observed effects with the systemic level of the drug [1]. Determination of acute oral toxicity is usually an initial screening step in the assessment and evaluation of the toxic characteristics of all compounds. The methods so far utilized for the determination of median lethal dose LD_{50} and the new changes which could be made.

Sub-acute toxicity: It is similar to acute toxicity but measures the effects of multiple doses based on expected duration of clinical usage. It entails haematological, histology and electron microscope studies to identify organs which might be affected by toxicity. It usually lasts between one to three months. This enables the selection of putative compounds for subsequent studies [1]. Sub-acute toxicity tests are employed to determine toxicity likely to arise from repeated exposures of several weeks to several months. Standardized tests are available for oral, dermal, and inhalation exposures. Detailed clinical observations and pathology examinations are conducted.

Sub-chronic and chronic toxicities: They occur when the repetition of administrations for a long enough time is followed by tissue lesions characteristic of the product. The chronic toxicity is therefore dose-dependent and its frequency increases with the duration of the treatment. It is predictable and its occurrence can sometimes be detected early by monitoring treatment. In principle, the lesions regress more or less quickly when the treatment is stopped. However, the regression may be incomplete [7]. Repeat-dosing toxicity studies are required when the drug is intended to be used in humans for prolonged periods [1]. They are conducted to determine what side effects will arise from repeated administration of a drug at lower dosages than those used in acute toxicity studies and to determine safe dosages to be used in the initial human clinical trials. The goals of this investigation are mostly similar to those of sub-acute toxicity [1]. Sub-acute and chronic toxicity studies are designed to characterize the toxic effects of drugs upon repeated daily administration for periods of time ranging from two weeks to one year and to determine non-toxic-effect dosage levels for short to long term repeated dosing.

b. ***Cumulative effect***

Cumulative drug effect is the condition in which repeated administration of a drug may produce effects that are more pronounced than those produced by the first dose [7]. Accumulation of drug in the body can produce additive or adverse effect. It is due to too frequent doses or too long continued administration. Additive effect is the combined effect produced by the action of two or more agents, being equal to the sum of their separate effects. Cumulative toxicity occurs when each administration provoke an elementary irreversible lesion. Clinical manifestations happen when the level dose is reached, by adding the totality of received quantities all along life **[7]**. This is the condition in which repeated administration of a drug may produce effects that are more pronounced than those produced by the first dose. A cumulative drug effect may be seen in those with liver or kidney disease because these organs are the major sites for the breakdown and excretion of most drugs. For example: The renal toxicity of aminoglycoside antibiotics (eg, gentamicin) is greater when administered as a constant infusion than with intermittent dosing. It is the accumulation of aminoglycoside in the renal cortex that is thought to cause renal damage.

c. Side and adverse effects

In medicine, a side effect is an effect, whether therapeutic or adverse, that is secondary to the one intended. Although the term is predominantly employed to describe adverse effects, it can also apply to beneficial, but unintended consequences of the use of a drug. According to [10], adverse events are unintended pharmacologic effects that occur when a medication is administered correctly while a side effect is a secondary unwanted effect that occurs due to drug therapy. It is a common misconception that adverse events and side effects are the same thing.

An adverse event is an undesired occurrence that results from taking a medication correctly. The event can either be type A reaction or type B reaction. Type A reactions are predictable adverse events which are commonly dose-dependent and can be mild, moderate, or severe. Type B reactions are completely unpredictable and have nothing to do with doses. They occur less often and are influenced by patient-specific susceptibility factors such as drug allergies and intolerances. A patient may experience an adverse event due to the healthcare provider's lack of knowledge of the drug and the medications complete mechanism. The event is not expected by either the doctor or the patient and the effects can be reduced by lowering the dose or just stopping the medication all together [10]. Adverse immunostimulation refers to any antigen-nonspecific, inappropriate, or uncontrolled activation of some component of the immune system. Chronic inflammation can result from adverse immunostimulation and would be considered as exaggerated pharmacodynamic activity.

A side effect is an undesired effect that occurs when the medication is administered regardless of the dose. Unlike adverse events, side effects are mostly foreseen by the physician, and the patient is told to be aware of the effects that could happen while on the therapy. Side effects differ from adverse events and later resolve on their own with time after taking the medication for several weeks. Some medications are even utilized due to their side effects, one example being mirtazapine used in anorexic patients due to the medication potential to cause weight gain. Side effects are tracked and investigated extensively during clinical trials before entering the market [10]. Side effects may express only when a drug is mixed with certain other things. This might be called a drug interaction . For example, drinking alcohol while you are taking narcotic painkillers can cause an accidental overdose. Some drugs can't help but trigger side effects because of their chemical structure. The common allergy drug diphenhydramine is an example. Some drugs have barely noticeable side effects at the right dose. Typically, warfarin used to prevent blood clots, but serious internal bleeding can happen in the wrong situation [11].

d. Teratogenic effect

In reproductive toxicity, it consist of the administration of the test substance to pregnant animals during the period that the internal organs of the fetus are forming, and determine what damage to the birth of the fetus is caused by the test substance, in particular the teratogenicity of the test substance.

Teratogens are harmful substances from the environment, or also some drugs, which can endanger normal embryonic development during the first trimester of gravidity and thus cause congenital development defects [12]. Teratogens are substances that cause harm to the fetus or embryo during pregnancy, causing birth defects while the mother shows no signs

of toxicity. Common teratogens include ethanol, lead compounds, phenol, carbon disulfide, toluene and xylene. According to [12], others examples of teratogens substances are PCBs (polychlorinated biphenyls), heavy metals (methylmercury), ethanol, cytostatic drugs, some antibiotics, warfarin, marijuana, pervitin, many components of cigarette smoke. Drugs taken by the mother can pass on transplacentally route or via breast milk and can adversely affect the unborn or the neonate [9].

The reproductive performances are measurements intended to determine the effects of the drug agents on; mating behaviour, reproduction, parturition, progeny birth defects, and postnatal development [1].

e. Immunological effects

The immune system consists of a diverse and complex set of cells and organs that have complicated interactions with each other and with other physiological systems. These complexities make the detection and evaluation of drug-induced immunotoxicity in animal models difficult. Nonetheless, regulatory considerations for immunotoxicologic effects discovered during the development of a drug are no different than for other adverse effects [13].

The drug allergy (Hypersensitivity) is due to immune reactions related to the repetition of administrations. These reactions are related to the usual mechanisms of allergy. The clinical manifestations, more or less frequent according to the drugs, are similar to those of the banal allergy from the most benign to the most dramatic [7]. A pseudoallergic reaction can result from activation of inflammatory or anaphylactic mechanisms independent of antigen-specific immune responses [13]. Immunoallergic reactions require sensitization for several days or during an immediate or delayed dose. The re-administration of the drug causes a recurrence often more serious. Prediction almost impossible before preclinical trials, clinical trials [14]. Drug-induced autoimmunity and adverse reactions suggestive of drug-induced hypersensitivity are suspected in toxicology studies [13].

Concerning Drug immunogenicity, it refers to the ability of a drug to induce an immune response and is unpredictable for low molecular weight compounds which are immunogenic only if covalently bound to proteins to form hapten-protein complexes. There are two major concerns associated with drug immunogenicity: (1) drug allergenicity, and (2) the ability of antidrug immune responses to alter the biological activities of the drug (pharmacokinetics, pharmacodynamics, and/or toxicities) [13].

f. Mutagenic and carcinogenic effects

Mutagens are substances that change the genetic information of an organism, usually

by changing DNA. Mutagens are usually also carcinogens as mutations often cause cancer. Common mutagens include ethidium bromide, formaldehyde, dioxane, and nicotine. Mutagenicity studies look at the genetic stability and mutations of bacterial or mammalian cells in culture. These studies are at the academic research level and are intended to provide data for future research [1].

Carcinogenic substances can provoke irreversible changes of cellular DNA and malignant proliferation either directly or after biotransformation (indirect carcinogens – procarcinogens, e.g. polycyclic aromatic hydrocarbons,..) [12]. Carcinogenic substances are associated with causing or promoting cancer in humans and animals. Common carcinogens include benzene, vinyl chloride, formaldehyde, dioxane, and acrylamide. Carcinogenicity studies are required to determine the effects of prolonged usage of the drug under investigation. They involve hematological and histological autopsy analysis [1].

g. Abuse, Addiction and Dependence

Abuse is the Drug use without medical supervision and misuse is the wrong use of drug under medical supervision. In drug abuse, the drug is obtained illicitly and the prescribed drugs are used in dosages beyond that prescribed medically. Over the counter drugs used is beyond the amount recommended on the package. Drug abuse is associated with urban crime. Most heroine also abuse a variety of psychoactive substances, either in combination or in succession. Drug abuse is a complicated phenomenon which is related to interpersonal need, psychic and physical problems, and social adaptation [15]. Drug abuse usually involves a persistent and excessive, non-medical or non-prescription use of chemical substances. Those drugs that are abused in our society are those that produce mind or mood altering effects. Drugs may be misused rather than abused if they are taken occasionally but in an indiscriminate or inappropriate way [15]**.** Drug most likely to be misused if not compulsively abused are those that can alter mood or behavior in ways that satisfy the emotional needs of certain individual.

Addiction is the specific side or adverse effect of drugs caused by prolonged use. In the case of addiction WHO recommends the use of the term dependence, subdivided into psychological or physical. Further, such terms as “habit-forming” and “tolerance” should also be properly defined in advance of dealing with problems of drug use [15].

Addiction here shows that there is a compulsion to continue taking the drug whereas in habit is a mere desire to continue taking the drug. In addition, the harmful effect is to the individual and the society at large while in habit the harm is to the individual alone. This difference cannot be quantified in the sense that, what is considered to be addiction in one subject could be a mere habit in another. In some other cases in addiction, the individual could have both emotional and physical dependence. In habit the subject is confined to only emotional dependence [15]. Addictive Substances are a special group of substances harmful to human

health. They include narcotic (psychotropic) substances which very often cause addiction and influence the function of the central nervous system in such way that they suppress or stimulate its function**;** alcohol, drug of addiction, in which the individual becomes physically dependent on it and without it could become ill [12,15]. According to [12], Addiction is characterized by the presence of several of the following features: pronounced desire or urge to use the psychotropic substance, tolerance to increasing doses of a substance, withdrawal symptoms physical and mental, limited control of personal behavior, limitation or neglecting of other interests and hobbies and continuation in taking the substance even when its harmful effects are known

Drug dependence is a complex phenomenon involving social, personal and pharmacological factors. It is a state which arises from a repeated, periodic or continuous use or administration of drug. The individual feels a desire or a need or compulsion to continue taking the drug. It is at the same time a disease, a result of other diseases and a cause of criminal act. Fundamentally, it is an interaction of human being, their environment and a variety of drugs or chemical substances. The term drug abuse is difficult to define, since it is based on social and cultural norms. In our culture the use of nicotine is not considered to be an abuse but it is considered to be a deviation from the dogmas of certain religious sect. Alcohol is a socially accepted drug usage in our society, yet certain degree and pattern of alcohol ingestion considered to be deviant or abnormal [15]. There are several groups of drug of dependence: Opioids, cocaine, Amphetamine, and Ecstasy, Barbiturates, Nicotine, Alcohol, Hallucinogens, Caffeine etc… All drugs that produce dependency in individual are liable to cause tissue toxicity with excessive use. According to [15], dependence is characterized by the following phenomenon: Emotional or psychic dependence, Physical dependence and Tolerance.

5. Idiosyncratic Effects

Idiosyncratic effects are manifestations that occur only in subjects with a particularity, which are essentially genetic. In these particular subjects, they are usually dose-dependent effects. In medicine, it refers to the particular personal disposition, generally innate, to react to the action of external agents, physical or chemical [14]. In pharmacovigilance, it is the qualitatively abnormal (genetically determined) reaction of unknown mechanism, not related to a pharmacological action and which resembles to hypersensitivity, but does not imply an immunological mechanism [14].

Idiosyncratic drug reactions (IDRs) are unpredictable adverse drug reactions that do not occur in most patients but when they do occur they can be life-threatening. They are often called dose-independent but this is not true - nothing is dose independent - but what is true is that the incidence may not vary within the narrow range of doses that are used clinically and IDRs do not occur in most patients at any dose. IDRs also introduce a significant amount of

uncertainty into the process of drug development, because they are not predicted by animal testing and it is only after many patients have been treated that the extent of the problem can be determined, often leading to the withdrawal of an otherwise good drug.

a. Placebo Effect

A positive psychosocial context may induce the beneficial nonspecific effects of a treatment are called placebo [16]. A placebo is a dosage form devoid of an active ingredient, a dummy medication. Administration of a placebo may elicit the desired effect (relief of symptoms) or undesired effects that reflect a change in the patient's psychological situation brought about by the therapeutic setting [9]. Physicians may consciously or unconsciously communicate to the patient whether or not they are concerned about the patient's problem, or are certain about the diagnosis and about the value of prescribed therapeutic measures. In the case of a physician who projects personal warmth, competence, and confidence, the patient in turn feels comfort and less anxiety and optimistically anticipates recovery. The physical condition determines the psychic disposition and vice versa. Consider gravely wounded combatants in war, oblivious to their injuries while fighting to survive, only to experience severe pain in the safety of the field hospital; or the patient with a peptic ulcer caused by emotional stress**.** One-third of therapeutic success in moderately severe depression can be attributed to a placebo effect [9]. The placebo effect is the result of positive expectations. For example, Endogenous opioids secretion in the brain is the main event in placebo pain modulation [16].

B. Nocebo Effects

Nocebo effects are a result of the complex interactions between the patient, his surrounding general psychosocial context, the healthcare provider, and the way the information is delivered and received [2]. They are related to drug intake and not to the nature or pharmacodynamic effects of the drug. They are psychic and not biological. Individual and random, concerning few or all patients, nocebo effects are probably the most common adverse effects or events that produced by negative expectations. They remain in good standing, but very often disrupt treatment observance [7,16]. Nocebo effects can be observed not only in everyday clinical practice, but also in clinical trials. They can modulate the outcome of a given therapy in a negative way, as to placebo effects in a positive way. The way in which adverse events are presented affects not only risk perception, but, more importantly, also clinical outcomes [16]. These nonspecific side effects distress patients, add to the burden of their illness, and increase the costs of their care. The nocebo effect was considered as the nonspecific negative symptoms occurring in clinical trials with both placebo and the active drug. Nocebo seems to be stronger in women than in men. Nocebo responses are common and can produce discontinuation of trial participation, alteration of treatment schedules, and lack of adherence [16]. The nocebo effect is the result of negative expectations. For example, according to [17], the nocebo response to

an expectation of hyperalgesia showed signal increases in brain regions including bilateral dorsal anterior cingulate cortex (ACC), insula, superior temporal gyrus; left frontal and parietal operculum, medial frontal gyrus, orbital prefrontal cortex, superior parietal lobule, and hippocampus; right claustrum/putamen, lateral prefrontal gyrus, and middle temporal gyrus.

6. Iatrogenic Effects

The term "iatrogenic" is commonly used to characterize the adverse consequences of medical treatment, particularly the deleterious effects of a drug prescribed by a physician. Iatros in Greek means "doctor", and gene means "who bring about". Strictly speaking, this term is poorly constructed; it would be better to speak of "iatropathogeny", a disorder caused by medical intervention; or "iatrous disorder", in relation with the doctor [18].

Drug iatrogenic means the adverse effects caused by drugs. It brings together very different symptoms from simple fatigue to digestive hemorrhage or hip fracture. Medication has become commonplace today and these risks are too often underestimated. However, iatrogenic risks are avoidable in the majority of cases. This is for example an interaction between the different medications that you are taking or an error in taking your medicine: bad schedule, double dose, etc.

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