Saudi Pharmaceutical Journal (2017) **25**, 165–175

King Saud University

Saudi Pharmaceutical Journal

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REVIEW

An overview of pharmacodynamic modelling, ligand-binding approach and its application in clinical practice

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Received 3 February 2016; accepted 1 July 2016
Available online 9 July 2016

KEYWORDS

Pharmacodynamics;
Pharmacodynamic model;
Ligand binding;
E_{max} model;
Competitive binding;
Receptor;
Fractional occupancy

Abstract The study of the magnitude and variation of drug response is defined as pharmacodynamics (PDs). PD models examine plasma concentration and effect relationship. It can predict the archetypal effect (E) of a drug as a function of the drug concentration (C) and estimate an unknown PD parameter (θ_{pd}). The PD models have been described as fixed, linear, log-linear, E_{max}, sigmoid E_{max}, and indirect PD response. Ligand binding model is an example of a PD model that works on the underpinning PD principle of a drug, eliciting its pharmacological effect at the receptor site. The pharmacological effect is produced by the drug binding to the receptor to either activate or antagonise the receptor. Ligand binding models describe a system of interacting components, i.e. the interaction of one or more ligands with one or more binding sites. The E_{max} model is the central method that provides an empirical justification for the concentration/dose-effect relationship. However, for ligand binding models justification is provided by theory of receptor occupancy. In essence, for ligand binding models, the term *fractional occupancy* is best used to describe the fraction of receptors occupied at a particular ligand concentration. It is stated that the *fractional occupancy = occupied binding sites/total binding sites*, which means the effect of a drug should depend on the fraction of receptors that are occupied. In the future, network-based systems pharmacology models using ligand binding principles could be an effective way of understanding drug-related adverse effects. This will facilitate and strengthen the development of rational drug therapy in clinical practice.
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Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.jsps.2016.07.002
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1. Introduction to pharmacodynamic modelling aspects

1.1. Pharmacodynamics

The study of the magnitude and variation of drug response is defined as pharmacodynamics (PDs). To be explicit, it is the study of the drug which reaches the systemic circulation after the onset of administration, its intensity, and duration of action or response or effect, which are related to the drug concentration at its receptor site of action (Rosenbaum, 2011). The relationship between concentration and effect is usually non-linear, i.e. double the concentration does not result in a twofold increase in effect but, it will increase the duration of effect by one half-life. PD encompasses use of quantitative tools to measure affinity and efficacy of drugs. Clinical pharmacology can be divided into pharmacokinetics (PK), PDs and its integration as pharmacokinetic-pharmacodynamic (PKPD) models combine the time course of drug concentration with binding of drug to the target site(s) and subsequent drug effects. The PKPD relationship is presented in Fig. 1. PKPD models are therefore useful to describe, understand, and predict the extent and time course of drug effects. It follows that the greater the endeavour to incorporate mechanistic behaviour into the PKPD model the greater its ability to predict new situations.

1.2. Receptors, ligands, binding

Receptors can be defined simply as specific macromolecules at which a ligand binds and alters the biochemical activity (note that a ligand may do this by inhibiting the effects of endogenous substances from stimulating the receptor). Any macromolecular tissue site where a drug may bind can be considered a *binding site* and if this site has some functional activity then it is a *receptor*. Drug response is a result of chemical interactions between a drug and a binding site. The classification of drug receptors is based on tissue location, specificity of the drug, and the primary amino acid sequence. Majority (95%) of the total receptors are protein in nature. Not all proteins in the plasma membrane are receptors, some serves as transporters, enzymes or ion channels.

A drug can interact with four principle protein targets such as ion channels (nimodipine and voltage-gated Ca^{2+} ion channels), enzymes (neostigmine and acetylcholinesterase), membrane carriers (tricyclic antidepressants and catecholamine uptake-1) and receptors (Lambert, 2004). A drug binds and activates a receptor causing an alteration to a number of intracellular messengers/proteins (effectors). Generally, drugs are considered to bind to receptors and any chemicals that bind to receptors are usually termed *ligands* (e.g. drugs). A ligand is usually considered to be smaller in size than the receptor;

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