Clinical pharmacology — the basics

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Abstract

Clinical pharmacology is the study of pharmacodynamics and pharmacokinetics in humans. The relationship between dose, concentration and pharmacodynamic response may be explored using biomarkers for both desired and undesired effects of drugs. The action of drugs is due to receptor affinity, efficacy and the concentration of drug at the site of action. Factors affecting the drug concentration include bioavailability, determined by absorption and pre-systemic metabolism, distribution, clearance and elimination. Drug interactions may occur due to pharmacodynamic and pharmacokinetic factors, many of the latter being attributable to changes in drug metabolism and transport. The pharmacology of biologics is substantially different from that of small chemical molecules. As well as contributing to our understanding of established treatments, clinical pharmacology plays a critical role in the development of new medicines. Some pharmacological approaches to targeted therapies for cancer are briefly discussed.

Keywords Absorption; affinity; bioavailability; biomarkers; cancer; clinical pharmacology; disposition; drug interactions; efficacy pharmacodynamics; pharmacogenomics; pharmacokinetics; potency; receptors; targeted therapies; transporters

Introduction

What is clinical pharmacology?

Clinical pharmacology (CP) is a very broad subject involving a variety of disciplines and is conducted in clinical, academic and pharmaceutical industry settings. A drug may be well established and useful as a CP tool with which to investigate normal or pathological processes. Alternatively, CP studies may be designed to investigate the properties of the drug itself, often with the aim of assessing its potential for development as a new medicine or for a new indication. Perhaps it is helpful to conceptualise the determinants of drug activity as comprising two components: the properties of the drug, by which it exerts its action on the body, *pharmacodynamics* (PD), and the systems by which the body affects the fate of a drug after its administration, *pharmacokinetics* (PK). In this article we shall discuss some of the principles underlying PD and PK and how they apply to the use of well-established therapeutic drugs and to the evaluation of potential new medicines.

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Pharmacodynamics

Drug targets and mechanism of action

Most medicines that have become available in the past few decades are the result of rational design; that is, a target has been identified, molecules synthesized with the intention of hitting that target and the structure—activity relationship has been elucidated. Eventually, a lead compound with the appropriate properties has been identified for development. Many of these drugs are small chemicals of molecular weight typically in the range of 300—600 Daltons; others are biologicals such as monoclonal antibodies. Table 1 shows examples of rationally designed small molecule *antagonists*, which block the action of agonists at specific receptors.

Receptor *agonists* also play an important role in our therapeutic armamentarium. Thus morphine produces analgesia by its agonist activity at mu and delta opioid receptors; salbutamol and salmeterol are respectively short- and long-acting bronchodilators acting as agonists at $beta_2$ adrenoreceptors. Full agonists produce a maximal response while *partial agonists* bind to the receptor and elicit a response but their efficacy is less than that of *full agonists* (e.g. buprenorphine at the mu opioid receptor).

Some agonists exhibit 'negative efficacy'; that is they produce an effect that is opposite to that of a normal agonist; therefore, they are called *inverse agonists*. The sedative effect of benzodiazepines such as diazepam is due to agonism at the gamma-amino butyric acid $(GABA)_A$ receptor while an inverse agonist acting at the $GABA_A$ receptor is associated with an anxiogenic effect. Inverse agonism is the result of binding and stabilization of receptors that are constitutively active, thereby reducing their basal level of activity. Inverse agonists are distinct from antagonists, which have no activity of their own. Some drugs that were originally classed as antagonists are now understood to be acting as inverse agonists (e.g. propranolol at beta adrenoreceptors and chlorphenamine at H1 receptors). The activation of receptors in response to full, partial and inverse agonists is illustrated in Figure 1.

Many of the targets for drug agonists and antagonists are G-protein coupled receptors situated in the cell membrane. These include serotonergic (5-HT), muscarinic cholinergic, dopaminergic, adrenergic, opioid, and purinergic receptors. Receptors for some drugs are located in the cell nucleus with a DNA-binding domain for the action of hormones such as corticosteroids, thyroxine and cholecalciferol (vitamin D3) and enzymes involved in DNA synthesis, targeted by some cytotoxic agents. Other drugs act by inhibition of enzyme activity; Table 2 shows some examples.

Drugs may also act on transporter molecules, such as those for reuptake of noradrenaline and 5-HT, targeted by tricyclic antidepressants. Finally, some drugs do not act on discrete receptors in the membrane or nucleus or at the active site of enzymes; instead they affect ion channels. Table 3 provides some examples.

Affinity, efficacy and potency

Underpinning the assessment of PD responses is the basic principle of a drug binding to a target which triggers a series of cellular events. These, in turn, result in a measurable response. The *affinity* of a drug is a measure of its ability to bind to a

Examples of receptor antagonists

Receptor	Drugs	Target antagonist effect	Indication
Histamine 2	Cimetidine, ranitidine	Histamine-induced gastric acid secretion	Peptic ulceration
β1, β2 and α-adrenoceptors	Carvedilol, bucindolol	Noradrenaline effects on heart and blood vessels	Hypertension, angina, arrhythmias, secondary prevention of myocardial infarction, heart failure
Angiotensin1	Candesartan, losartan	Angiotensin-II induced vasoconstriction and Na^+/H^+ exchange in proximal renal tubule	Hypertension, left ventricular dysfunction
Muscarinic cholinergic	Tiotropium, aclidinium	Acetylcholine-induced bronchoconstriction	Relief of airways obstruction in chronic obstructive pulmonary disease
Nicotinic cholinergic	Atracurium, rocuronium	Acetylcholine at skeletal neuro-muscular junction	Skeletal muscle relaxation with general anaesthesia
$5\text{-}HT_3$	Granisetron, ondansetron	5-hydroxytryptamine (serotonin) actions in CNS and GI tract	Chemotherapy-induced and post-operative nausea and vomiting

Table 1

Dose–response curves

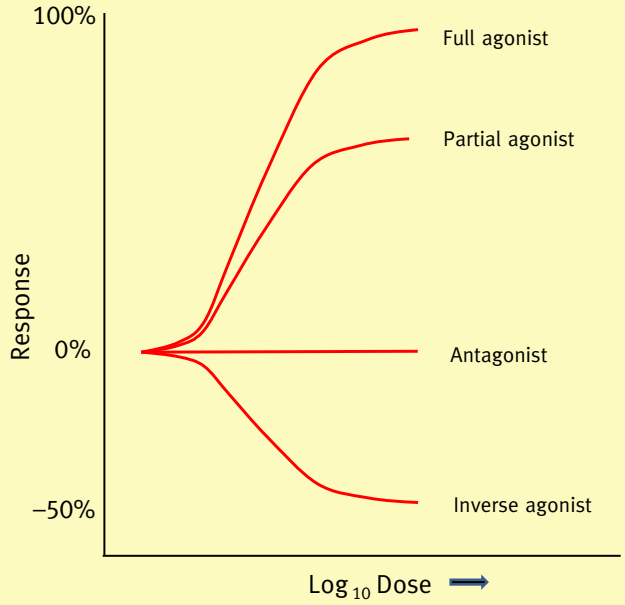

Figure 1

particular receptor. This can be quantified by binding and displacement of radioactive ligands to cloned receptors in vitro. The relative specificity or selectivity of a drug for certain receptors can thereby be characterized.

However, affinity does not tell us about function. *Efficacy* is the ability of a drug to elicit a response, once bound to its target and in terms of the dose-response curve it defines the maximum response. This can be studied in vitro and in vivo in animals and humans.

Efficacy should not be confused with *potency*, which refers to the amount of drug required to produce a response of a certain magnitude. Thus, the ED_{50} is the *dose* at which 50% of the maximal effect is produced and the EC_{50} and IC_{50} are the *concentrations* producing 50% of maximum effect or inhibition respectively. It is often impossible to quantify these parameters in humans, as the maximum effect would not be well tolerated or is simply unattainable. However, based on data points obtained over a range of concentrations, the maximum effect and the nature of the relationship between PK and PD can often be simulated using computer modelling. Of course, while the IC_{50} may be highly relevant as a guide to target concentrations for many pharmacological agents, we usually need to know the IC_{90} of anti-infective agents to achieve a satisfactory antimicrobial and likewise for neuromuscular blocking agents to produce skeletal muscle paralysis during surgical anaesthesia.

Biomarkers and surrogates for assessment of dose–concentration–response

What matters to patients treated with medicines is the clinical outcome but such outcomes may be difficult to measure and dependent on treatment over a prolonged period. We need to be able to predict outcomes and, when necessary, alter our treatment on the basis of *biomarkers* which serve as reliable *surrogates* for *clinical endpoints*. A biomarker is defined as 'a characteristic that is measured and evaluated as an indicator of normal biological or pathological processes or pharmacological responses to a therapeutic intervention'. Thus biomarkers may be prognostic and/or predictive. A *prognostic biomarker* provides information on outcome irrespective of therapy, whereas a *predictive biomarker* provides information on response to a therapeutic intervention. For example, blood pressure serves as a prognostic biomarker for adverse cardiovascular events. A breast cancer which overexpresses receptors to the epidermal growth factor ErbB2 has a worse than average prognosis without treatment. However, overexpression of ErbB2 also provides us with a predictive biomarker of response to treatments which target this receptor.

Biomarkers are used in CP to explore the relationships between dose, concentration and response to a drug. They may be mechanistic (e.g. the activity of an enzyme, hormone or gene) or functional (e.g. cognition, blood flow, spirometry). Caution must always be exercised in the interpretation of data and biomarkers