Chapter 7
Dose Response Relationship

Choo Hock Tan

Abstract Drugs act either by receptor or non-receptor-mediated mechanism. A receptor is usually a macromolecule of a cell with which an endogenous substance or a drug interacts (through specific recognition of binding domain) and elicits its effect (through transduction of signal into response). The intensity of response generally increases with plasma drug concentrations (reflected by doses administered), yielding a sigmoidal curve when the response is plotted against logarithmic values of drug concentrations or doses. The linear slope indicates the range of doses in direct proportion to the intensity of response, while the maximum indicates that receptors are fully occupied by the drug, and doses given close to and more than this response point can potentially cause overdose toxicity. A drug that is able to elicit a maximal response of a receptor is called a full agonist, while the response elicited by a partial agonist is submaximal. In the presence of a partial agonist, the effect of a full agonist can be reduced and the condition may precipitate a withdrawal syndrome for drugs like narcotic opiates. A drug that blocks the action of an agonist is called an antagonist; increasing the agonist concentration may overcome the blockade caused by a competitive antagonist (i.e. regaining the maximal response), but not that caused by a non-competitive antagonist (the response achieved is always below the maximum). Understanding of the relationship between drug dose and response as well as the effect of agonist and antagonist is important for dosing optimization. Dose-dependent adverse effect can be avoided with finely tailored drug dosages for patients, especially those with impaired organ function. Therapeutic index serves as an indicator to estimate the safety margin of a drug over a range of dose.

Keywords Drug-receptor interaction • Log dose-response curve • Full agonist • Partial agonist • Competitive antagonist • Non-competitive antagonist • Median effective dose (ED_{50}) • Median toxic dose (TD_{50}) • Therapeutic index • Therapeutic drug monitoring

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Introduction

When a drug is administered, the desired response of the drug is what most providers will aim for whilst trying to avoid the undesirable or toxic responses. For most drugs, the toxic response comes with a higher dose of the drug. Knowing the relationship between the dose and response will help a provider refine his dosing for the patient so that he consistently keeps the patient in the desirable response range.

Whilst there is no standard patient, most patients when given the usual recommended dose will respond appropriately, almost similarly to trial patients during the drug testing stage. Dose response relationship studied in populations of patients especially to look either at desirable response or undesirable response is an all or none phenomenon but offers useful information about appropriate dose to administer.

Mechanism of Drug Action

A drug is defined as a chemical when applied to a physiological system; it affects the function of the system in a specific way. Most drugs act by associating with specific 'target' macromolecules in the body to produce their effects – either a desired one (therapeutic), or an adverse one (toxic). Generally, drug receptors are classified into four major types: receptor, ion channel, enzymes, transport protein/carrier molecule. The majority of drugs act on receptors, and their actions are mediated through receptor-effector linkages, differentiated based on several distinct characteristics (Table 7.1). The ligand-gated ion channel is known to produce the fastest response (within milliseconds).

Table 7.1 The four main types of proteins as drug targets and their characteristics

	Ligand-gated ion channel	G-protein-coupled receptors	Receptor kinase	Nuclear receptors
Location	Membrane	Membrane	Membrane	Intracellular
Coupling	Direct	G-protein	Direct	Through DNA
Effector	Ion channel (resulting in membrane hyperpolarization or depolarization)	Enzyme (adenylate cyclase, phospholipase C) or channel	Protein kinases	Gene transcription
Time scale to response	Milliseconds	Seconds	Hours	Hours
Example	Nicotinic cholinoceptor $GABA_A$ receptor	Muscarinic cholinoceptor Adrenergic receptor	Growth hormone, insulin, cytokines	Steroid receptor

Note: G-protein-coupled receptors are also called metabotropic receptors

The basic concept of drug-receptor (receptor is used loosely to mean the binding target) interaction can be described by the lock-and-key model, where the structure of drug molecule influences the binding to a receptor. The affinity (the tendency of binding) of a drug for a receptor is determined by the fitting and the number of bonds formed between them. In general, the more fitted the "key and lock" feature and the number of bonds formed, the stronger the attractive forces and the binding between them. Drug-receptor binding as such is needed for drug action that produces a stimulatory or inhibitory effect as the drug response.

A few drugs act by physicochemical mechanism without the involvement of receptor. These include drugs like desferrioxamine (a chelating agent) in heavy metal poisoning, aluminium hydroxide (an antacid) to neutralize gastric acid, and mannitol (an osmotic diuretic) in treating cerebral edema.

Relationship Between Drug Response and Drug Concentration

The effect of a drug is dependent on the concentration of the drug at the target site (receptor), where drug-receptor binding is in equilibrium. The drug concentrations, in turn, depend on pharmacokinetic and dosing factors. Generally, the intensity of response increases with drug concentrations. The response can be plotted against drug concentration, yielding a hyperbolic curve that illustrates a sharp increment in effect that diminishes toward a plateau (maximal effect) while drug concentration increases (Fig. 7.1). Using this plot, unfortunately, we would not be able to visualize and appreciate the range of doses over which a linear relationship between dose and response is generated. When doses (x-axis) are converted from arithmetic to logarithmic scale, the plotted log dose–response curve will change to a sigmoidal curve where the important linear slope (25–75 % of the maximum) becomes visible for further characterization (Fig. 7.1). Therapeutic concentrations usually range along the linear portion of the curve; doses lower than the range (near threshold dose) can be sub-therapeutic, while toxic effects are likely to occur with higher doses (near the maximal effect).

Drug–Receptor Interaction: Agonism and Antagonism

Agonist

This refers to a drug that binds to a receptor eliciting its response. If the response elicited is maximal, the drug is said to be a full agonist with intrinsic efficacy of 1. A partial agonist is one that elicits submaximal response and possesses intrinsic efficacy between 0-1. An example of a full agonist for μ-receptor is the narcotic morphine, which antinociceptive and euphoric effect (referred to as maximum) can only be achieved at a lesser degree by buprenorphine, a partial agonist. The interaction of the two opioids is described in the clinical correlation.

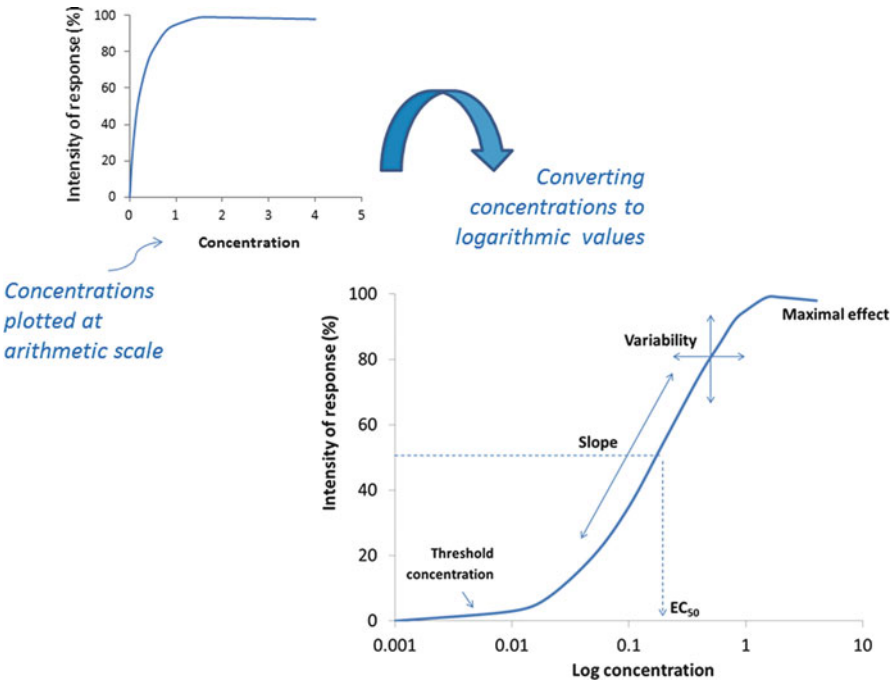

Fig. 7.1 This is a representative log concentration-effect curve, illustrating its four characteristic variables. The effect is measured as a function of increasing drug concentration surrounding the target receptor inferred from plasma drug concentration. Note that the data plotted in arithmetic scale produces a hyperbolic curve instead. *EC_{50} = effective dose at half maximal response, as an indicator of potency especially useful when comparing different agonists for the same receptor*. Similar relationship can be plotted as the function of the dose of drug administered, and referred to as dose-response curve, assuming that the doses administered and plasma drug concentrations remain in equilibrium

Clinical correlation – Effect of a partial agonist on a full agonist

Buprenorphine dose-response curve is usually submaximal compared to morphine when used as an antinociceptive agent in acute severe pain. It is an opioid drug with similar affinities to both μ- and κ- receptors, possesses intermediate efficacy at the μ-receptor (partial agonism), but antagonizes the activity of κ-receptors. The clinical significance of buprenorphine as a partial opioid agonist is explained essentially by its submaximal effect on μ-receptor: it can be used as a potent analgesic with a lower risk of abuse, addiction, and side effects compared to a full opioid agonist like morphine; in addition at low doses it is also a treatment for opioid addiction without causing significant withdrawal symptoms. However, being a partial agonist, it can (especially at high doses) provoke a withdrawal in those physically dependent, who has just taken their usual "high doses" of heroin or morphine – a classical illustration of a normally useful partial agonist that has turned offensive by antagonizing the effect of a full agonist, bringing on the withdrawal syndrome.

A less typical agonist type called 'inverse agonist' is one that binds to a receptor but dose-dependently suppresses the constitutive activity (basal level of activity without any ligand present) of the receptor. An example is metoprolol, though widely known as a β-adrenergic antagonist, is in fact also an inverse agonist at the adrenergic receptor, reducing the sympathetic activity of the heart for the optimization of heart failure management.

Antagonist

An antagonist is a drug that binds a receptor and prevents its activation by agonist (resulting in a flat response). The effect of drug antagonism can be achieved via:

(i) **Competitive antagonism**: antagonist and agonist compete for receptor binding site. Competitive agonist lacks intrinsic efficacy (0) but retains affinity for receptor's binding site. This produces a characteristic concentration-dependent parallel shift to the right of the dose–response curve without altering the maximal response. Clinically, the anticipated response at a given dose of agonist drug will not occur. However, the response can be regained once the agonist concentration is increased (i.e. reversible block) [Fig. 7.2]. A competitive agonist with beneficial use in acute care of opiate overdose is exemplified by naloxone in the following clinical correlation.

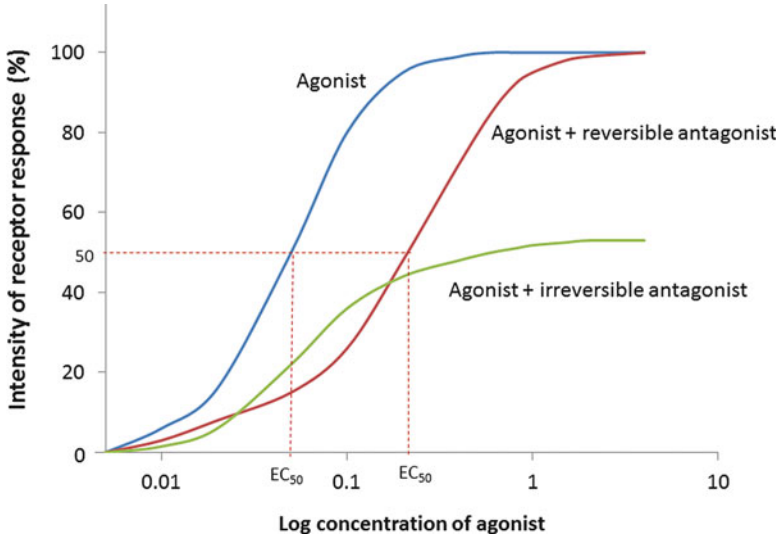

Fig. 7.2 Comparison of the effects of reversible (competitive) and irreversible (non-competitive) antagonists on the response induced by an agonist

Clinical Correlation – Effect of Naloxone in Drug Addicts

Naloxone binds with high affinity to μ-opioid receptors in the central nervous system and rapidly blocks the action of opioid narcotics on the receptors, hence reversing the respiratory depression. Administering this drug to drug addicts however can precipitate a withdrawal syndrome rapidly, more potent than that caused by the partial agonist buprenorphine. The reduction in the μ-receptor-mediated effect sustained by morphine essentially causes the withdrawal syndrome in these patients.

(ii) **Non-competitive antagonism**: In the presence of a non-competitive antagonist, an agonist fails to elicit maximal response despite increasing concentrations. Two mechanisms have been described: (a) pseudo-irreversible block: the affinity of antagonist is so strong that it binds very tightly via covalent bond to the receptor. Its slow dissociation from the target site prevents the agonist from binding to the receptor; (b) true irreversible block: the antagonist binds to a receptor site (allosteric site) different from that targeted by agonist, resulting in a conformational change in receptor that renders it unfavorable for agonist binding. On the concentration-time curve, the agonistic response is achieved below maximum even when its concentration increases (Fig. 7.2).

Relationship Between Drug Response and Drug Doses in the Population

Most adverse effects can be viewed as an extension of a drug's pharmacological action, secondary to accumulation or overdose of a drug in the body exceeding the maximal tolerable concentration. Dose-dependent toxic drug effects are usually studied in a population during drug trials as a quantal drug response (the drug effect either occurs, or it does not). Quantal dose-response curves are useful to estimate doses to which most of the population responds – both therapeutic and toxic responses to a drug [Fig. 7.3]. In the instance of the opioid drugs, the dose range between the median analgesic dose and median respiratory depressant dose is a 'safety margin' which indicates the likelihood that the toxic effect will occur – generally, the wider the margin, the safer a drug is. Most forgiving among the opioid analgesics is probably remifentanil, which offers a therapeutic index of 33,000:1, while morphine has an index of 70:1 (still considered safe). Drugs such as digoxin and phenytoin have very narrow therapeutic indices of approximately 2:1, mandating close monitoring of therapeutic and toxic effects, either by clinical assessment or investigation (plasma drug monitoring).

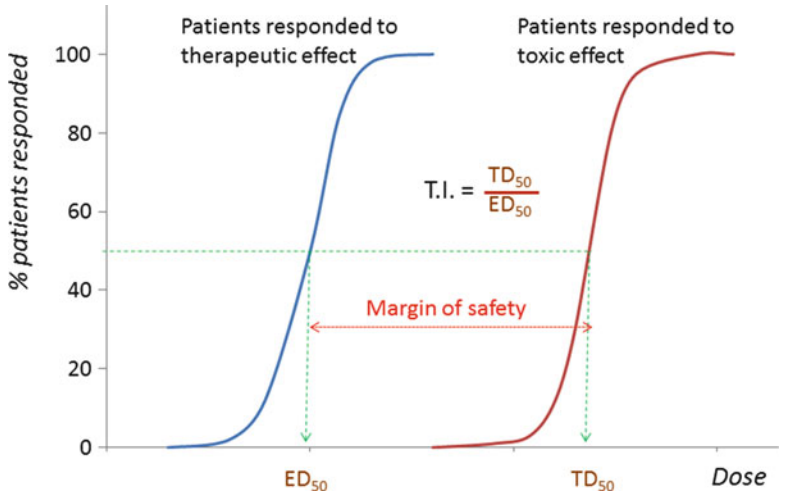

Fig. 7.3 A log dose-response curve depicting the percentage of patients responding to the therapeutic effect and the toxic effect of a drug. Drug toxicity develops at higher doses, indicating it as an extension of pharmacological action of the drug on the body. ED_{50} = median effective dose; TD_{50} = median toxic dose; TI = therapeutic index

Clinical Correlation – Therapeutic Drug Monitoring

One of the criteria in necessitating therapeutic drug monitoring of a drug is the safety profile of the drug. The safety profile can be determined by the therapeutic index (TI) of the drug; essentially, the lower the TI, the more toxic a drug can be. Drugs that require therapeutic monitoring to balance its therapeutic effect with minimal toxicity include theophylline (cardiac and neurological toxicity), gentamycin and vancomycin (renal and ototoxicity). Therapeutic drug monitoring depends greatly on the pharmacokinetic profile and hence sampling time is of utmost importance to provide accurate information for valid interpretation. It can also be applied in acute acetaminophen poisoning, where the plasma level of acetaminophen interpreted with the time course of ingestion indicates the need to initiate antidote (acetylcysteine) treatment.

Key Concepts

- Drug response is usually elicited by drug-receptor interaction.
- Administration of a partial agonist or antagonist essentially reduces the maximal response sustained by a full agonist, and can cause withdrawal symptoms.
- Doses should be tailored and fine-tuned to keep within the therapeutic range especially for drugs with a narrow therapeutic window.

- Monitoring and dose adjustment is particularly important in the critically ill patient with impaired organ functions because the pharmacokinetics and pharmacodynamics of drugs are altered even if the drug concentration is in the normal therapeutic ranges.

Summary

The majority of drugs act through binding of receptors. The presence of agonists or antagonists can alter the dose (concentration)-response relationship. Adverse or toxic drug effects often occur with high doses of a drug, manifested as an extension of the pharmacological action of the drug. The ratio between median effective dose (ED_{50}) and median toxic dose (TD_{50}) indicates the margin of safety of a drug, and is useful as an indicator of the relative safety profile of different drugs. Close monitoring of response to guide adjustment of dosages is especially important in those who are acutely ill as their pharmacokinetic and pharmacodynamic profiles are altered.

Further Reading

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