General Principles of Pharmacology

HOW DO DRUGS ACT?

Drugs produce their effects on biological systems by several mechanisms; these include physicochemical action, activity at receptors and inhibition of reactions mediated by enzymes. Physicochemical Properties Sodium citrate is anlkali and neutralizes acid; it is often administered orally to reduce the likelihood of pneumonitis after regurgitation of gastric contents. Chelating agents (chel Is the Greek word for a crab's claw) combine chemically with metal ions, reducing their toxicity and enhancing elimination, usually in the urine.Such drugs include desferrioxamine (chelates iron and aluminium),dicobalt edetate (cyanide toxicity), sodium calcium edetate (lead) and penicillamine (copper And lead).

Stored blood contains a citrate-based anticoagulant which prevents clotting; this chelates calcium ions and may cause hypocalcaemia after massive blood transfusion.

Action On Receptors

A receptor is a complex structure on the cell membrane which can bind selectively with endogenous compounds or drugs, resulting in changes within the cell which modify its function.

These include changes in selective ion channel permeability (e.g. acetylcholine, glutamate, GABA receptors), cyclic adenosine monophosphate (e.g. opioid, β, α2 and dopamine receptors),

The classic dose–response relationship of an agonist the concentration of the agonist increases,a maximum effect is reached as the receptors in the system become saturated

Antagonists combine selectively with the receptor but produce no effect. They may interact with the receptor in a competitive (reversible) or non-competitive (irreversible)

antagonist, the dose–response but the maximum effect remains unaltered . Examples of this effect include the displacement of morphine by naloxone and endogenous catecholamines by β-blockers

A non-competitive (irreversible) with increasing concentrations , reduces the maximum effect For example, the α1 antagonist phenoxybenzamine, used in the preoperative preparation of patients with phaeochromocytoma, has a long duration of action

Action On Enzymes

Drugs May act by inhibiting the action of an enzyme or competing for its endogenous substrate. Reversible inhibition is the mechanism of action of edrophonium (acetylcholinesterase), aminophylline (phosphodiesterase) and captopril (angiotensin-converting enzyme).

Irreversible enzyme inhibition occurs when a stable chemical bond is formed between drug and enzyme, resulting in prolonged or permanent inactivity e.g. omeprazole (gastric hydrogen-potassium ATPase), aspirin (cyclo-oxygenase) and organophosphorus compounds (acetylcholinesterase). However, the interaction between drug and enzyme may Be more complex than this simple classification implies. For example, neostigmine inhibits acetylcholinesterase in a reversible manner,

THE BLOOD–BRAIN BARRIER AND PLACENTA

Many drugs used in anaesthetic practice must cross the blood–brain barrier in order to reach their site of action. The brain is protected from most potentially toxic agents by tightly overlapping endothelial cells which surround the capillaries and interfere with passive diffusion.

In addition, enzyme systems are present in the endothelium which break down many potential toxins. Consequently, only relatively small, highly lipid-soluble molecules (e.g. Intravenous and volatile anaesthetic agents, opioids, local anaesthetics) have access to the central nervous system (CNS). Compared with most opioids, morphine takes some time to reach its site of action because it has a relatively low lipid solubility. Highly ionized drugs (e.g. muscle relaxants, glycopyrronium) do not cross the blood–brain barrie

The transfer of drugs across the placenta is of considerable importance in obstetric anaesthesia . In general, all drugs which affect the CNS cross the

placenta and affect the fetus. Highly ionized drugs (e.g. Muscle relaxants) pass across less readily

PLASMA PROTEIN BINDING

Many drugs are bound to proteins in the plasma. This is important because only the unbound portion of the drug is available for diffusion to its site of action. Changes in protein binding may have significant effects on the active unbound concentration of a drug, and therefore its actions.

Albumin is the most important protein in this regard and is responsible mainly for the binding of acidic and neutral drugs. Globulins, especially α1-glycoprotein, bind mainly basic drugs. If a drug is highly protein bound (> 80%) , any change in plasma protein concentration or displacement of the drug by another with similar binding properties may have clinically significant effects. For example, most NSAIDs displace warfarin, phenytoin and lithium from plasma binding sites, leading to potential toxicity.

METABOLISM

Most drugs are lipid-soluble and many are metabolized in the liver into more ionized compounds which are inactive pharmacologically and excreted by the kidneys. However, metabolites may be active .The liver is not the only site of metabolism. For example, succinylcholine are metabolized by plasma cholinesterase, esmolol by erythrocyte esterases, remifentanil by tissue esterases and, in part, dopamine by the kidney .

A substance is termed a prodrug if it is inactive in the form in which it is administered, pharmacological effects being dependent on the formation of active metabolites. Examples of this are codeine (morphine), diamorphine

Drugs under go two types of reactions during metabolism: phase I and phase II. Phase I reactions include reduction, oxidation and hydrolysis .

Drug oxidation occurs in the smooth endoplasmic reticulum

Phase II reactions involve conjugation of a metabolite or the drug itself with an endogenous substrate. Conjugation but others include acetylation, methylation and conjugation

Enzyme Induction And Inhibition

Some drugs may enhance the activity of enzymes responsible for drug metabolism, . Such drugs include phenytoin, carbamazepine, phenylbutazone, barbiturates, ethanol, steroids and some inhalational anaesthetic agents (halothane,enflurane). Cigarette smoking A lso induces cytochrome P450 enzymes. Drugs with mechanisms of action other than on enzymes may also interfere significantly with enzyme systems. For example, etomidate inhibits the synthesis of cortisol and aldosterone – effect which may explain the increased mortality in critically ill patients which occurred when it was used as a sedative in intensive care. Cimetidine is a potent enzyme inhibitor and may prolong the elimination of drugs such as diazepam, propranolol, oral anticoagulants, phenytoin and lidocaine.

DRUG EXCRETION

Ionized Compounds with a low molecular weight (MW) are excreted mainly by the kidneys. Most drugs and metabolites diffuse passively into the proximal renal tubules by the process of glomerular filtration, but some are secreted actively (e.g. penicillins, aspirin, many diuretics, morphine, lidocaine and glucuronides) Ionization is a significant barrier to reabsorption at the distal tubule. Consequently, basic drugs or metabolites are excreted more efficiently in acid urine and acidic compounds in alkaline urine. Some drugs and metabolites, particularly those with larger molecules (MW > 400 D), are excreted in the bile (e.g. glycopyrronium, vecuronium, pancuronium and the metabolites of morphine and buprenorphine). Ventilation is responsible for excretion of volatile anaesthetic agents.

PHARMACOKINETIC PRINCIPLES

Pharmacokinetics is the study of what happens to drugs after they have been administered . In contrast, pharmacodynamics is concerned with their effects on biological systems. An understanding of the basic principles of pharmacokinetics is an important aid to the safe use of drugs in anaesthesia, pain management and intensive care medicine. Pharmacokinetics is an attempt to fit observed changes in plasma concentration of drugs into mathematical equations which may then be used to predict concentrations under various circumstances. Derived values

describing volume of distribution (V), clearance (Cl) and half-life (t1/2) give an indication of the likely properties of a drug

Volume Of Distribution

Volume of distribution is a good example of pharmacokinetics; volume but merely a concept which helps us to understand what we observe. Nevertheless, it is a very useful notion which enables us to predict certain properties of a drug and also calculate other pharmacokinetic values. Imagine that a patient receiving an intravenous dose of an anaesthetic induction agent is a bucket of water and that the drug is distributed evenly through out the water immediately after injection. The volume of water represents the initial volume of distribution (V). It may be calculated easily Drugs which remain in the plasma and do not pass easily to other tissues have a small V and therefore a large C0. Relatively ionized drugs (e.g. Muscle relaxants) or drugs highly bound to plasma proteins (e.g. NSAIDs dehydrated, or have lost blood, have a significantly greater plasma C0 after a normal dose of intravenous induction agent, increasing the likelihood of severe side-effects, especially hypotension.

Neonates have a roportionally greater volume of extracellular fluid compared with adults,

Clearance

Clearance is defined as the volume of blood or plasma from which the drug is removed completely in unit time. Drugs may be eliminated from the blood by the liver, kidney or occasionally other routes The relative proportion of hepatic and renal clearance of a drug is important. Most drugs used in anaesthetic practice are cleared predominantly by the liver

Elimination Half-Life

Methods of administration of a drug are influenced considerably by its plasma t1/2, as this often reflects duration of action. It is important to remember that t1/2 is influenced not only by clearance (Cl) but also by V:

Half-life often reflects duration of action but not if the drug acts irreversibly (e.g. some NSAIDs, omeprazole, phenoxybenzamine) or if active metabolites are formed

Two-Compartment Models

The body is not, of course, a single homogeneous compartment; drug plasma concentrations are the result of elimination by metabolism and redistribution to and from tissues such as brain, heart, liver, muscles and fat . The mathematics describing this real situation are extremely complex. However,plasma concentrations of many drugs behave approximately as if they were distributed in two or three compartments. Applying these mathematical models is a reasonable compromise

METHODS OF DRUG ADMINISTRATION

1- Oral 2- Lingual And Buccal 3- Intramuscular

4- Subcutaneous 5- Intravenous 6- Rectal 7- Transdermal

8- Inhalation 9- Epidural 10- Spinal(Subarachnoid)

Thank you