

Mechanisms of drug interactions: pharmacodynamics and pharmacokinetics

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Abstract

The classification of drug interactions is first considered in this article, with an explanation of the terminology. Emphasis is placed on the importance of the topic in relation to the polypharmacy employed in anaesthesia and critical care. Pharmacodynamic interactions are then discussed. Further classification of these interactions is explained using examples of drugs in everyday use in anaesthesia and critical care medicine. Non-specific pharmacodynamic interactions are considered at some length, being the largest group of drug interactions that occur in anaesthesia. Synergy and summation are extremely relevant to anaesthetic practice and are employed in both induction and maintenance of anaesthesia everyday. The article then explains pharmacokinetic interactions under the headings of absorption, distribution, metabolism and elimination. Again, emphasis is placed on drugs used in current practice to highlight the relevance of each type of interaction to the reader.

Keywords Pharmaceutical incompatibility; pharmacodynamic interaction; pharmacokinetic interaction; summation; synergy

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Relevance and classification of drug interactions

A drug interaction occurs when the spheres of activity of two drugs overlap, so the action of one drug will affect the behaviour of another. All physicians involved in drug prescribing should be aware of the potential for drug interaction, but particularly those involved in anaesthesia and critical care where there is a greater potential for drug interaction due to polypharmacy. A patient may receive 9 or 10 drugs as part of their anaesthetic regimen. In addition, the drugs we utilize have responses that include depression of the central nervous system and inhibition of the protective reflexes. This makes potential drug interactions hazardous if they are not anticipated. It must be remembered, however, that we employ drug interaction every day for advantageous purposes. During induction of anaesthesia and in the sedation of critical care patients, we are using drug synergy to

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Learning objectives

After reading this article, you should be able to:

- classify drug interactions
- explain the difference between pharmacodynamic and pharmacokinetic drug interactions
- give examples of pharmacodynamic and pharmacokinetic drug interactions, naming drugs commonly used in anaesthetic and intensive care practice

reduce the dosage of drugs required and hence minimize unwanted side effects.

Drug interactions are usually considered in terms of three broad classes of underlying mechanisms: pharmacodynamic, pharmacokinetic and pharmaceutical incompatibility. Pharmacodynamics describes the relationship between drug concentration and drug response. Pharmacokinetics describes the relationship between the rates of change of drug concentrations in the different parts of the body. Pharmacodynamic interactions occur between drugs with similar or opposite pharmacological effects. The underlying mechanisms include competition at molecular or cellular sites of action. The effects are generally common to related drugs. Pharmacokinetic interactions occur when one drug alters the absorption, distribution, metabolism or excretion of the other drug. This type of response varies between patients without any particular drug pattern and can be difficult to predict. The third class consists of pharmaceutical interactions relating to chemical or physical incompatibility between the drug preparations being used, calcium chloride and sodium bicarbonate preparations being an example of such an interaction (Box 1).

Pharmacodynamic interactions

Pharmacodynamic interactions can be classified into three main areas: interactions that occur at a single receptor site; those occurring at a variety of receptor sites; and the general non-specific interactions mediated through unspecified sites of action. The variety of actual and potential drug interactions in terms of pharmacodynamics is limitless.

Receptor site interactions

Many drugs exert their effects by interacting with specific receptors located on cell membranes, or within the cytoplasm or

Classification of drug interactions

Pharmacodynamic interactions

- Interaction at or near site of action

Pharmacokinetic interactions

- Interaction altering absorption
- Interaction altering distribution
- Interaction altering metabolism
- Interaction altering excretion

Pharmaceutical incompatibility

Box 1

nucleus. Drugs with affinity for specific receptors, both agonists and antagonists, will inevitably interact when administered concurrently.

There are several examples of such drug interactions employed in clinical practice that are of benefit to the patient. The reversal of unwanted opioid-induced side effects by naloxone is one such example. The competitive antagonism of benzodiazepines by flumazenil would be another. These may be referred to as direct drug interactions. Potential disadvantageous interactions involving receptor sites also exist. Consider the formation of a neurotransmitter agent, its release, movement across the synaptic cleft, binding and activation of a receptor, and its dissociation and elimination. Interaction may occur at any of these stages. Certain drugs will alter the effect of catecholamines at the adrenergic receptor. Phentolamine, a competitive α antagonist, will increase the quantity of catecholamine required by the receptor to bring about a maximal effect. Phenoxybenzamine, a non-competitive antagonist, will reduce the maximal effect achievable, regardless of the amount of drug given. The reuptake of dissociated catecholamine at the adrenergic receptor is prevented by cocaine and tricyclic antidepressants. The breakdown of noradrenaline and adrenaline is prevented by monoamine oxidase inhibitors (MAOIs). MAOIs in combination with indirect sympathomimetic agents can lead to dangerous hypertension. (Figure 1)

An illustration of interaction at different receptor sites, which is used in everyday anaesthetic practice, is the administration of neuromuscular blocking reversal agent. Neostigmine is a non-specific cholinesterase inhibitor, which binds to acetylcholinesterase and stabilizes the complex. Acetylcholine, therefore, can not reach the active site of the enzyme. Levels of acetylcholine increase throughout the body except behind the blood–brain barrier. However, muscarinic receptors are stimulated in addition to nicotinic receptors. This would lead to unwanted side effects if it were not for the concurrent administration of glycopyrrolate or atropine.

Non-specific interactions

The largest single group of interactions occurring in anaesthetic practice is non-specific.

Agents used for induction and maintenance of anaesthesia display interactive properties. Synergy is said to occur when the combined action of two drugs is greater than would be expected from a purely additive effect, as is seen with co-induction using thiopentone and midazolam. Although not a traditional anaesthetic agent, midazolam can significantly reduce the dose of thiopentone required to bring about anaesthesia, increasing its potency twofold in some studies. Although both drugs involve the γ -aminobutyric acid (GABA) complex, they have different receptor binding sites. One suggestion for the synergy displayed is the barbiturate potentiation of benzodiazepine receptor binding.

In contrast to synergy, nitrous oxide and the volatile agents show summation. Fifty per cent of the nitrous oxide minimum alveolar concentration (MAC) plus 50% of a second anaesthetic agent MAC, is approximately equal in anaesthetizing effect to that of 100% MAC of either agent alone. This additive effect displayed by the inhalational agents is not strictly considered a drug interaction, because an interaction is a response that leads to a result different from the effects of the two agents given separately. The difference may be qualitative or quantitative.

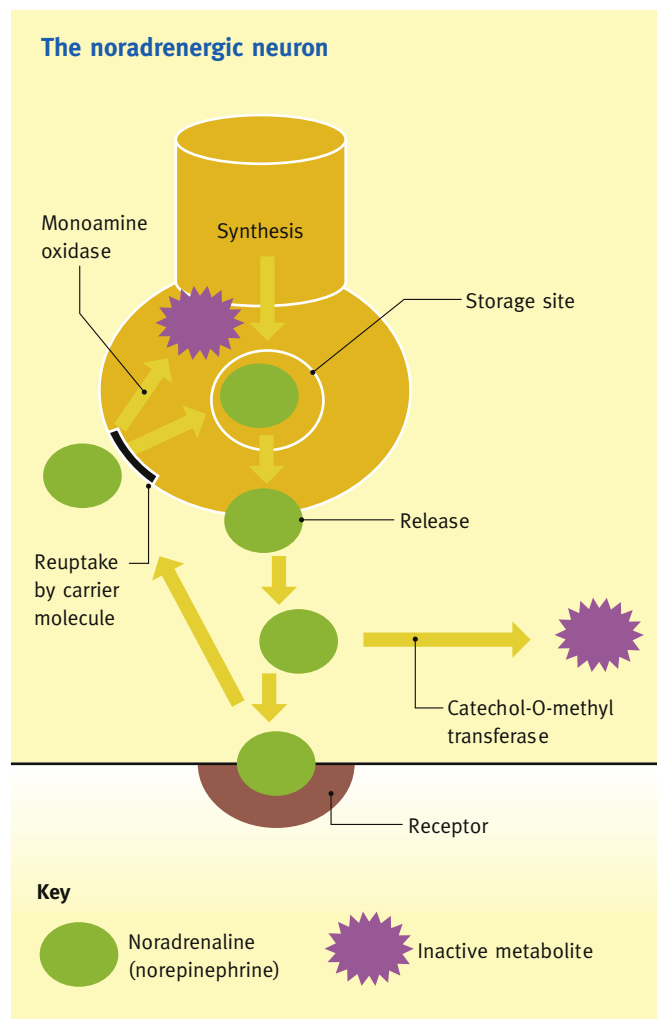


Figure 1

Volatile agents interact with many other substances when one takes into consideration their side effect profile. Cardiovascular effects caused by depression of cardiac and smooth muscle contractility are of concern in patients taking medication for hypertension or ischaemic heart disease. Calcium channel antagonists, angiotensin-converting enzyme inhibitors and β -blockers interact with volatile agents. The same applies to intravenous agents that cause cardiac depression.

Interactions may be mediated by alterations in electrolyte balance. Many drugs alter the electrolyte concentration in the body. Some, in addition, alter intravascular volume. The pharmacological effects of other agents may then be modified by the electrolyte status of the individual (Box 2). Hypokalaemia is relatively common and easily treated. It tends to increase cardiac excitability and reduce the threshold for arrhythmias. This potentiates interaction with any drugs that increase arrhythmia susceptibility, including catecholamines and anticholinergics. Hyperkalaemia tends to reduce cardiac automaticity. Hyperkalaemia may achieve dangerous levels if suxamethonium is administered to a patient whose potassium is already raised due to renal impairment or inappropriate medication. Hyponatraemia is often associated with a depleted volume status, and may potentiate local anaesthetics. Magnesium has effects on both neuromuscular transmission and

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