BJA

British Journal of Anaesthesia, 118 (1): 44–57 (2017)

doi: 10.1093/bja/aew312
Review Article

Pharmacokinetic and pharmacodynamic interactions in anaesthesia. A review of current knowledge and how it can be used to optimize anaesthetic drug administration

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Abstract

This review describes the basics of pharmacokinetic and pharmacodynamic drug interactions and methodological points of particular interest when designing drug interaction studies. It also provides an overview of the available literature concerning interactions, with emphasis on graphic representation of interactions using isoboles and response surface models. It gives examples on how to transform this knowledge into clinically and educationally applicable (bedside) tools.

Key words: anesthetics; drug interactions; pharmacology

Drug interactions can be described as the pharmacological influence of one drug on another drug (Fig. 1), when administered in combination.[1,2] Anaesthetists routinely combine drugs such as opioids and hypnotics in clinical practice. However, dosing is often based on building experience throughout years of training and local habits. It remains a challenge to teach clinicians how to combine these drugs in order to reach and maintain optimal anaesthetic conditions while minimizing side-effects such as haemodynamic alterations or prolonged recovery times. It has to be clear that not all drug combinations lead to similar and adequate anaesthetic conditions. A good understanding and knowledge of drug interactions may improve the ability to titrate multiple drugs more effectively.[3]

Although physicians are typically more interested in controlling the time course of drug effect than in controlling plasma concentrations, research on anaesthetic drug interactions is often also focused on pharmacokinetics and pharmacodynamics. Pharmacodynamic drug interaction studies provide information about drug effect when two or more drugs are administered. This review provides an overview of the available literature concerning interactions, with emphasis on graphic representation of interactions using isoboles and response surface models. It closes with an overview of newly developed computer software to apply this knowledge in clinical practice.

Pharmacokinetic drug interactions

Drug interactions can occur on a pharmacokinetic (PK) or a pharmacodynamic (PD) level, or both. Pharmacokinetic drug interactions will generally also result in an altered PD effect. As most drug administration in the daily clinical practice of anaesthesia is titrated toward a desired clinical effect, PK

Key points

- Safe and effective combinations of several agents are needed to provide optimal anaesthesia.
- It is important for anaesthetists to have a good understanding of pharmacokinetic and pharmacodynamic interactions.
- Isoboles and response surface models can be used to explore clinical effects of drug combinations.
- Drug administration software is being developed for training, simulation, and clinical use.

interactions are often not considered separately from PD interactions for application. Nevertheless, clinicians should understand the mechanisms of PK interactions to be able to appreciate fully the consequences of dosing schemes involving drug combinations. It becomes of importance when one drug affects another drug, in means of quantity or time course of absorption, the volume and rate of distribution, the elimination of another drug, or any of these particular in combination.

Absorption

Absorption is the process by which drug molecules cross biological membranes from the site of administration into the plasma. When anaesthetic drugs are administered i.v., absorption problems are largely bypassed. With the use of volatile anaesthetics, the absorption might be influenced by ventilation–perfusion ratios or membrane pathology, but also by ventilator settings, as this is mainly dependent on gradients between alveoli and pulmonary capillaries.

After anaesthesia with halothane and diazepam, peak plasma paracetamol concentrations of paracetamol administered 1 h after surgery were significantly delayed and decreased, compared with conditions without anaesthesia, as a result of delay in gastric emptying and therefore slower absorption.[4] Therefore, higher doses of orally administered drugs may be considered before anaesthesia to guarantee equivalent plasma concentrations.

Distribution

The volume of distribution is the apparent volume in which an administered dose would need to be dissolved in order to yield some particular plasma concentration. When a drug has a higher affinity for tissues other than plasma, the volume of distribution may be large and can even be much larger than the dimensions of the human body. This is the case for propofol, which is characterized by considerable redistribution to adipose tissue, resulting in a large volume of distribution of ~300 litres.[5 6]

Simultaneously administered drugs can affect the volume of distribution through several mechanisms. First, drugs may compete for binding sites on plasma proteins (e.g. on albumin and α1-acid glycoprotein), thereby potentially increasing the unbound fraction and resulting in a higher volume of distribution. The clinical relevance of this concept, however, appears to be overestimated in the current literature.[7–10] Second, drugs that decrease cardiac output may decrease the perfusion of tissues involved in redistribution of other drugs, thereby altering their volume of distribution.[11] A decrease in propofol requirements has been found in the presence of esmolol, probably as a result of distribution alterations.[12]

Elimination

Drugs can be eliminated by excretion (e.g. renal elimination of sugammadex and renal and biliary excretion of rocuronium),[13 14] biotransformation (e.g. hepatic metabolism of propofol),[15] or spontaneous degradation (e.g. Hofmann degradation of cisatracurium).[16] The elimination capacity of the body is quantified as clearance, which may be defined as the volume of plasma that is cleared of the active drug per unit time or as the rate of drug elimination divided by the plasma concentration.

Elimination of a drug is often influenced by the presence of other drugs.[17] Drugs that alter cardiac output also alter liver blood flow and may influence clearance as described in an animal model by Ludbrook and colleagues.[18] Generally, in a sheep model, cardiac output is found to be inversely related to arterial and brain propofol concentrations.[18] Lange and colleagues[19] first described how propofol decreases liver perfusion and thereby decreases its own elimination. In a more recent study, it was shown that a decreased cardiac output, induced by a remifentanil infusion, led to a higher propofol concentration as a result of decreased hepatic and renal blood flow.[11 18 20–23]

Hepatic clearance is a complex process, dependent on several families of enzymes responsible for drug metabolism. The cytochrome P450 (CYP450) family is responsible for metabolizing many anaesthetic drugs. Some drugs cause CYP450 enzyme induction, resulting in an accelerated breakdown of drugs metabolized by this enzyme. For example, activation of liver enzymes by anti-epileptic drugs leads to decreased plasma concentrations of fentanyl, methadone, pethidine, paracetamol, and some non-depolarizing neuromuscular blocking agents, such as pancuronium, rocuronium, and vecuronium.[24 25] Conversely, CYP450 enzyme inhibition leads to reduced breakdown of some drugs. An example of this is decreased *in vitro* enzymatic degradation of alfentanil and sufentanil in hepatic microsomes because of the presence of propofol.[26]

The clinical applicability of pharmacokinetic interaction studies

Research into PK interactions is relevant to promote safe practice and to investigate toxicity and side-effects. Technical software is available to warn physicians and pharmacists of potential unintended PK interactions,[27] but this is not commonly used in daily anaesthetic practice. Current attempts to measure individual plasma drug concentrations at the bedside of the patient are promising but still have significant limitations.[28–34] In order to obtain an idea of the time course of the plasma concentration, we are limited to pharmacokinetic predictions based at best on intermittent blood sample analysis or on estimations based on current knowledge of interactions. As a consequence, the effect of a drug on the plasma concentration of another drug is currently not directly known or quantifiable by the clinician. As anaesthetists are generally more focussed on control of the time course of the desired drug effect, rather than plasma concentrations, a mathematical description of the resultant combined effect of two drugs administered together may be of more clinical value than a detailed description of PK interactions in anaesthesia. Available tools and their development are described in the last section of this article.