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. 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.

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
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. 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.

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. Second, drugs that decrease cardiac output may decrease the perfusion of tissues involved in redistribution of other drugs, thereby altering their volume of distribution. A decrease in propofol requirements has been found in the presence of esmolol, probably as a result of distribution alterations.

**Elimination**

Drugs can be eliminated by excretion (e.g. renal elimination of sugammadex and renal and biliary excretion of rocuronium), biotransformation (e.g. hepatic metabolism of propofol), or spontaneous degradation (e.g. Hofmann degradation of cisatracurium). 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. Drugs that alter cardiac output also alter liver blood flow and may influence clearance as described in an animal model by Ludbrook and colleagues. Generally, in a sheep model, cardiac output is found to be inversely related to arterial and brain propofol concentrations. Lange and colleagues 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.

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.

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.

**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, 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. 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.

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**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.
Pharmacodynamic drug interactions

Pharmacodynamics describes the relationship between the drug concentration at its site of action, typically a receptor, and the corresponding effect of a drug. Administration of a combination of drugs may result in an alteration of this dose–response relationship. A clinically relevant example of such an interaction is given in Fig. 2. The assumption in PD interaction studies is that the underlying PK interaction inevitably leads to a subsequent alteration in clinical effect. By studying the clinical effect directly, the underlying PK interaction is handled as one of the covariates that cause variability in the model. Ideally, PK and PD interactions should be studied simultaneously in a selected population to capture as much information as possible on the mechanisms underlying the observed effect. Many designs for drug interaction studies have been developed in the past, thereby taking into account that anaesthetists are not only interested in knowing 50% of a specific maximal drug effect, but rather in the entire spectrum, and especially in the effect in the clinical range, usually occurring between 95 and 99% of the maximal drug effect. The criss-cross design appears to be the most efficient and effective way to study interactions.33 With this approach, a randomly selected group of participants receives a fixed concentration of Drug A and varying concentrations of Drug B, whereas in a second subset of participants a fixed target concentration of Drug B is applied while varying concentrations of Drug A are administered.36

Interaction studies reveal the nature of the PD interaction between two or more drugs. In general, three different types of interactions can occur: additivity, supra-additivity (i.e. synergism), and infra-additivity (i.e. antagonism), as shown in Fig. 3. Besides their direct clinical relevance, these models give an impression of the underlying PK pathways involved. Strict additivity implies that two drugs have a common site of action, whereas deviation from additivity implies different sites of action.2 The relationship between drug plasma (or target) concentrations and the resulting effect can be described using two types of figures: isoboles and response surface graphs (Fig. 4).39 Isoboles are two-dimensional graphs showing drug combinations throughout a clinical range that evoke some predefined effect (e.g. the 50% probability of tolerance to surgical incision). Response surface models are more complex but more informative.40 They predict the probability of clinical effect of the full clinical range of combinations of two drugs. This is often illustrated by a three-dimensional representation of the interaction throughout a spectrum of drug doses and drug effects. In this respect, a response surface model represents an infinite number of isoboles, representing numerous drug plasma concentration combinations.36 39

A number of different response surface models have been developed in the literature to handle different types of drug interaction mechanisms. This implies that it would be useful to determine which theoretical type fits the new data set the best. Heyse and colleagues41 compared the ability of four different response surface models to fit a single sevoflurane–remifentanil interaction data set and found that there was considerable difference between the response surface models in their ability to fit the observed data. For response surface models to be useful in daily clinical practice, two methodological aspects for the study design are of great importance: reproducible drug titration and clinically relevant drug end points (i.e. ‘effect’).

Reproducible drug titration

The effects observed after administration of drugs can only be clinically relevant if the methodology of dosing can be reproduced by others. For volatile agents this is not a major issue, because the end-tidal alveolar concentration of the volatile agent is routinely monitored and is a reasonable surrogate representation of the plasma concentration in the individual. Once the end-tidal concentration is maintained at a desired target for a sufficiently long time (so that steady-state conditions are reached), one can assume that the plasma and effect-site compartments are in equilibrium.42 43 Nevertheless, Frei and
A propofol bolus of 1.5 (A, C, and E) or 2.5 mg kg$^{-1}$ is given 2 min after the start of the remifentanil infusion. To maintain a probability of tolerance to laryngoscopy (PTOL) of 90% (pharmacodynamic end point), sevoflurane has to be started 1, 3, and 4 min after the smaller propofol bolus (A, C, and E, respectively) or 3.3, 4.5, and 5.6 min after the larger propofol bolus (B, D, and F, respectively). Note the pharmacodynamic interaction as the PTOL is maintained in steady-state remifentanil infusion during changing plasma concentrations of two different hypnotics (i.e. propofol and sevoflurane). Used with permission from Hannivoot and colleagues, previously published as a web supplement.45

For i.v. drug delivery, we lack this ability to continuously measure or accurately predict the plasma concentrations in the individual. In order to improve reproducible drug titration for i.v. drugs, a different approach of dosing guidelines was necessary.45–47 A fixed-infusion regimen based on volumetric infusion (in millilitres per hour or millilitres per kilogram per hour) may lead to a large difference in plasma concentration between individuals because of the inevitable biological variability in pharmacokinetics within the population.14 48 49 When compared with the fixed-infusion pumps, target-controlled infusion (TCI) pumps (i.e. with microprocessor-equipped syringe pumps driven by calculations obtained from PK models), are able to reach and maintain a steady-state plasma concentration more accurately in clinical practice and validation studies.48a 50–52 However, one of the inevitable limitations of all population PK models is the residual prediction error, which is the discrepancy between the (population-derived) prediction and the individual plasma (or effect-site) concentration. Experts have recommend that in terms of the Vanvel criteria, median absolute prediction error (MDAPE) should not exceed more than 20% for plasma concentration estimations for a TCI system to be useful in clinical application.53 54 Strategies such as Bayesian optimization are and will be studied to reduce population-based errors.55–57 However, Coppens and colleagues45 showed that the strength of certain models does not lie in predicting effects in the individual patient, but rather in the ability to maintain this effect once it is reached.
Commonly used PK models for anaesthesia drugs in clinical practice are the Schnider and Marsh model for propofol, the Minto model for remifentanil, and the Gepts model for suxamethonium. An example of the ongoing search for improvement of individual drug titration is the work of Eleveld and colleagues, who recently presented a generalized model for propofol, based on data from a large population with a wide range of demographic characteristics. This model was validated in obese patients and appeared to perform well in this group.

Prediction errors are also likely to exist in interaction models. In a recent study, Short and colleagues prospectively validated the Bouillon interaction model for propofol and remifentanil on bispectral index (BIS) and showed an overall performance as described by median prediction error (MDPE) of 8% (SD 24%) and bispectral index (BIS) and showed an overall performance as described by median prediction error (MDPE) of 8% (SD 24%) and median absolute prediction error (MDAPE) of 25% (SD 13%) of the individual patient. The (unwanted) side-effects of anesthetic agents, such as respiratory depression, have also been studied as end points.

Monitors that measure the neurophysiological changes evoked by anesthetics have been proposed as a surrogate indicator of hypnotic drug effect. They provide continuous information on the patient’s state, based on changes in cortical electrical activity. These measures allow quantification of a gradual change in individual patients, even in the situation when clinically detectable responses may have dissipated. Some of these indices are widely used in clinical practice, such as the BIS, spectral entropy, the index of consciousness, the patient state index, and the auditory evoked potential index. However, these methods lack the ability to evaluate the balance between noceception and antinociception. For this purpose, some new variables have been developed. qNOX (Quantum Medical, Barcelona, Spain) has been shown to be able to predict this balance in the presence of a noxious stimulus, but further research is required to confirm these findings. The composite variability index (CVI), which is derived from bispectral index variability and frontal EMG activity, appears to correlate with motor responses to shake and shout, according to a recent study by Sahinovic and colleagues. However, this index has been shown to be more dependent on the hypnotic than the analgesic drug component. The study also shows that heart rate and mean arterial pressure are poor predictors of movement on noxious stimulation. This stands in apparent contrast to the widespread routine clinical monitoring of these signals for the purposes of drug titration towards previously mentioned balance. In a more recent study, the authors combined antinociception parameters (i.e. cortical input and CVI) and hypnotic parameters (i.e. composite cortical state and BIS), showing a potency to predict responsiveness of patients to tetanic stimuli more accurately. As such, the search for the ideal predictor of responsiveness to noxious stimuli remains work in progress.

Clinically relevant end points

In theory, any drug effect can serve as an end point to explore the nature of drug interaction. However, if it is the intention to apply the findings in clinical practice then the chosen effect needs to be unambiguous and relevant for the clinical setting. Clinical end points of responsiveness to a stimulus are generally used to observe whether the patient is sufficiently anaesthetized. A variety of verbal, tactile, or noxious stimuli have been proposed as precipitants of a subsequent motor, haemodynamic, or EEG response. The first is more dichotomous (i.e. the patient responds or does not), whereas the latter two are continuous and allow observation of a gradual change over time within the individual patient. The (unwanted) side-effects of anaesthetic agents, such as respiratory depression, have also been studied as end points.

From minimal alveolar concentration to isoboles to response surface models

The first PD interaction studies in anaesthesia (MAC reduction) studies were mainly focused on inhaled anaesthetics in
combination with opioids, as a result of the direct availability of end-tidal concentration measurements which, at the steady state, are reasonably representative of plasma concentration. The MAC$_{50}$ (or EC$_{50}$) is defined as the minimal alveolar concentration required to prevent 50% of subjects from moving in response to a noxious stimulus.\textsuperscript{80} Later, the ability to standardize and predict plasma concentration arose, and it became possible to study interactions in patients receiving total i.v. anaesthesia (TIVA). As such, one may state that the isoboles as discussed earlier for TIVA are analogous to the family of MAC reduction curves for inhalation anaesthesia.

**Volatile anaesthetic–opioid interactions**

Volatile anaesthetics and opioids exhibit strong supra-additive interactions. Even small doses of opioids reduce the MAC of volatile anaesthetics.

Synergy between volatile anaesthetics and opioids is found for skin incision, for verbal response at emergence, and for haemodynamic response on skin incision. In the presence of fentanyl 0.5 ng ml\textsuperscript{−1}, the MAC$_{50}$ of desflurane (for skin incision) is reduced by 50%.\textsuperscript{81} For isoflurane, an equivalent MAC reduction has been shown with fentanyl 1.67 ng ml\textsuperscript{−1},\textsuperscript{42} alfentanil 28.8 ng ml\textsuperscript{−1},\textsuperscript{82} remifentanil 1.37 ng ml\textsuperscript{−1},\textsuperscript{24} and sufentanil 0.15 ng ml\textsuperscript{−1}.\textsuperscript{83} Likewise, the MAC of sevoflurane is reduced by 50% by a plasma concentration of fentanyl 1.8 ng ml\textsuperscript{−1},\textsuperscript{86} or remifentanil 1.69 ng ml\textsuperscript{−1} (with the latter reduction based on laryngoscopy as stimulus).\textsuperscript{41}

Response surface models are rarely available in the literature concerning volatile anaesthetic–opioid drug interactions. In the interaction between sevoflurane and alfentanil, a model developed for more continuous end points showed supra-additivity for heart rate and respiratory control, but independence of the BIS with respect to alfentanil concentration.\textsuperscript{87} The effect on BIS (and state entropy and response entropy) was confirmed for sevoflurane–remifentanil anaesthesia. Manyam and colleagues\textsuperscript{88} developed a model showing supra-additivity in preventing movement to pain with sevoflurane and remifentanil, which was later enhanced by using a physiological model for sevoflurane pharmacokinetics instead of end-tidal concentrations.\textsuperscript{89} Bi and colleagues\textsuperscript{90} presented a model of sevoflurane and remifentanil showing that the supra-additive effect on prevention of haemodynamic responses to laryngoscopy is stronger than for the occurrence of circulatory depression. Heyse and colleagues\textsuperscript{41} aimed to fit multiple interaction models to the data from a sevoflurane–remifentanil anaesthesia and multiple stimuli (verbal, tactile, and painful). They found that the hierarchical model of Bouillon and colleagues fit the data best.\textsuperscript{41} The addition of nitrous oxide showed an additive interaction.\textsuperscript{92} Finally, using MAC equipotency and opioid equivalencies, it has been shown that previous findings can be extrapolated to other volatile anaesthetic–opioid combinations.\textsuperscript{42} This is supported by a study revealing that 50% of the subjects undergoing fentanyl–isoflurane anaesthesia woke within 2 min of the time predicted by extrapolation from a sevoflurane–remifentanil model-predicted wake-up time, on the basis of equivalence.\textsuperscript{93} More recently, a study showed accurate predictions for wake-up time from a sevoflurane–remifentanil interaction model adapted to equipotent sufentanil–desflurane doses that were used.\textsuperscript{94}

**I.V. anaesthetic–opioid interactions**

The interaction between opioids and the i.v. anaesthetic agents is also supra-additive, although it is less strong for hypnotic end points such as sedation and unresponsiveness [loss of consciousness (LOC)] than for anaesthetic end points (such as response to noxious stimuli). However, characterizing this interaction is different because the volatile anaesthetics possess some analgesic effects (or at least attenuate movement responses to noxious stimuli via peripheral/spinal effects), whereas this has not been shown for the i.v. anaesthetic agents.

The 50 and 95% probability of LOC isoboles for fentanyl and propofol show a supra-additive interaction. However, the effect of fentanyl is limited, because the maximal reduction of 50% probability is reached at a fentanyl concentration of 3 ng ml\textsuperscript{−1}.\textsuperscript{95} The haemodynamic effects (heart rate and systolic blood pressure) of propofol and fentanyl responses to skin incision and peritoneal wall retraction have also been studied.\textsuperscript{96}

The interaction between propofol and sufentanil has been examined in a response surface model describing the probability of LOC, and shows a more additive interaction.\textsuperscript{97} The lesser influence of sufentanil on LOC was confirmed by a later study with fixed sufentanil concentrations whilst changing propofol to keep the BIS within a certain range.\textsuperscript{98} In contrast, sufentanil is able to suppress motor and haemodynamic responses to noxious stimuli.\textsuperscript{99} Indeed, a combination of propofol 1.2 μg ml\textsuperscript{−1} and sufentanil 0.456 ng ml\textsuperscript{−1} has been successfully used for conscious sedation during (very painful) burn wound dressing changes, without respiratory depression and with good doctor and patient satisfaction scores in 95% of patients.\textsuperscript{99}

Studies of the interaction between propofol and alfentanil on loss of response to eye lash reflex, laryngoscopy, and various surgical stimuli in patients undergoing elective surgery showed supra-additive interactions.\textsuperscript{100}–\textsuperscript{102} However, it has also been shown that alfentanil amplifies the depressant effect of propofol on blood pressure and does therefore not contribute to haemodynamic stability during induction.\textsuperscript{101} In an innovative study, Vuyk and colleagues\textsuperscript{102} used simulation of recovery times for various opioids to an isobole of 50% probability for return of consciousness. Midazolam and alfentanil tend to act supra-additively with regard to responses to verbal command.\textsuperscript{103}

The interaction between propofol and remifentanil has been studied extensively and is supra-additive for noxious stimuli and hypnotic end points. Shake and shout,\textsuperscript{104–106} laryngoscopy,\textsuperscript{104} intubation,\textsuperscript{107} intra-abdominal surgery,\textsuperscript{105} tibial pressure algometry,\textsuperscript{105} electrical tetany,\textsuperscript{105} recovery times,\textsuperscript{106} and postoperative pain responses\textsuperscript{106} have all been shown exhibit supra-additive interactions. For more continuous, EEG-derived parameters, the results for remifentanil are contradictory, showing no synergism (with propofol) for BIS in one study,\textsuperscript{108} additivity,\textsuperscript{104, 109} and supra-additivity in other studies.\textsuperscript{23} For propofol and remifentanil, Nieuwenhuijs and colleagues\textsuperscript{102} described a supra-additive interaction on cardiopulmonary control. More recently, a triple drug interaction (propofol, sevoflurane, and remifentanil) model was described by Hannivoort and colleagues\textsuperscript{35} for tolerance of laryngoscopy and its derivate, the newly developed noxious stimulation response index. In this triple drug interaction study, they described all drug combinations with regard to the probability of tolerance to laryngoscopy (PTOL). They showed an additive interaction between sevoflurane and propofol when titrated towards PTOL$_{50}$ doses. A synergic effect was found for remifentanil when combined with propofol and sevoflurane.\textsuperscript{35}

As a result of its ultra-short-acting pharmacokinetics and its PD profile, remifentanil is suitable for use for sedation, and this indication is becoming more frequently the responsibility of anaesthetists. Several studies have been performed to provide insight into the effects of propofol–remifentanil drug...
combinations on end points relevant to sedation, such as prevention of the gag reflex on oesophageal instrumentation.112 Higher propofol–lower remifentanil combinations have been found to obtain responses to oesophageal instrumentation while avoiding intolerable ventilatory depression.15 A simulation study of various commonly used propofol–remifentanil combinations for upper gastrointestinal endoscopy revealed that this combination is associated not only with better conditions for oesophageal instrumentation, but also with rapid return of responsiveness, compared with propofol-only regimens.113 Other investigators have produced models for the effect of different propofol–remifentanil combinations on the BIS and index of consciousness (IOC) during endoscopic procedures.114

Overall, after an era during which many studies modelled the blunting of responses to noxious stimuli, the search for strategies to optimize the balance between reaching the preferred effect, while taking into account the unwanted (side)-effects, continues. For this purpose, the ‘well-being’ model was designed for propofol–remifentanil, which describes not only the preferred effect, but also balances between negative and positive effects of drug combinations.67

Hypnotic–hypnotic interactions

In common daily practice, hypnotics are often combined, most frequently in the contexts of benzodiazepine premedication, drugs used for sedation, or the switch from bolus propofol administration for induction to volatile maintenance anaesthesia.

A few studies have addressed midazolam–propofol interactions, and these have shown varying results of supra-additivity115–117 or additivity.118 119 Remarkably, adding alfentanil to these two sedatives led to a weaker synergistic interaction than expected when compared with dual combinations.118 120 Most data were collected in a non-steady state and without accurate PK models; therefore, a high variability of effect-site concentration could have confounding effects. A standardized, well-performed interaction study at the steady state has not yet been performed. Although the nature of the interaction appears to be clear, a full quantification has not yet been revealed.

The combination of σ2-agonists, such as clonidine and dexmedetomidine, with other anaesthetics has been less well described. The addition of dexmedetomidine 0.66 μg ml⁻¹ using TCI reduces the EC50 for motor response to electrical stimulation of propofol from 6.63 to 3.89 μg ml⁻¹. However, the type of interaction could not be identified clearly because of methodological reasons.121 Another study showed that a loading infusion of dexmedetomidine 1 μg kg⁻¹ during 10 min, followed by a maintenance infusion dose of 0.5 μg kg⁻¹ h⁻¹, did not reduce the EC50 of propofol for responses to oesophagogastrroduodenoscopy in children.122 As for propofol and midazolam, well-performed interaction studies are still absent. Ideally, these studies should apply response surface models and newly developed PK/PD models, such as the three-compartmental dexmedetomidine model produced by Hannivoort and colleagues.123

For clonidine, a response surface model has been developed, showing that clonidine 5.0 μg kg⁻¹ given orally 90 min before arrival at the operating room reduces the propofol EC50 for response to verbal command ~65% from 2.67 to 0.91 μg ml⁻¹ and that the interaction appears to be additive.124 For laryngeal mask placement, oral clonidine premedication has been shown to reduce propofol requirements.125 Whether the nature of this interaction is comparable needs to be confirmed.

Simple additivity was found for the propofol–sevoflurane interaction on response to shake and shout, tetanic stimulus, laryngeal mask insertion, laryngoscopy,126 LOC, and movement in response to skin incision.127 The interaction on BIS, state entropy, and response entropy was also additive.126 128 When looking at the arousal response (i.e. the increase of BIS after a noxious stimulus), combining propofol with sevoflurane or desflurane does not seem to lead to a complete blunting of this response. However, in contrast to sevoflurane, desflurane seems partly to blunt this response.129 The additivity was confirmed in an in vitro study for stimulation of γ-aminobutyric acid receptors, suggesting a single receptor interaction.130

The clinical applicability of pharmacodynamic drug interaction models

Despite the more clinically oriented and applicable end points, PD studies still have one major clinical limitation, namely that it is impossible for the clinician to learn all the possible drug combinations and their accompanying pharmacodynamic results by heart. Nevertheless, well-performed application of pharmacology may lead to better patient care, and it appears also to be one of the most important parts.3 In order to serve as a handle for teaching and training, many computer-based tools or simulation programs have been developed,131 of which some will be discussed in the next section.3

Teaching drug interaction by applying simulated drug administration

Simulation of drug administration can help anaesthetists to improve the quality of anaesthetic care by assisting with selection of appropriate and optimal drug doses and combinations.132 The quality of simulations and didactic techniques has improved during recent years. Simulators vary from basic Excel worksheets to advanced, realistic, attractive (virtual) reality simulators.3 A distinction can be made in tools helpful for experimentation in a simulation setting, such as PKPD-Tools, TIVA-trainer, Gasman, RUGLOOP II, and virtual anaesthesia machine, with other types of (commercially available) tools that focus more on providing real-time information, such as SmartPilot® View and Navigator™ Application Suite, at the bedside. A brief overview of some available simulators and their options of applicability is given in Table 1.

Drug advisory displays are currently being commercialized as a new concept in anaesthetic drug administration and for facilitated education in anaesthetic pharmacology.65 Through direct measurement (e.g. for the volatile agents) or prediction of effect-site concentration (e.g. for propofol and opioids), the device tracks the anaesthetic drug doses that are administered to the patient throughout the procedure. The drug doses and predicted concentrations are used as input for a response surface model to predict the combined anaesthetic effect.66 Figure 5 shows two advisory screens that have been commercialized: the Navigator™ Application Suite (GE Healthcare, Helsinki, Finland), which reflects the effects (i.e. tolerance of intubation and shake and shout) in a time-based plot, whereas the SmartPilot® View (Dräger Medical, Lübeck, Germany) adds a two-dimensional graph with multiple isoboles and a measure of general anaesthetic potency called the noxious stimulation response index.133 The probabilities of tolerance of several stimuli are shown on screen either through isoboles (SmartPilot® View) in a two-dimensional graph or as an indicator of combined
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<td>Palma Healthcare Systems LLC, Madison, WI, USA</td>
<td><a href="http://www.palmahealthcare.com">www.palmahealthcare.com</a></td>
<td>Software for iPad, iPhone, and iPOD</td>
<td>Educational tool used for understanding and seeing pharmacokinetics, pharmacodynamics, and interactions of commonly used anaesthetic drugs</td>
</tr>
<tr>
<td>Gasman</td>
<td>Med Man Simulations(^\text{R})</td>
<td><a href="http://www.gasmanweb.com">www.gasmanweb.com</a></td>
<td>PC-based software</td>
<td>Educational simulation tool to teach pharmacokinetics and economics Visual PK models, pill dosage/compliance simulations, anaesthesia machine simulation with inhaled anaesthetics, and more</td>
</tr>
<tr>
<td>Virtual Anesthesia Monitor</td>
<td>University of Florida, USA</td>
<td><a href="http://www.vam.anest.ufl.edu">www.vam.anest.ufl.edu</a></td>
<td>PC-based software</td>
<td></td>
</tr>
<tr>
<td>RUGLOOP II</td>
<td>Ghent University and Demed Medical, Ghent, Belgium</td>
<td><a href="http://www.demed.be">www.demed.be</a></td>
<td>PC-based software</td>
<td>Visualization of PK and PD models, online PK/PD monitoring, TCI, closed loop</td>
</tr>
<tr>
<td>Navigator\textsuperscript\texttrademark Application Suite</td>
<td>GE Healthcare, Helsinki, Finland</td>
<td><a href="http://www3.gehealthcare.co.uk/">http://www3.gehealthcare.co.uk/</a></td>
<td>Stand-alone device, coupled with used syringe pumps (either TCI or volumetric)</td>
<td>Bedside-applicable tool intended to apply the available knowledge of PD drug interaction into a clinical guidance tool for drug delivery</td>
</tr>
<tr>
<td>SmartPilot\textsuperscript\texttrademark View</td>
<td>Dräger Medical, Lübeck, Germany</td>
<td><a href="http://www.draeger.com">www.draeger.com</a></td>
<td>Stand-alone device, coupled with used syringe pumps (either TCI or volumetric)</td>
<td>Bedside-applicable tool intended to apply the available knowledge of PD drug interaction into a clinical guidance tool for drug delivery</td>
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Fig 5 The top panel shows SmartPilot® View (Dräger, Lubeck, Germany). This specific screenshot shows anaesthesia based on sevoflurane, propofol, remifentanil, and pancuronium. The graph on the left provides retro- and prospective information about the drug interaction between hypnotic and analgesic drugs. It provides predictive information regarding the following minutes from ‘now’. This screen introduces the noxious stimulation response index (NSRI; right) as a new parameter. It also provides past and predictive information of BIS over time. (Printed with permission, ©Dräger Medical GmbH, Lübeck, Germany). The bottom panel shows the Navigator™ Application Suite (GE Healthcare, Helsinki, Finland). This display provides a diagram and modelling tool for common volatile and i.v. anaesthetic drugs (in this example, propofol, sevoflurane, remifentanil, and rocuronium). It calculates effect-site concentrations and displays these in a time-based graphical format. The total effect line (black line) shows the combined effect of the analgesic and sedative drugs. The display calculates the models for up to 1h into the future. (Printed with permission, ©General Electric Company, Helsinki, Finland).
effect vs time (Navigator™ Application Suite). Despite their common objectives, the predictions of the devices are slightly different because of the use of different interaction models and the fact that they are based on data from separate interaction studies, i.e. the Navigator™ Application Suite uses the Minto model \(^{134} \) to predict propofol–opioid interaction and the Greco model \(^{135} \) for inhaled anaesthetic–opioid interaction, whereas the SmartPilot™ View uses the hierarchical model of Bouillon and colleagues \(^{104} \) for both i.v. and inhaled anaesthesia administration. SmartPilot™ View also allows a continuous estimation of effect during the transition from i.v. to inhaled anaesthetics and vice versa. Whether these drug displays are beneficial in daily clinical practice and to what end points has not yet been revealed. A recent small non-randomized controlled study by Cirillo and colleagues \(^{136} \) showed that there might be benefits in the use of these displays, as it appeared that the consumption of volatile anaesthetics was lower in the groups where anaesthetic drug displays were used.

In conclusion, knowledge of pharmacokinetic and pharmacodynamic drug interactions in anaesthesia can contribute to the optimization of anaesthetic drug administration. Drug interaction studies aim to rationalize combined drug dosing by quantifying the nature of interaction between opioids, hypnotics, and volatile agents. Reproducible drug titration and unambiguous end points are essential in such studies for them to be clinically applicable. Validation studies of many interaction models are still required. Although many of these drug interaction studies have been performed, the information is not accessible and applicable at the bedside without computer assistance. Advisory screens and computer-based training tools can teach physicians and help them to apply this knowledge in clinical anaesthetic practice.

**Authors’ contributions**

Attest to the integrity of the original data, helped to write the manuscript, and approved the final manuscript: J.P.B., H.E.M.V., J.H.P., D.J.E., J.K.G.W., A.R.A., M.M.R.F.S.

**Declaration of interest**

J.P.B has no conflict of interest to declare. H.E.M.V.’s research group has received grants and funding from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Drager (Lübeck, Germany), Acacia Design (Maastricht, The Netherlands) and Medtronic (Dublin, Ireland). J.H.P. has no conflict of interest to declare. D.J.E. has no conflict of interest to declare. J.K.G.W. has no conflicts of interest to declare. A.R.A. is an editor of the British Journal of Anaesthesia and a senior editor of Anesthesia & Analgesia.

**Funding**

The department of Anesthesiology, University of Groningen, University Medical Center Groningen, The Netherlands received funding from Drager Medical (Lübeck, Germany) in the past for some of the research described in this review.

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Handling editor: Lesley Colvin