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The role of pharmacokinetics and pharmacodynamics in clinical anaesthesia practice

Laura N. Hannivoort^a, Anthony R. Absalom^a, and Michel M.R.F. Struys^{a,b}

Purpose of review

Growing concerns about the environmental effects of volatile anaesthetics are likely to lead to increased use of intravenous anaesthetic drugs. Pharmacokinetic/pharmacodynamic (PKPD) models can increase the accuracy of intravenous drug titration, especially in populations that differ from the 'average.' However, with a growing number of PKPD models, and other technology available to date, it can be hard to see the wood for the trees. This review attempts to guide the reader through the PKPD jungle.

Recent findings

General purpose PKPD models for propofol and remifentanyl designed to apply to a broader population, including children, the elderly and the obese, reduce the need for population-specific models. PKPD models for drugs such as dexmedetomidine and antimicrobial agents may be useful for procedural sedation or in the ICU. Technological advances such as Bayesian model adjustment based on point-of-care plasma concentration measurements, closed-loop drug delivery and artificial intelligence may improve the ease of use of the anaesthetic drugs and increase the accuracy of titration.

Summary

Newer and more complex modelling techniques and technological advancements can help to deliver anaesthetic drugs, sedatives and other drugs in a more stable and thereby safer way.

Keywords

Bayesian model adjustment, closed loop, machine learning, target-controlled infusion

INTRODUCTION

Total intravenous anaesthesia (TIVA) is a widely accepted general anaesthetic technique. Intravenous anaesthetic drug administration relies heavily on pharmacokinetic and dynamic research in an attempt to further optimize drug titration. Pharmacokinetic and pharmacokinetic–pharmacodynamic (PKPD) models have been developed for several intravenous hypnotic and analgesic drugs. These models can be used to improve the accuracy of TIVA delivery when implemented in target-controlled infusion (TCI) technology, to target desired plasma or effect-site concentrations. Additionally, advisory systems depicting the time course of predicted concentrations and interactions have been commercialized. Nonetheless, many hospitals still rely heavily on the use of volatile anaesthetics, and TIVA is still often delivered through manual boluses and fixed-rate infusion schemes, without the application of more advanced pharmacological knowledge.

However, things may be changing rapidly. In many countries, there is a growing awareness of the environmental effects of volatile anaesthetics.

Nitrous oxide is ozone depleting; nitrous oxide and halogenated volatile anaesthetics (desflurane in particular) are very potent greenhouse gasses [1,2]. As these concerns may shift the balance toward TIVA and TCI, now appears to be a good time to review what is known about pharmacokinetic, PKPD and TCI.

In this article, recent advances in PKPD modelling will be discussed. Also, other techniques such as Bayesian PKPD model adjustment, closed-loop

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KEY POINTS

- PKPD models suitable for use in a broader range of patients, including children, the elderly and the obese, reduce the need for multiple models for a single drug in PKPD-assisted drug delivery.
- Models for other sedatives such as dexmedetomidine, and for antimicrobial drugs such as cefepime or vancomycin, can help provide PKPD-assisted drug delivery in the ICU.
- Bayesian model adjustment based on point-of-care concentration measurements and closed-loop drug delivery based on measurements of clinical effect can help individualize anaesthetic drug titration.
- Artificial intelligence in the form of machine learning may make these technologies obsolete in the future, being able to predict effect and guide drug dosing without advanced pharmacologic knowledge.

anaesthesia and artificial intelligence, will be touched upon.

PHARMACOKINETIC/ PHARMACODYNAMIC MODELS IN CLINICAL PRACTICE: GENERAL ANAESTHESIA

For several anaesthetic drugs, pharmacokinetic and PKPD models have been implemented in TCI systems and drug administration advisory systems and are in clinical use worldwide. In fact, for drugs like propofol, so many models have been developed that choices have to be made which model to use, or whether to change models as newer models are published. Therefore, it's important to know the advantages and disadvantages of these models.

A disadvantage of many current models is that they were developed from studies in select populations and under select circumstances. Extrapolation of these models to other populations or other circumstances may result in inadequate or excessive doses. At present some TCI pumps are programmed with multiple models for the same drug – such as separate models for use in children, adults, the elderly and the obese – but such complexity can increase the risks of user error. Table 1 shows a (nonexhaustive) overview of commercially available PKPD models for anaesthetic drugs, but many more models have been published but not yet implemented in TCI pumps.

In recent years, general-purpose models have been developed for propofol and remifentanyl. These models were designed for TCI administration

Table 1. Commercially available PKPD models for TCI

Propofol	
Marsh [3]	Adults
Schnider [4,5]	Adults
Paedfusor [6,7]	Paediatric
Kataria [8]	Paediatric
Eleveld [9 ^a]	Paediatric–adults–elderly–obese
Remifentanyl	
Minto [10,11]	Adults
Eleveld [12] ^a	Paediatric–adults
Kim–Obara–Egan [13] ^a	Adults–obese
Fentanyl	
Shafer [14]	Adults
Sufentanyl	
Gepts [15]	Adults
Alfentanyl	
Maitre [16]	Adults
Scott [17]	Adults
Dexmedetomidine	
Dyck [18]	Adults
Hannivoort–Colin [19–21] ^a	Adults

^aExpected end of 2020.

of these drugs to a wide variety of patient populations, thereby reducing the need for the clinician to have to select from one of several models for one drug or to have to extrapolate from a single model developed for a different population. In 2014, Eleveld *et al.* [22] published a ‘general purpose’ propofol pharmacokinetic model, which they expanded to a PKPD model in 2018. This model is based on data from 30 published pharmacokinetic studies, with five including pharmacodynamic data (bispectral index – BIS) [9^a]. The population included (premature) neonates, children, healthy adult volunteers and patients, obese adults and elderly patients.

This model has several characteristics that allow application over a diverse range of patients:

- The concept of allometry, originally used for extrapolation between species (‘from mice to elephants’), is applied to allow more accurate scaling of body size descriptors in a wide range of patients (from premature neonates to obese adults). In the Eleveld model, compartment volumes are scaled to a body size descriptor (total body weight, fat-free mass) to the power of 1, and clearances are scaled to a body-size descriptor to the power of 0.75.
- Fat-free mass (FFM) is calculated according to the Al-Sallami equation [23]. Unlike the James formula for lean body mass (LBM) used in the Schnider propofol model, the Al-Sallami formula

does not show a paradoxical decline in the morbidly obese.

- (Premature) neonates have underdeveloped metabolism pathways. The Eleveld model uses a maturation model for elimination clearance, which is 95% complete at five months of age. Intercompartmental clearance CL3 slowly increases with age, whereas CL2 decreases, suggesting a change in body composition from more total body water to more body fat from childhood into adolescence.
- Elimination clearance CL1 and distribution volume V3 decrease with age, but only when opioids are used concomitantly. This factor perhaps helps define, in part, the difference in PKPD between healthy volunteers and patients.

The pharmacodynamic component of the model can help with the choice of target concentration. When the age-specific Ce50 (50% of maximal effect) of the Eleveld propofol model is used, the model predicts a BIS of 47, which is a rational choice of the initial target concentration during induction of anaesthesia. Prospective validation of this model is underway, and if the results are favourable, it should be available in commercial pumps in the near future.

Two new remifentanyl models were published recently [12,13]. Eleveld *et al.* [12] combined data from multiple pharmacokinetic studies in adults and children, with one adult study also including pharmacodynamic data. There were only limited data from obese patients, with a maximum BMI of less than 34 kg/m². Kim *et al.* [13] focused on the influence of obesity on the pharmacokinetic of remifentanyl, by combining data from studies in lean and obese adults up to a BMI of 73.7 kg/m². As the model was developed without pharmacodynamic data, it is only a pharmacokinetic model.

Although Kim used the Janmahasatian formula for FFM, Eleveld again used the Al-Sallami formula (which is based on Janmahasatian, but extended to include children), therefore both avoid the problems encountered with James' LBM equation (as implemented in the Minto remifentanyl model [10,11]). Both models also used allometric scaling. The exponents in the Eleveld model were fixed to 1 for volumes and to 0.75 for clearances, but Kim estimated the exponents during the modelling process. Eleveld used a maturation model for the clearances in young children. In populations where both models overlap (normal-weight adults), dose predictions are nearly identical. These models therefore appear to complement each other, so perhaps in the future these models will be combined to an even more 'general' model.

Commercially available TCI pumps sometimes include models for other anaesthetic drugs, such as the opioids fentanyl, sufentanil and alfentanil. These are mainly older models (the Shafer fentanyl model [14], the Gepts sufentanil model [15] and the Maitre alfentanil model [16]), that were developed with data from nonobese adults. These models should strictly speaking not be used in children, the elderly or obese patients, with the exception of the Maitre model, which also included data from elderly patients.

PHARMACOKINETIC/ PHARMACODYNAMIC MODELS IN CLINICAL PRACTICE: SEDATION

For procedural sedation, the margin of error is narrower than in general anaesthesia. Patients should be sufficiently sedated to be able to tolerate the procedure, whereas overdosing can lead to airway obstruction, loss of airway reflexes, hypoventilation and/or haemodynamic instability. PKPD-controlled drug administration may help to reduce these risks by delivering a more stable effect.

TCI propofol (with or without TCI remifentanyl) is already widely used in clinical practice for procedural sedation [24]. The previously mentioned Eleveld propofol model also includes simulations and recommendations for procedural sedation [9^{*}]. The recommended initial 'sedation' target concentration is the age-specific Ce10 (10% of maximal effect), which predicts a BIS of 84.

Dexmedetomidine is registered for use for procedural sedation in nonintubated adult patients. Advantages of dexmedetomidine are that the patient remains responsive to verbal commands at concentrations within the manufacturer's dosing guidelines [25] and that airway patency, airway reflexes and ventilatory drive are maintained. Dexmedetomidine induces bradycardia and has a biphasic effect on blood pressure, with hypotension at lower concentrations and hypertension at higher concentrations. Bolus doses can cause significant hypertension and should be avoided. Multiple dexmedetomidine pharmacokinetic models have been developed. However, only one PKPD model has been published. The Hannivoort–Colin PKPD model [19–21] has a weight-based pharmacokinetic model with allometric scaling. The pharmacodynamic model is complex and describes four clinical effects: the BIS, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score, heart rate and mean arterial pressure. Despite the complexity, use of this model for TCI enables the anaesthetist to titrate the drug to achieve a desired BIS or probability of a certain MOAA/S score [26], whereas the

model also provides information about the other effects (magnitude of bradycardia and the likely change in blood pressure from baseline).

PHARMACOKINETIC/ PHARMACODYNAMIC MODELS IN THE ICU

PKPD for optimized drug delivery has yet to really gain foothold in the ICU. Although PKPD models for TCI are available for several sedative drugs used in the ICU, a possible reason why TCI is not used is that longer duration of sedation will result in an extrapolation of the model. A second possible reason is that a rapid onset and offset of sedation, two advantages of TCI, are often not particularly necessary in ICU patients. Possible advantages of TCI sedation in the ICU setting is greater stability of sedation level, with fewer respiratory and haemodynamic side-effects. Greater haemodynamic stability is especially desirable in patients with for instance cardiogenic or septic shock and maintained respiratory drive is of particular interest in nonintubated patients [27] and in patients undergoing weaning from the mechanical ventilation. In any case, use of TCI is rare, and studies with TCI sedation or analgesia are sparse.

Another area of interest for PKPD in the ICU is antibiotics. Stable plasma concentrations are especially advantageous for antimicrobial drugs with a narrow therapeutic range or drugs that depend on the duration that concentrations remain in the therapeutic range for efficacy. For such drugs, fixed-rate infusion schemes are commonly used and therapeutic drug monitoring (TDM) of the achieved plasma concentrations is used to adjust the infusion rate.

The time it takes for a new stable concentration to be achieved after changing the infusion rate can be long, depending on drug pharmacokinetics. TCI administration can help to improve the efficacy by generating more rapid changes, followed by stable concentrations. The only clinical study that has been performed to date involved TCI administration of cefepime, showing acceptable performance [28[■]]. A problem in the ICU population is that pharmacokinetic parameters change according to the condition of the patient. Pharmacokinetic status is not the same during deep septic shock compared with the recovery phase. A simulation study compared TCI administration of vancomycin with and without model adjustment based on TDM, and routine dosing strategies with TDM [29]. The authors concluded that adaptive TCI may be useful in patient-tailored antibiotic drug titration in the ICU.

TARGET-CONTROLLED INFUSION FEEDBACK SYSTEMS: BAYESIAN-DRIVEN TARGET-CONTROLLED INFUSION, CLOSED-LOOP TARGET-CONTROLLED INFUSION

One of the advantages of the use of volatile anaesthetics compared with intravenous anaesthetics is the availability of measured (end-tidal) concentrations, which correspond reasonably with arterial concentrations and effect, with some time-delay for equilibration. For propofol, progress is being made in this regard. The Pelorus 1500 system can be used to provide point-of-care propofol plasma concentrations within 4 min [30,31]. Methods of measuring exhaled concentrations of propofol metabolites are currently being developed [32–35] to make it possible to estimate plasma concentrations [36–38].

Accurate POC measurements of propofol plasma concentrations may inform adjustments to the TCI target or may be used to adjust the pharmacokinetic algorithm to correct for the inevitable interindividual variability and increase accuracy of the TCI model. A recent study showed that a single adjustment 60 min into a procedure (cardiac surgery) using Bayesian adaptation of the pharmacokinetic model improved bias, but not precision, provided that an appropriate and accurate pharmacokinetic model was used [39].

Another possible feedback system for TCI is closed-loop administration, in which the target concentration is automatically adjusted by a computer system. This requires an adequate and reliable measurement of clinical effect. Closed-loop systems may provide even more stable depth of anaesthesia [40–42]. Possible feedback systems include EEG monitors such as BIS [43,44], or in case of procedural sedation, some form of patient input similar to patient-controlled analgesia [45]. A recent validation study by Neckebroek *et al.* [46] showed that propofol closed-loop TCI performed adequately at different remifentanyl concentrations. Multiple closed-loop systems have also been developed, which enables controlled delivery of both propofol and remifentanyl [47[■],48,49], or even more systems [50[■]].

ADVISORY DISPLAYS AND DRUG INTERACTIONS

Advisory displays showing predicted concentrations and/or effect corresponding to the administered drug amount may help where TCI is unavailable. Aside from single drug concentrations, these monitors can help to visualize drug interactions, such as hypnotic–opioid interactions. Examples of such monitors are the SmartPilot View (Dräger, Lübeck,

Germany), GE Navigator Applications Suite (GE Healthcare, Chicago, Illinois, USA) and Medvis Anesthesia Displays (Medvis, Salt Lake City, Utah, USA).

Drug interaction response surface models (RSM) were originally described by Bouillon for the propofol–remifentanyl interaction [51]. Similar studies quantifying the interaction between propofol and sevoflurane [52], and sevoflurane and remifentanyl [53,54] have been published, as well as a triple-interaction model between propofol–sevoflurane–remifentanyl [55]. With tolerance of laryngoscopy as endpoint, the sevoflurane–propofol interaction was additive, whereas the propofol–remifentanyl and the sevoflurane–remifentanyl interactions were synergistic. A propofol–remifentanyl interaction model has also been developed for procedural sedation [56,57].

Recently, Weerink *et al.* [58[¶]] published an RSM for the interaction between dexmedetomidine and remifentanyl. They found that remifentanyl did not influence the probability of tolerance to nonnoxious and noxious stimuli.

ARTIFICIAL INTELLIGENCE

TCI, advisory displays, Bayesian model optimization and closed-loop titration are all methods that allow us to apply very complex systems and mathematics involved with pharmacokinetics and –dynamics, to the management of our patients. These are far too complex for our human brains to understand and calculate bedside. Artificial intelligence can take this a few steps further. Although the concepts of artificial intelligence and machine learning are not new, their use in anaesthesia is still at an early stage [59[¶]].

Lee [60^{¶¶}] and Ramaswamy [61[¶]] have recently published studies on the use of machine learning in TIVA. Lee modelled propofol and remifentanyl infusion data and BIS. The deep learning model was superior to traditional PKPD models in predicting BIS, within the population of learning, validation and testing cases (adults only, weight ≤ 92 kg). Ramaswamy used machine learning with multiple quantitative EEG features to predict sedation level, regardless of whether propofol, sevoflurane or dexmedetomidine was used.

As in all science, the methodology needs to be sound, with the right data, and the right outcome measurements. The complexity and ‘black box’-image of machine learning make it difficult to unearth causes for false conclusions [62,63]. Also, a large amount of data is needed to account for the variability in patients, practices and procedures [64]. Monitoring during anaesthesia or sedation generally produces high-quality and density data. To

make full use of the available monitoring data and drug-infusion history, large volumes of data should be captured. This should result in more accurate and more useful machine learning. Healthcare provider-entered data, such as patient history and other drug use, is more prone to errors or incompleteness, but may still perhaps prove useful in predicting pharmacological effect and, in turn, guiding drug dosing.

CONCLUSION

Current and ongoing PKPD research has provided tools to increase the accuracy of drug titration in clinical practice. Other tools combined with PKPD and TCI, such as Bayesian model adaptation systems or closed-loop titration may further increase accuracy and stability of effect. However, in the not-too-distant future, this may all become obsolete, as machine learning systems may prove more accurate than ‘advanced’ PKPD systems, without the system requiring any knowledge of the pharmacological concepts. The cliché phrase is ‘Further research is needed,’ but artificial intelligence and machine learning may very well be unavoidable and research on this topic will likely multiply rapidly, and so perhaps the more correct phrase is: ‘AI is coming.’ Whether that results in a harsh winter or a pleasant summer, only time will tell.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Ryan SM, Nielsen CJ. Global warming potential of inhaled anesthetics. *Anesth Analg* 2010; 111:92–98.
 2. Andersen MP, Sander SP, Nielsen OJ, *et al.* Inhalation anaesthetics and climate change. *Br J Anaesth* 2010; 105:760–766.
 3. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth* 1991; 67:41–48.
 4. Schnider TW, Minto CF, Gambús PL, *et al.* The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; 88:1170–1182.
 5. Schnider TW, Minto CF, Shafer SL, *et al.* The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; 90:1502–1516.
 6. Absalom A, Amutike D, Lal A, *et al.* Accuracy of the 'Paedfusor' in children undergoing cardiac surgery or catheterization. *Br J Anaesth* 2003; 91:507–513.
 7. Absalom A, Kenny G. 'Paedfusor' pharmacokinetic data set. *Br J Anaesth* 2005; 95:110.
 8. Kataria BK, Ved SA, Nicodemus HF, *et al.* The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology* 1994; 80:104–122.
 9. Eleveld DJ, Colin P, Absalom AR, Struys MM. Pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation. *Br J Anaesth* 2018; 120:942–959.
- This is the first PKPD propofol model that encompasses a broad range in population from premature neonates to the elderly and including obese adults, with allometry and maturation used to adjust for the differences between these groups.
10. Minto CF, Schnider TW, Egan TD, *et al.* Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl. I. Model development. *Anesthesiology* 1997; 86:10–23.
 11. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanyl. II. Model application. *Anesthesiology* 1997; 86:24–33.
 12. Eleveld DJ, Proost JH, Vereecke H, *et al.* An allometric model of remifentanyl pharmacokinetics and pharmacodynamics. *Anesthesiology* 2017; 126:1005–1018.
 13. Kim TK, Obara S, Egan TD, *et al.* Disposition of remifentanyl in obesity: a new pharmacokinetic model incorporating the influence of body mass. *Anesthesiology* 2017; 126:1019–1032.
 14. Shafer SL, Varvel JR, Aziz N, Scott JC. Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. *Anesthesiology* 1990; 73:1091–1102.
 15. Gepts E, Shafer SL, Camu F, *et al.* Linearity of pharmacokinetics and model estimation of sufentanil. *Anesthesiology* 1995; 83:1194–1204.
 16. Maitre PO, Vozeh S, Heykants J, *et al.* Population pharmacokinetics of alfentanil. *Anesthesiology* 1987; 66:3–12.
 17. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; 240:159–166.
 18. Dyck JB, Maze M, Haack C, *et al.* Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology* 1993; 78:821–828.
 19. Hannivoort LN, Eleveld DJ, Proost JH, *et al.* Development of an optimized pharmacokinetic model of dexmedetomidine using target-controlled infusion in healthy volunteers. *Anesthesiology* 2015; 123:357–367.
 20. Colin PJ, Hannivoort LN, Eleveld DJ, *et al.* Dexmedetomidine pharmacokinetic-pharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation. *Br J Anaesth* 2017; 119:200–210.
 21. Colin PJ, Hannivoort LN, Eleveld DJ, *et al.* Dexmedetomidine pharmacodynamics in healthy volunteers: 2. Haemodynamic profile. *Br J Anaesth* 2017; 119:211–220.
 22. Eleveld DJ, Proost JH, Cortinez LI, *et al.* A general purpose pharmacokinetic model for propofol. *Anesth Analg* 2014; 118:1221–1237.
 23. Al-Sallami HS, Goulding A, Grant A, *et al.* Prediction of fat-free mass in children. *Clin Pharmacokinet* 2015; 54:1169–1178.
 24. Barends CR, Driesens MK, van Amsterdam K, *et al.* Moderate-to-deep sedation using target-controlled infusions of propofol and remifentanyl: adverse events and risk factors: a retrospective cohort study of 2937 procedures. *Anesth Analg* 2019; doi:10.1213/ane.0000000000004593. [Epub ahead of print]
 25. European Medicines Agency. Summary of product characteristics: Dexdor (dexmedetomidine).
 26. Kim KM, Seo KH, Lee JM, *et al.* Target-controlled infusion of dexmedetomidine effect-site concentration for sedation in patients undergoing spinal anaesthesia. *J Clin Pharm Ther* 2019; 45:347–353.
 27. Clouzeau B, Bui HN, Vargas F, *et al.* Target-controlled infusion of propofol for sedation in patients with noninvasive ventilation failure due to low tolerance: a preliminary study. *Intensive Care Med* 2010; 36:1675–1680.
 28. Jonckheere S, Neve ND, Verbeke J, *et al.* Target-controlled infusion of cefepime in critically ill patients. *Antimicrob Agents Chemother* 2019; 64:e01552–19. First clinical trial of target-controlled infusion of antibiotics in critically ill patients. TCI performance was comparable to TCI systems in anaesthesia. This may be a good alternative method of drug delivery for antimicrobial drugs with a relatively narrow therapeutic window.
 29. Colin PJ, Jonckheere S, Struys MM. Target-controlled continuous infusion for antibiotic dosing: proof-of-principle in an in-silico vancomycin trial in intensive care unit patients. *Clin Pharmacokinet* 2018; 57:1435–1447.
 30. Cowley NJ, Laitenberger P, Liu B, *et al.* Evaluation of a new analyser for rapid measurement of blood propofol concentration during cardiac surgery. *Anaesthesia* 2012; 67:870–874.
 31. Cowley NJ, Hutton P, Clutton-Brock TH. Assessment of the performance of the Marsh model in effect site mode for target controlled infusion of propofol during the maintenance phase of general anaesthesia in an unselected population of neurosurgical patients. *Eur J Anaesth* 2013; 30:627–632.
 32. Hornuss C, Wiepcke D, Praun S, *et al.* Time course of expiratory propofol after bolus injection as measured by ion molecule reaction mass spectrometry. *Anal Bioanal Chem* 2012; 403:555–561.
 33. Perl T, Carstens E, Hirn A, *et al.* Determination of serum propofol concentrations by breath analysis using ion mobility spectrometry. *Br J Anaesth* 2009; 103:822–827.
 34. Grossherr M, Hengstenberg A, Meier T, *et al.* Propofol concentration in exhaled air and arterial plasma in mechanically ventilated patients undergoing cardiac surgery. *Br J Anaesth* 2009; 102:608–613.
 35. Hornuss C, Praun S, Villinger J, *et al.* Real-time monitoring of propofol in expired air in humans undergoing total intravenous anesthesia. *Anesthesiology* 2007; 106:665–674.
 36. Colin P, Eleveld DJ, van den Berg JP, *et al.* Propofol breath monitoring as a potential tool to improve the prediction of intraoperative plasma concentrations. *Clin Pharmacokinet* 2015; 55:849–859.
 37. Ziaian D, Herrmann R, Kleiboer K, *et al.* Pharmacokinetic modeling of the transition of propofol from blood plasma to breathing gas. 2014 IEEE Int Symp Med Meas Appl MEMEA 2014; pp. 80–84.
 38. Kreuer S, Hauschild A, Fink T, *et al.* Two different approaches for pharmacokinetic modeling of exhaled drug concentrations. *Sci Rep* 2014; 4:5423.
 39. Berg JP, van den Eleveld DJ, Smet TD, *et al.* Influence of Bayesian optimization on the performance of propofol target-controlled infusion. *Br J Anaesth* 2017; 119:918–927.
 40. Brogi E, Cyr S, Kazan R, *et al.* Clinical performance and safety of closed-loop systems: a systematic review and meta-analysis of randomized controlled trials. *Anesth Analg* 2017; 124:446–455.
 41. Loeb RG, Cannesson M. Closed-loop anesthesia: ready for prime time? *Anesth Analg* 2017; 124:381–382.
 42. Pasin L, Nardelli P, Pintaudi M, *et al.* Closed-loop delivery systems versus manually controlled administration of total IV anesthesia: a meta-analysis of randomized clinical trials. *Anesth Analg* 2017; 124:456–464.
 43. Smet TD, Struys MM, Greenwald S, *et al.* Estimation of optimal modeling weights for a Bayesian-based closed-loop system for propofol administration using the bispectral index as a controlled variable: a simulation study. *Anesth Analg* 2007; 105:1629–1638.
 44. Smet TD, Struys MM, Neckebroek MM, *et al.* The accuracy and clinical feasibility of a new Bayesian-based closed-loop control system for propofol administration using the bispectral index as a controlled variable. *Anesth Analg* 2008; 107:1200–1210.
 45. Stonell CA, Leslie K, Absalom AR. Effect-site targeted patient-controlled sedation with propofol: comparison with anaesthetist administration for colonoscopy. *Anaesthesia* 2006; 61:240–247.
 46. Neckebroek M, Boldingh JW, Smet TD, Struys MM. Influence of remifentanyl on the control performance of the bispectral index controlled Bayesian-based closed-loop system for propofol administration. *Anesth Analg* 2020; 130:1661–1669.
 47. West N, Heusden K, van Gorges M, *et al.* Design and evaluation of a closed-loop anesthesia system with robust control and safety system. *Anesth Analg* 2018; 127:883–894.
- Using a single sensor, the authors used the different effects of propofol and remifentanyl on the measured parameter, driving the closed-loop system for both drugs simultaneously.
48. Hemmerling TM, Arbeid E, Wehbe M, *et al.* Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial. *Br J Anaesth* 2013; 110:1031–1039.
 49. Liu N, Chazot T, Hamada S, *et al.* Closed-loop coadministration of propofol and remifentanyl guided by bispectral index: a randomized multicenter study. *Anesth Analg* 2011; 112:546–557.
 50. Joosten A, Rinehart J, Bardaji A, *et al.* Anesthetic management using multiple closed-loop systems and delayed neurocognitive recovery: a randomized controlled trial. *Anesthesiology* 2020; 132:253–266.
- This study describes a triple closed-loop system, controlling propofol and remifentanyl infusion, as well as fluid management and ventilation, with the intervention group spending less time at BIS less than 40, less hypoxaemia and a lower fluid balance. The intervention group had a better postoperative neurocognitive recovery, though it is unknown which of, and in how far these three controllers contributed to this recovery.
51. Bouillon TW, Bruhn J, Radulescu L, *et al.* Pharmacodynamic interaction between propofol and remifentanyl regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology* 2004; 100:1353–1372.

52. Schumacher PM, Dossche J, Mortier EP, *et al.* Response surface modeling of the interaction between propofol and sevoflurane. *Anesthesiology* 2009; 111:790–804.
 53. Heyse B, Proost JH, Schumacher PM, *et al.* Sevoflurane remifentanyl interaction: comparison of different response surface models. *Anesthesiology* 2012; 116:311–323.
 54. Johnson KB, Syroid ND, Gupta DK, *et al.* An evaluation of remifentanyl-sevoflurane response surface models in patients emerging from anesthesia. *Anesth Analg* 2010; 111:387–394.
 55. Hannivoort LN, Vereecke HE, Proost JH, *et al.* Probability to tolerate laryngoscopy and noxious stimulation response index as general indicators of the anaesthetic potency of sevoflurane, propofol, and remifentanyl. *Br J Anaesth* 2016; 116:624–631.
 56. LaPierre CD, Johnson KB, Randall BR, *et al.* An exploration of remifentanyl-propofol combinations that lead to a loss of response to esophageal instrumentation, a loss of responsiveness, and/or onset of intolerable ventilatory depression. *Anesth Analg* 2011; 113:490–499.
 57. LaPierre CD, Johnson KB, Randall BR, Egan TD. A simulation study of common propofol and propofol-opioid dosing regimens for upper endoscopy. *Anesthesiology* 2012; 117:252–262.
 58. Weerink MA, Barends CR, Muskiet ER, *et al.* Pharmacodynamic interaction of remifentanyl and dexmedetomidine on depth of sedation and tolerance of laryngoscopy. *Anesthesiology* 2019; 131:1004–1017.
- Interaction study between dexmedetomidine and remifentanyl, based on response surface modelling. Interestingly, remifentanyl did not influence tolerance of noxious and nonnoxious stimuli in the presence of dexmedetomidine.
59. Connor CW. Artificial intelligence and machine learning in anesthesiology. *Anesthesiology* 2019; 131:1346–1359.
 - A very interesting and informative review on artificial intelligence and its possible applications in anaesthesia.
 60. Lee HC, Ryu HG, Chung EJ, Jung CW. Prediction of bispectral index during target-controlled infusion of propofol and remifentanyl. *Anesthesiology* 2018; 128:492–501.
 - A deep learning model was developed to predict BIS in patients receiving propofol and remifentanyl anaesthesia, using demographic data and drug dosing histories. This model was more accurate in predicting BIS in the testing data than traditional PKPD including interaction (response surface) modelling, though its accuracy is highly dependent on the initial training data.
 61. Ramaswamy SM, Kuizenga MH, Weerink MA, *et al.* Novel drug-independent sedation level estimation based on machine learning of quantitative frontal electroencephalogram features in healthy volunteers. *Br J Anaesth* 2019; 123:479–487.
 - Machine learning systems were trained to recognize awake and sedated states, using quantitative EEG in healthy volunteers sedated with either propofol, sevoflurane or dexmedetomidine, creating a drug-independent algorithm for predicting level of sedation.
 62. Grote T, Berens P. On the ethics of algorithmic decision-making in healthcare. *J Med Ethics* 2020; 46:205–211.
 63. Riley P. Three pitfalls to avoid in machine learning. *Nature* 2019; 572:27–29.
 64. Gambus P, Shafer SL. Artificial intelligence for everyone. *Anesthesiology* 2018; 128:431–433.