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Sneyd, J

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Title: The current status of perioperative hypnotics, the role of benzodiazepines and the case for remimazolam.

J Robert Sneyd[1], M.D., F.R.C.A.

Pedro L Gambus[2,3], M.D., Ph.D.

Ann E Rigby-Jones[1], Ph.D.

1. Faculty of Medicine and Dentistry, University of Plymouth, John Bull Building, Plymouth Science Park, Plymouth PL6 8BU, UK.

2. Anesthesiology Department, Systems Pharmacology Effect Control & Modelling (SPEC-M) Research Group, Hospital Clinic de Barcelona, Barcelona, Spain.

3. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Neuroscience Department, NeuroImmunology Research Group, Barcelona, Spain.

Corresponding author: J Robert Sneyd, Emeritus Professor, Faculty of Medicine and Dentistry, University of Plymouth, John Bull Building, Plymouth Science Park, Plymouth PL6 8BU, UK.

+44 7870 271531 robert.sneyd@pms.ac.uk @robsneyd

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Abstract

Anaesthesiologists and non-anaesthesiologist sedationists have a limited list of intravenous hypnotics, further reduced by the withdrawal of thiopental in the USA and its near disappearance in Europe. Meanwhile, demand for sedation increases and new clinical groups are using what were traditionally anaesthesiologist's drugs. Improved understanding of the determinants of perioperative morbidity and mortality have spotlighted hypotension as a potent cause of patient harm and practice must be adjusted to respect this. High dose propofol sedation may be harmful and a critical reappraisal of drug choices and doses is needed.

The development of remimazolam, initially for procedural sedation, allows reconsideration of benzodiazepines as the hypnotic component of a general anaesthetic even if their characterisation as intravenous anaesthetics is questionable. Early data suggest that a combination of remimazolam and remifentanil can induce and maintain anaesthesia. Further work is needed to define use-cases for this technique and to determine the effects (if any) on patient outcomes.

Key words

Hypnotic, sedation, hypotension, benzodiazepine, pharmacokinetics, pharmacodynamics, remimazolam

Intravenous hypnotics are deployed throughout the perioperative period, from premedication and procedural sedation through induction and maintenance of anaesthesia to intensive care sedation. This narrative review considers the pharmacological demands of these clinical tasks and the fit of current agents. A short acting benzodiazepine, remimazolam has recently been licensed for procedural sedation (USA & China, July 2020) and for induction and maintenance of anaesthesia (Japan, January 2020, South Korea, January 2021), further applications for approval have been submitted in Europe and are being prepared elsewhere. The history of benzodiazepine anaesthesia* is reviewed and the characteristics of remimazolam considered against contemporary requirements.

Historic benchmarks[1, 2] and European and USA product approvals were used as a starting point for comparisons of current compounds with clinical requirements. Additional themes for analysis were identified from anaesthesia journals, conference topics and personal contacts. Literature searching (PubMed, Embase) began around key concepts (perioperative hypotension, anaesthetic neurotoxicity, perioperative neurocognitive disorders, cancer recurrence, benzodiazepine anaesthesia, remimazolam and flumazenil reversal) and extended through relevant citations.

WHAT DO WE WANT FROM INTRAVENOUS HYPNOTICS?

What are we trying to achieve?

To evaluate current options and critique future possibilities we must first address the question 'What does good look like?'. In 1985, Dundee wrote: "Ideally one would like a water-soluble, non-irritant, rapidly-acting, smooth induction agent, with no antalgesic action. Cardiovascular and respiratory depression should be minimal with normal dosage." and "A slight delay in onset would not be a major obstacle, provided this is predictable…".[1]

The converse of good is bad and again we have a blueprint. Whitwam succinctly reviewed adverse reactions to i.v. induction agents[2] and identified tissue irritation, pain, excitation, 'respiratory upset'

* The use of a benzodiazepine as the hypnotic component of a balanced anaesthetic technique.

(coughing/laryngospasm), cardio-respiratory depression, allergy and recovery issues (PONV, psychic phenomena) as areas for concern. Table 1 summaries the characteristics of injectable hypnotics licensed for anaesthesia or sedation in the USA or Europe.

Table 1 near here

Subsequently, new themes have emerged for consideration and (possibly) for concern.

Maintaining arterial blood pressure

Although both Dundee[1] and Whitwam[2] identified hypotension as an issue, recent data have highlighted its importance. Hypotension after induction of anaesthesia is common[3] and associated with unfavourable outcomes.[4, 5] A review of the relationship between arterial blood pressure and organ dysfunction identified that 10 minutes or more with mean arterial pressure below 80 mm Hg may represent a threshold for organ injury.[6] Further understanding the differential consequences of various causes of perioperative hypotension remains a priority.[7] Patients in whom perfusion is already compromised may be especially vulnerable to harm by hypnotic induced hypotension.[8]

Propofol is particularly problematic, in addition to directly inducing hypotension, its hypotensive effects are exaggerated by haemorrhage[9] with disturbed pharmacokinetics causing higher than anticipated blood concentrations.[10] Etomidate[11] and ketamine[12] have a remarkable capacity for supporting and even sometimes improving blood pressure in compromised patients however, other shortcomings in these agents make them inferior choices to propofol in routine use.

Maintaining arterial blood pressure therefore becomes a goal for developers of new anaesthetics and has already been claimed for alfaxalone reformulated in 7-sulfobutylether beta-cyclodextrin as PHAXANCD™.[13, 14]

Maintaining ventilation

Respiratory depression and airway obstruction are potentially life-threatening concomitants of anaesthesia and sedation. Whilst both are routinely addressed by anaesthesiologists, European,[15]

UK[16] and US[17] guidelines for sedation remind us that sedationists must demonstrate and maintain the competencies necessary to support their patient both in the target state and in the event of inadvertent progression to a deeper state. Respiration is less affected by etomidate, ketamine and dexmedetomidine than by propofol and all hypnotics interact with opioids with consequent increased hypnotic effect and at least some degree of respiratory depression.

The antagonists naloxone and flumazenil can reverse respiratory depression caused by opioids and benzodiazepines respectively however this will also reverse analgesia or hypnosis.

Supraglottic airways, laryngoscopy and intubation without paralysis

Surgical practice has shifted towards ambulatory care and a high proportion of patients are now managed with a supra-glottic airway rather than a tracheal tube. Propofol suppresses laryngeal responsiveness[18] and induction of anaesthesia with propofol rather than thiopental is preferred when a supra-glottic airway is anticipated[19] because insertion under propofol anaesthesia is quicker, less eventful and requires less supplementary does of hypnotic.[20] The ability to support swift and atraumatic placement of supra-glottic airways is thus a necessary characteristic of modern anaesthetic induction agents. The use of benzodiazepine anaesthesia for facilitating supra-glottic airway placement has been reported[21] but has not yet been formally evaluated. Propofol-opioid combinations are often used to support tracheal intubation without paralysis although the intubating conditions are consistently inferior to those achieved with paralysis.[22]

Avoiding neurotoxicity

Whether anaesthetics harm the developing brain is controversial.[23] In pre-clinical systems, adverse effects have been demonstrated for NMDA receptor antagonists (ketamine) and GABA agonists (propofol, barbiturates, benzodiazepines).[24] Whilst clinical trials continue, preliminary results are reassuring and experts recommend that we do not need to change our practice.[24, 25] Appreciation of

the limitations of animal models and the biases of retrospective studies have recently downgraded the perceived risk to 'negligible'.[24]

Although ketamine enjoys some usage for induction of anaesthesia in the critically ill,[26] concerns about possible perturbation of intracranial pressure and cerebral blood flow have precluded its consideration for patients with brain injury. Recently the recognition of an apparently favourable effect on EEG suggests ketamine deserves re-evaluation.[27]

Post-operative delirium (correctly characterised as a perioperative neurocognitive disorder[28]) is distressing for patients and staff, associated with impaired outcomes and adds to costs.[29] Accordingly, its avoidance is a clinical priority although the downstream deterioration towards dementia may reflect an underlying trajectory of cognitive decline rather than the direct consequences of perioperative medication. The American Geriatrics Society 'Beers criteria' list drugs to be avoided in older patients including benzodiazepines.[30] However, although 'periprocedural anesthesia' is mentioned, the examples cited all relate to chronic oral administration and midazolam is not mentioned at all. Further, although sedation and anaesthesia are achievable without benzodiazepines, their absence implies an alternative which may have undesirable effects i.e. propofol and hypotension which might contribute to perioperative neurocognitive disorders.[31]

Nevertheless, if benzodiazepines are to be used in high doses or prolonged duration, especially in the elderly then we need data to understand their potential for postoperative delirium.

Rapid onset and fast offset

The ability to titrate to effect an hypnotic or opioid is valued by clinicians inducing sedation or anaesthesia. Likewise, predictability of effect duration and clear-headed recovery of cognitive function support patient throughput and (possibly) patient safety.

Consequently, a major development axis of anaesthetic pharmacology has been the acceleration of drug effect and its offset. Whilst onset can be hastened by increased dose (albeit perhaps at the cost

of off-target effects), offset is determined by redistribution and elimination. Although redistribution can yield rapid recovery from bolus doses of propofol, thiopental and etomidate and reasonably swift emergence after well managed infusions of propofol,[32] all these agents are prone to accumulation after prolonged administration. The advent of 'soft'[33] drugs whose effect is terminated by esterase metabolism to inactive metabolites brought us the ultra-short acting opioid remifentanil, and less usefully mivacurium and AZD-3043[34] as well as anaesthesia stalwarts succinylcholine and atracurium. Remimazolam, a novel short acting benzodiazepine now joins this disparate group and offers typical benzodiazepine effects with accelerated offset.

Active metabolites prolong drug effect, often unpredictably and become a significant issue with extended administration. Thus alpha-hydroxy midazolam accumulates during ICU sedation with midazolam and morphine-6-glucuronide, and norpethidine extend opioid effect.

The shift of most surgery and almost all investigations to an outpatient basis is challenged by residual effects of sedation and anaesthesia. Residual hypnotic effect or the fear of it precipitates minimum times before discharge, prohibition of driving and strictures against working, making decisions or operating machinery which adversely impact patients' lives. In the UK, colonoscopy patients self-sedated with 50% nitrous oxide are considered safe to drive home 30 minutes later.[35] If advances in anaesthetic pharmacology could achieve the same through 'soft' analgesia and hypnosis or improved titration and neuropsychological assessment,[36] the effect would be usefully disruptive and of great health-economic benefit.

Avoiding idiosyncratic reactions

Current peri-operative hypnotics all have some propensity to off-target effects. These range in severity from inconvenient (extraneous muscle movements with etomidate) to catastrophic (anaphylaxis with thiopental) and from frequent (pain on injection with propofol) to rarity (green urine with propofol ICU sedation). None of the agents are exempt: etomidate causes adrenocortical

depression, ketamine causes hallucinations and dexmedetomidine can cause bradycardia and hypotension.

Idiosyncratic reactions have underpinned the failure of numerous candidate new hypnotics including pregnanolone[37] (urticaria), ORG-21465[38], ORG-25435[39], AZD-3043[40] and ABP-700[41] (excitation), and fospropofol[42] (perineal pain). Whilst these events may not be predictable, rigorous monitoring of clinical trials and effective post-launch pharmacovigilance will facilitate their early identification thereby minimising risk to volunteers and patients whilst reducing development costs.

Post-Operative Nausea and Vomiting, PONV

PONV is a frequent reason for unplanned hospital admission after day-surgery. Propofol has direct anti-emetic properties[43] and when used as an induction agent, lowers rates of PONV. Further benefit is demonstrated when Total Intra-Venous Anaesthesia, TIVA is used in place of volatile anaesthesia.[44] Perioperative midazolam also has a useful anti-emetic effect.[45] Etomidate is associated with PONV[46] and it is this characteristic rather than extraneous muscle movements or adrenocortical depression that constrains its routine use.

Alignment with existing practice: non-physicians, non-anaesthesiologists and medical politics

Anaesthesiologist provided sedation of fit patients for endoscopy is expensive.[47, 48] Protocols for Non-Anaesthesiologist Administration of Propofol (NAAP) are evidence based[49] and safe[50, 51] but unacceptable to many national societies.[52] Indeed, anaesthesiologist administered deep sedation with propofol may impose avoidable risks.[53] Attempts to develop alternatives have not gone well. The propofol pro-drug fospropofol[42] received "…a person trained in general anesthesia…" only labelling leaving it without users given anaesthesiologists preference for propofol. An editorial in Chest advised "It should be kept in mind that fospropofol is a different drug than propofol and that fospropofol is not a general anesthetic. Based on the available data, fospropofol appears to be safe

for moderate sedation and should not require anesthesia monitoring."[54] How things would have transpired had non-anaesthesiologist labelling been permitted remains unknown.

The semi-autonomous Sedasys® system[55] was demonstrably safe and effective but lost out to in-person care delivered by an anaesthesiologist and failed commercially. The etomidate derivative ABP-700 was aimed at non-anaesthesiologist sedationists but failed in development due to excitatory effects.[41]

Reducing the environmental impact of anaesthesia

Although the environmental impact of anaesthesia has been highlighted for decades[56, 57] its reach into clinical decision making has been limited. Life Cycle Assessment[58] shows inhalational agents are considerably more destructive than propofol and the abandonment of desflurane has been recommended.[59] Presumably intravenous agents also sit within a hierarchy of impact/virtue and further work is needed to characterise current and developmental injectable hypnotics.

Can we improve outcomes from cancer surgery through anaesthetic choice?

The potential for anaesthetic agents to influence outcomes after cancer surgery has been suggested.[60] In a large non-randomised series at a major UK cancer centre, mortality was lower after anaesthesia maintained with propofol than with sevoflurane or isoflurane.[61] However, this and other reports are based on retrospective analysis of routinely collected data, accordingly they can only be considered hypothesis generating. Properly designed randomised controlled trials are required and some are underway. Recently, differential effects of intravenous hypnotics on cancer cell biology have been demonstrated with dexmedetomidine but not midazolam promoting cancer cell survival and midazolam suppressing cancer cell migration.[62] Equally, the entire question of whether putative effects on cancer biology are meaningful to clinical practice remains unresolved.[63]

HOW WELL DO AVAILABLE HYPNOTICS MEET OUR NEEDS?

Flexibility and coverage of the perioperative workspace

Each step of the perioperative journey imposes distinct requirements for sedation/anaesthesia. In addition to procedural sedation for pre-operative investigations, hypnotics are used for premedication and induction and maintenance of anaesthesia. A minority of patients may also require sedation during transport and intensive care. The required therapeutic scope of hypnotics can be demonstrated by considering how propofol might be used at multiple stages of trauma care. Thus, a patient might require tracheal intubation in the emergency department, sedation for transport and scans, undergo surgery followed by further transport then ICU ventilation. Appropriate hypnosis for all of these can be provided with propofol albeit with caveats about haemodynamic control. Although midazolam is licensed for all these indications, Table 2, its use during induction of anaesthesia is uncommon and clinicians seeking to avoid propofol typically prefer etomidate or ketamine.

Table 2 near here

The challenge of induction

The start of anaesthesia seeks to deliver a safe transition to unconsciousness, in order to undertake surgery or deliver critical care. The highest priority is to sustain life by securing the airway and maintaining circulation whilst avoiding inappropriate haemodynamic responses, conscious awareness and adverse reactions.

Propofol has been used to induce anaesthesia in all manner of clinical circumstances. Its propensity to haemodynamic disturbance may be attenuated by judicious administration of reduced doses at slower than usual rates[64] and by co-administration of fluids, vasopressors or ketamine. Nevertheless, many anaesthesiologists look to alternative induction agents, notably etomidate[65] or ketamine,[66] for compromised patients or in emergencies. Etomidate depresses adreno-cortical function, even when used in single doses and argument persists regarding the possible adverse consequences for patients.[67-69] This anxiety comes in addition to etomidate's propensity to extraneous muscle movements and postoperative nausea and vomiting. A systematic review of ketamine in rapid

sequence induction found no important differences in comparison with other agents and the authors concluded that clinically relevant benefit or harm cannot be excluded.[66] However, a large study which randomised critically ill patients requiring intubation to ketamine 2mg kg^{-1} or etomidate 0.3mg kg^{-1} found intubation conditions were comparable but adrenocortical depression much more frequent with etomidate (Odds Ratio 6.7, 95%CI 3.5-12.7).[26]

In obstetric anaesthesia, induction of general anaesthesia for caesarean section has traditionally been based on thiopental because propofol was linked to slightly inferior Apgar scores in the neonate.[70] Thiopental has been removed from the World Health Organisation Model List of Essential Medicines and is no longer available in the USA following physician and pharmaceutical industry rejection of its use in judicial killing. In Europe and elsewhere, thiopental remains available and locally popular but repeated accidental syringe swaps[71] for antibiotic or local anaesthetic and clinician unfamiliarity have driven obstetric anaesthesiologists towards propofol.

The shortcomings of etomidate and ketamine plus clinician reluctance to use propofol in challenging cases provides a rationale to look for alternatives.

PERIOPERATIVE BENZODIAZEPINES –EXPERIENCE BEFORE REMIMAZOLAM

Benzodiazepine history

Since the introduction of chlordiazepoxide in 1960, the benzodiazepines have been used as sedatives, anxiolytics, anticonvulsants, antispasmodics and to a limited degree as anaesthetics.

Attempts at benzodiazepine anaesthesia commenced with diazepam in the 1960's.[72] McClish induced anaesthesia with diazepam and 50% nitrous oxide in 88 unselected vascular cases (n= 9, 26 and 53 for ASA grades 3, 4 and 5 respectively) including 30 requiring extracorporeal circulation and referred to "the absence of side-effects on respiratory, circulatory and autonomic nervous systems". The favourable descriptions were backed up by data with mean arterial blood pressures of 130 and 128 mmHg before and after induction.[73] However, prior to the introduction of the contemporary

lipid formulation, diazepam injection was associated with pain and thrombophlebitis.[74] The use of (water soluble) midazolam as an anaesthetic was explored at an early stage in its development and the lack of venous irritation and phlebitis combined with cardiovascular stability were considered attractive. Investigators focussed on identifying the correct induction dose of midazolam and its haemodynamic characteristics.

In 1978 Reves gave thirty unpremedicated patients midazolam 0.1, 0.15 or 0.2mg kg^{-1} and reported induction of anaesthesia, defined as loss of eyelash reflex AND loss of response to commands in 30%, 50% and 100% of patients respectively.[75] A further ten patients received diazepam 0.3mg kg^{-1} of whom nine became anaesthetised. Reves described midazolam as "…a promising drug for induction of anaesthesia". In the same year, Fragen reported a blinded comparison of midazolam, diazepam and thiopental for induction of anaesthesia.[76] Initial doses were 0.15, 0.3, and 3mg kg^{-1} respectively with supplementary doses of 25% of the initial dose if required. Midazolam produced "…cardiovascular stability (and) mild transient respiratory depression…" in contrast, thiopental caused apnoea in 14/26 patients despite the relatively small dose. Further investigation in patients with cardiovascular disease was recommended.[76]

Foster gave midazolam 0.15mg kg^{-1} as an induction agent in 20 unpremedicated volunteers. Whilst all experienced drug effects including amnesia, only 17 ceased counting and ten lost eyelash reflexes.[77] Eisenkraft and Miller recommended midazolam 0.3 mg kg^{-1} to be a realistic dose of midazolam to consistently induce anaesthesia in unpremedicated patients and noted that loss of the eyelash reflex was (in contrast to thiopental) an unreliable indicator of induction.[78]

By 1982 a critical evaluation of available benzodiazepines as candidate anaesthetics identified diazepam, flunitrazepam and midazolam as offering induction within 1-2 minutes whilst commenting that great individual variation in induction doses and long acting residual effects were problematic.[79] The authors concluded "Generally these anxiolytics and sedatives should be considered as adjuvants to general anaesthesia, but not primarily as routine induction agents. The major reasons for this

limitation are a high variability in drug response, a relatively slow onset of action and long-lasting residual effect."[79] In 1988, Nilsson[80] rehearsed the problem of post-operative drowsiness advocating the judicious use of flumazenil whilst recognising the problem of resedation.[81] Subsequently, interest in benzodiazepine maintenance of anaesthesia waned, presumably reflecting the lack of any compelling use-cases.

How benzodiazepines are used today

Problems with dependency have substantially reduced prescriptions for anxiety/depression (lorazepam and diazepam) and for night sedation (temazepam). Currently, intravenous benzodiazepine use mainly comprises procedural, perioperative or intensive care midazolam sedation, with diazepam reserved for the treatment of seizures. Low doses of oral diazepam may be prescribed for anxiety or the relief of muscle spasm.

Midazolam is the dominant hypnotic used for procedural sedation by non-anaesthesiolgists.[82] Small IV doses of midazolam are commonly given as premedication to surgical patients after initial venous access has been achieved. In addition to anxiolysis, midazolam has synergistic interactions with both propofol and the fentanyl series opioids, thereby facilitating subsequent anaesthesia – especially if due attention is given to the time to peak effect of each drug.[83]

Midazolam still enjoys limited use for induction of anaesthesia in patients with haemodynamic compromise. Midazolam maintenance of anaesthesia has not been adopted. Recently, the use of remimazolam with remifentanil, to induce and maintain anaesthesia was reported.[84]

The lack of haemodynamic depression is a welcome characteristic of benzodiazepines and in consequence their use to sedate critically ill patients has been common for decades. Whilst midazolam has superseded lorazepam and diazepam in the ICU, it was initially considered inferior to propofol.[85] Midazolam infusion on ICU may be associated with slow recovery – perhaps due to

altered kinetics[86] or accumulation of active metabolites. Tolerance and tachyphylaxis to midazolam sedation is well recognised.[87]

When compared with midazolam, propofol provides superior titration of ICU sedation and faster recovery when sedation is discontinued.[85] However concerns over hypotension, lipid accumulation and the propofol infusion syndrome limit its applicability to unstable patients and those requiring long term sedation. Dexmedetomidine is non-inferior to midazolam for on-target sedation but causes more hypotension.[88]

Slow recovery of consciousness following prolonged sedation of intensive care patients with midazolam led to consideration of volatile anaesthetics as an alternative[89] however equipment issues and the need for scavenging have limited uptake. In addition, sedation with sevoflurane has been associated with diabetes insipidus.[90] Accordingly, IV sedation is preferred.

Are benzodiazepines anaesthetics?

The 1963 definition of MAC[91] relied on the ability of a single inhaled agent to produce immobility that persists without response to a surgical incision. With the exception of ketamine, this characteristic is not shared by intravenous hypnotics except at inappropriate doses with consequential cardiorespiratory depression or protracted recovery. Accordingly, it may be argued that none of propofol, etomidate, the barbiturates or the benzodiazepines are truly anaesthetics. Rather, they are the hypnotic component of a balanced anaesthesia technique. However, this nuanced approach is at odds with common parlance and chapters on 'Intravenous Anesthetics' are standard in major textbooks.[92, 93] Further, use of the terms 'induction of anaesthesia' and 'anaesthesia' with regard to intravenous hypnotics (with or without concomitant opioid) is well established in clinical practice and in medical literature.

Do benzodiazepines induce an anaesthetic state? Certainly, their EEG effects differ from those of inhaled anaesthetics. Volatile agents[94] and propofol[95] progressively delay and flatten the mid-latency

auditory evoked response, an effect that is reversible by surgical stimulation.[96] In contrast, midazolam,[97] diazepam and flunitrazepam have lesser effects with persistence of the evoked response during apparently satisfactory anaesthesia.[98] In patients undergoing cardiac surgery, evoked potentials were preserved in those anaesthetized with flunitrazepam and fentanyl whereas they were abolished when anaesthesia was maintained with isoflurane or propofol.[99] When a combination of midazolam and alfentanil was used to anaesthetize women for major gynaecological surgery there was a high level of responsiveness (72%) as determined by the Isolated Forearm Technique and 3/32 had some recall of intra-operative events.[100]

Midazolam produces a moderate depression of the Bispectral Index, BIS.[101] This likely reflects optimisation for benzodiazepines of the proprietary BIS algorithm rather than implying a common effect on the EEG with volatile anaesthetics. When adult patients were dosed with midazolam 0.2 or 0.3mg kg^{-1}, BIS values remained around 60 and there was no correlation between BIS and predicted effect site midazolam concentration.[102] The EEG effects of benzodiazepines are predominantly a monotonic beta-activation,[103, 104] especially in frontal areas and these effects map to higher BIS values.[102] In rats, the EEG response to benzodiazepines in the 11.5-30 Hz frequency range correlates with benzodiazepine receptor affinity confirming it as a direct measure of GABAergic inhibitory effect.[105] Deeper BIS levels relate to EEG burst-suppression[106] which is not a common benzodiazepine effect. Remimazolam also depresses BIS and the effect is synergistic with that of remifentanil.[107] In contrast, the BIS is little affected by ketamine, nitrous oxide or xenon - anaesthetics with atypical EEG effects.

CAN REMIMAZOLAM MEET OUR STATED GOALS?

Remimazolam is an archetypal 'soft'[33] drug, structurally similar to midazolam with an added ester linkage, Figure 1. The activity of remimazolam is terminated by esterase hydrolysis.

Figure 1 near here

Limited data is available to characterise this new hypnotic. Volunteer studies and clinical trials suggest that remimazolam pharmacodynamics are broadly similar to midazolam.

Maintaining arterial blood pressure

When 54 volunteers received single doses of remimazolam up to 0.35 mg kg^{-1}, there were no reports of hypotension.[108] Modest increases in heart rate occurred in some individuals in the higher dose groups. In patients sedated with remimazolam for colonoscopy,[109] upper GI endoscopy[110] and bronchoscopy,[111] arterial blood pressure and heart rate were stable in the remimazolam treatment groups.

Maintaining ventilation

In comparison to propofol, benzodiazepines produce minimal respiratory depression[112] although diazepam and midazolam can cause increased $PaCO_2$ when given in large doses. Further, if midazolam is dosed inappropriately in combination with fentanyl, severe respiratory depression and apnoea may occur.[113] When volunteers received midazolam (0.05 mg kg^{-1}) and fentanyl (2.0 mcg kg^{-1}) or the same doses of midazolam or fentanyl alone, minute ventilation and the ventilatory response to carbon dioxide were unchanged after midazolam alone but profoundly depressed by fentanyl, with or without midazolam.[114] Early clinical experience with midazolam was characterised by multiple deaths, typically in elderly patients. In 2008 the UK National Patient Safety Agency reviewed 1,529 patient safety incident reports and identified failure to properly titrate midazolam, the use of high strength midazolam formulations and reliance on routine reversal with flumazenil as areas in which practice could be improved.[115]

Perhaps in consequence, smaller doses are typically selected in contemporary sedation practice. In a UK snapshot survey of 360 patients sedated in 6 hospitals the most frequent sedative combination was midazolam and fentanyl with median doses of fentanyl 50mcg and midazolam 2mg.[82] Importantly, apnoea and airway obstruction are less common with midazolam than with propofol.[116]

In volunteers given remimazolam,[108] respiration was maintained and only two episodes of desaturation were noted and both managed with simple measures. In studies of remimazolam sedation for colonoscopy,[109] upper GI endoscopy[110] and bronchoscopy,[111] there were few episodes of respiratory depression or hypoxia and the incidence was similar to or less than with midazolam.

Avoiding neurotoxicity

Remimazolam binds with high affinity to the $GABA_A$ receptor whilst having no measurable affinity for any of a panel of 40 other receptors and ion channels.[117] Patch clamping experiments demonstrated remimazolam enhancement of GABA effect similar to that caused by midazolam with marginally greater potency and maximum effect.[117] Remimazolam's principal metabolite CNS-7054 binds with 410 times lower affinity than its parent and is considered inactive.[117] There is therefore, to date, no pharmacological reason to expect remimazolam's effects to be qualitatively different from those of midazolam.

As a development compound, basic science investigation of remimazolam has necessarily focussed on regulatory requirements. Future work could usefully consider remimazolam's profile with regard to the possible cellular determinants of neonatal neurotoxicity, delirium, postoperative cognitive impairment and cancer cell behaviours.

Rapid onset and fast offset

Initial pharmacodynamic modelling of remimazolam's hypnotic effect was developed using Bispectral Index and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) as measures of effect.[118] The authors concluded that the population pharmacodynamic parameters, k_{e0}, IC_{50}, and Hill coefficient, were broadly comparable with midazolam. Subsequently the original recirculatory and weight independent pharmacokinetic model has been superseded by a conventional mamillary model.[107] Simulations of time to peak effect and context sensitive half-time illustrate the swifter onset and offset of remimazolam effect in comparison to midazolam. Briefly, onset of remimazolam

effect is slightly slower than propofol but materially faster than midazolam, Figure 2. Swift hydrolysis of remimazolam is reflected in its context-sensitive half-time, offset is faster than midazolam but more like propofol than remifentanil, Figures 2 & 3.

Figure 2 near here

Figure 2 presents simulations of CNS effect of the common opioids fentanyl,[119] alfentanil[120] and remifentanil[121] and hypnotics currently indicated for procedural sedation - midazolam[122] remimazolam[107] and propofol.[123] In each case the time to peak effect site concentration (and therefore peak effect) of a bolus is presented together with its subsequent diminution due to redistribution and metabolism. Figure 3 presents simulated Context Sensitive Half Times.

Figure 3 near here

Alignment with existing practice

The USA licence for procedural sedation with remimazolam does not reserve the drug for anaesthesiologists. Although the safety of midazolam (when used appropriately) for procedural sedation is now well established, that experience is not automatically transferrable to remimazolam whose safety envelope requires demonstration on its own merits rather than as an entitlement of all benzodiazepines. The USA labelling for remimazolam in procedural sedation includes Boxed Warnings regarding staff training, equipment availability and the risks of interaction with opioids and other hypnotics. Remimazolam provides quicker onset and offset of sedation than midazolam,[109] however, comparisons with propofol are awaited. If proceduralist and patient satisfaction with non-anaesthesiologist remimazolam sedation is close that achieved by anaesthesiologist provided propofol then a significant change in practice might ensue.[48] Crucially, respect for patient safety demands a cautious introduction of the new hypnotic.

Procedural sedation with remimazolam.

When Rex compared midazolam and remimazolam for procedural sedation in patients undergoing colonoscopy,[109] the midazolam was administered in accordance with the published (FDA approved) prescribing information. The initial dose of remimazolam was 5 mg over 1 min followed if necessary by top-up doses of 2.5 mg. Onset of sedation (time to MOAA/S score of 3) was shorter with remimazolam (5.1 (3.82) min) than for midazolam (16.9 (6.31) min), mean (SD). Recovery (time from end of procedure to fully alert) was earlier with remimazolam (7.35 (5.78) min) than with midazolam (15.84 (11.57) min). A third group received placebo followed by (if necessary) midazolam doses at clinician preference. These patients received more midazolam (4.30 (1.62) mg) with quicker onset and slower recovery than those receiving the approved dosing scheme (1.75 mg initial/1 mg top-up dose for a patient aged <60 years, and 1.0 mg/0.5 mg for those aged 60 years, debilitated, or chronically ill) maximum three doses.

Remimazolam based anaesthesia

The development of remimazolam offers the opportunity to revisit benzodiazepine based anaesthesia. Doi[84] compared total intravenous anaesthesia based on remimazolam (no bolus, infusion started at 6 or 12 mg kg^{-1} hr^{-1}) or propofol (2.0-2.5 mg kg^{-1} then 4-10 mg kg^{-1} hr^{-1}) in 375 patients of ASA Physical Status 1-2. Propofol was injected over 1 min (i.e. compliant with the licensed prescribing information) whereas the remimazolam was infused more slowly (up to 2.5 min). All patients received remifentanil 0.25-0.5 mcg kg^{-1} min^{-1}. Mean (SD) times for loss of consciousness were slower for patients receiving TIVA with remimazolam (6 or 12 mg kg^{-1} hr^{-1}) than for propofol (102.0 (26.6), 88.7 (22.7) vs 78.7 (38.4) sec) respectively. Hypotensive events were more frequent with propofol than with remimazolam during all phases of the anaesthetic. The requirement for pressors was 64% (propofol) vs 40%/43% (two remimazolam groups). PONV was infrequent in all groups. A subsequent study enrolled 67 patients of ASA Physical Status 3 using the same remimazolam dosing for induction of anaesthesia and concluded "…clear evidence of an excellent safety and tolerability of remimazolam in a vulnerable patient population".[124] Both studies

used the Brice Questionnaire to elicit incidents of awareness however none were reported. A recently completed randomised controlled trial comparing propofol/remifentanil and remimazolam/remifentanil anaesthesia (ClinicalTrials.gov Identifier: NCT03661489) in 424 patients, ASA 3-4 at 20 European sites is currently unpublished. This and future studies will clarify the role of remimazolam in the maintenance of general anaesthesia. Looking ahead we need data to understand its impact, if any, on key clinical indicators: infection, stroke, death, ICU admission, readmission to hospital and length of stay.[125]

To date, remimazolam has not been evaluated for induction of anaesthesia prior to inhalational maintenance. Since remimazolam can provide the hypnotic underpinning of total intravenous anaesthesia, its use as an induction agent might be presumed. However, consideration of the onset of an inhaled agent and the offset of an IV induction agent implies the possibility of an interim period of inadequate anaesthesia unless proper attention is given to the transition. Thus, we need a properly conducted clinical investigation to demonstrate that the technique is practicable, reliable and safe. If the basic safety of using remimazolam in this way can be established then further work to refine the technique for rapid sequence induction, patients with significant co-morbidities and in emergencies is needed.

Recovery from anaesthesia and reversal with flumazenil

Reversibility by flumazenil is a class characteristic of all benzodiazepines and flumazenil reversal of midazolam sedation/anaesthesia has been useful after short procedures including cardioversion.[126] Flumazenil reversal is typically in response to overdosage whether self-administered or iatrogenic. The UK Summary of Product Characteristics for flumazenil (www.medicines.org.uk) includes hypertension, tachycardia, convulsions and anxiety as possible adverse events which might be precipitated by flumazenil reversal of benzodiazepine action. However, the same guidance also notes “Any side-effects associated with flumazenil usually subside rapidly without the need for special treatment” and mentions that anxiety and convulsions typically relate to long-term exposure

to benzodiazepines and previous epilepsy respectively. A synthesis of data from thirteen placebo controlled studies of flumazenil treatment for the management of suspected benzodiazepine intoxication identified that flumazenil caused significantly more adverse events than placebo and concluded "Flumazenil should not be used routinely, and the harms and benefits should be considered carefully in every patient".[127] However this work was criticised because of the very large flumazenil doses administered with smaller and titrated doses described as safer.[128]

Routine use of flumazenil to reverse hypnotic effect at the end of midazolam anaesthesia lasting over 90 minutes was associated with some instances of re-sedation and recovery scores were inferior to those after propofol anaesthesia.[129] In practice therefore, concerns about re-sedation have deterred routine midazolam general anaesthesia with flumazenil reversal.

To date, human experience of flumazenil reversal of remimazolam is confined to a few volunteers and some rescues during clinical trials. Consequent from its susceptibility to esterase hydrolysis and inactive metabolite, remimazolam is short acting. Certainly it is shorter acting than midazolam. Nevertheless, Doi[84] reported significantly slower median (range) times for extubation (15.5 (3-104), 18.0 (2-58) and 12.0 (3-42) min) and recovery room discharge (25.0 (4-144), 25.0 (5-125) and 16.0 (5-87) min) for patients receiving TIVA with remifentanil and remimazolam (6 or 12 mg kg^{-1} hr^{-1}) than for propofol respectively. Flumazenil was administered to 9% of the remimazolam group who then awoke within two minutes. Resedation was not reported. Thus, in comparison with propofol, the relative haemodynamic stability of remimazolam comes at a cost of (minimally) delayed loss of consciousness but materially slower recovery. Further work may determine whether the latter constraint can be diminished by judicious use of routine or semi-routine flumazenil.

Intensive care sedation

The potential application of remimazolam to intensive care sedation has already been identified[130] and it has been used to sedate pigs for 28 days.[131] A bioreactor study using human hepatocytes showed no adverse changes in remimazolam metabolism over a five day period.[132] However there

remains a need for it to be assessed in proper randomized clinical trials against the present standard drugs such as propofol, midazolam, and dexmedetomidine.

When a short-acting compound is used for long periods the cost of drug acquisition becomes a major obstacle and this will likely hinder development of remimazolam as an ICU sedative, at least in the first instance. Further, the successful (licensed) use of dexmedetomidine for the same indication at a time when there is great pressure to reduce sedation of ventilated patients may inhibit exploration of this role. Delirium is a recognised and unwelcome adverse outcome from intensive care sedation with midazolam/morphine and dexmedetomidine may be preferable.[133, 134] However, dexmedetomidine precipitates more adverse events, notably hypotension and bradycardia.[135] Recently ketamine has been re-evaluated as an ICU sedative and its use may reduce the incidence of delirium.[136] The relevance of remimazolam's rapid elimination to benzodiazepine induced delirium remains to be determined.

Dependency, abuse and inappropriate use

Regulators are sensitised to patients becoming dependent on prescribed medication and the US Food and Drug Administration recently issue a cautionary notice (Boxed Warning) for all benzodiazepines.[137] Emphasising "…the serious risks of abuse, addiction, physical dependence, and withdrawal reactions…" they now advise prescribers to "Limit the dosage and duration of each medicine to the minimum needed to achieve the desired clinical effect".[137] Clearly driven by adverse experiences from long-term prescribing, the relevance of this to procedural sedation and perioperative use is unclear.

Anaesthetic drugs are subject to abuse by anaesthesiologists and others. Hypnotics (20%) are second only to opioids (55%) as abused by staff with propofol, ketamine and benzodiazepines all implicated.[138] Cumulative incidence of abuse is 1.6% over 30 years amongst graduates of US anaesthesia residency programmes.[138] Propofol abuse is very dangerous because of the drugs steep dose-response relationship. Individuals have both committed suicide and been murdered using

propofol.[139] Nasally administered remimazolam is absorbed and effective but both powdered drug and its solution caused unpleasant local effects (severe pain, burning, irritation)[140] so self-administration by this route seems unlikely. It may be anticipated that those who abuse midazolam by injection may be drawn to inject remimazolam injection. Remimazolam undergoes high first-pass metabolism with consequentially near zero oral bioavailability rendering it ineffective for oral maladministration in drug-facilitated sexual assaults.[141]

Pre-hospital administration of hypnotics, especially ketamine, is a valued component of emergency care[142] however increasing use of ketamine for restraint, often at the behest of police, has been criticised[143] but may be safe.[142] Although the hypnotic effects of remimazolam occur sooner and have a briefer duration that those of midazolam, these differences should not imply licence for inappropriate pharmacological improvisation. The unpredictability of midazolam effect is illustrated by its association with adverse events when used as a chemical restraint.[144] In contrast midazolam was the chosen hypnotic in bungled judicial killings where it formed part of a supposedly lethal cocktail of IV injections.[145] In general terms, clinical use of remimazolam may sensibly be restricted to those who have received proper training in its use, possess the necessary competencies to manage its effects and do so in an appropriate environment.

Is remimazolam an ideal intravenous anaesthetic?

Remimazolam development has proceeded slowly since we asked whether it is simply a "Me-Too".[130] In addition to use for procedural sedation,[109] Doi and colleagues[84] have demonstrated its potential as a flexible intravenous anaesthetic and identified areas for future development. However, for a new agent, safety and efficacy is not enough. If clinicians are to adopt a method (in this instance a new hypnotic), they need a clear reason to do so, typically in terms of patient outcomes, patient safety, quality of patient experience or health economics. At present, the possibility of reduced perioperative hypotension may be the most rational reason for considering remimazolam (with opioid) for induction and maintenance of anaesthesia.

IS THERE ANYTHING ELSE ON THE HORIZON?

Adaptation of the propofol molecule remains a focus for drug discovery. Ciprofol (HSK3486) is a propofol analogue formulated in an oil-in-water emulsion. Its general characteristics are similar to those of propofol[146] with a decreased frequency of pain on injection,[147] possibly due to reduced concentrations of free drug in plasma. Ciprofol is currently undergoing late stage clinical trials for procedural sedation[148] and trial registries indicate studies in general anaesthesia however none are yet reported. Given that pain on injection of propofol may be attenuated by co-administration of lidocaine, the case for ciprofol remains unproven given the continued use of lipid formulation and a similar adverse haemodynamic impact to that of propofol.

Alfaxalone is an established IV hypnotic which has been reformulated in 7-sulfobutylether beta-cyclodextrin as PHAXANCD™.[149] In volunteers, PHAXANCD™ produced an hypnotic effect comparable to propofol with less haemodynamic disturbance.[13] Preliminary reports of a small (15 patient) double-blinded comparison with propofol in patients undergoing hip replacement suggest that the favourable characteristics described in volunteers are repeated in patient care.[150]

Conclusion

A great deal has changed since the overviews of Whitwam and Dundee in 1978 and 1985 respectively. Our patients are older and frailer and our surgeons more ambitious. Anaesthesia has morphed into perioperative medicine and new priorities have emerged. Our mainstream hynotics – propofol, midazolam, etomidate and ketamine continue to serve us well but fall short of ideal. Revisiting benzodiazepine anaesthesia (if it exists…) seems logical but we need to define its merits and boundaries with robust evidence.

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RS conceived and wrote the first draft. Revised the manuscript. Guarantor.

PG revised the manuscript, contributed to simulations

AR-J revised the manuscript, contributed to simulations

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RS Consultant to Paion, Germany, the manufacturers of remimazolam. Consultant to Altus, Canada. Consultant to Medtronic, UK.

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References

1 Dundee JW. Intravenous anaesthesia and the need for new agents. *Postgrad Med J* 1985; **61 Suppl 3**: 3-6
2 Whitwam J. Adverse reactions to iv induction agents. *Br J Anaesth* 1978; **50**: 677-87
3 Südfeld S, Brechnitz S, Wagner JY, et al. Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. *Br J Anaesth* 2017; **119**: 57-64
4 Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen Definition. Literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007; **107**: 213-20
5 McEvoy MD, Gupta R, Koepke EJ, et al. Perioperative Quality Initiative consensus statement on postoperative blood pressure, risk and outcomes for elective surgery. *Br J Anaesth* 2019; **122**: 575-86
6 Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth* 2018; **121**: 706-21
7 Ke JXC, George RB, Beattie WS. Making sense of the impact of intraoperative hypotension: from populations to the individual patient. *Br J Anaesth* 2018; **121**: 689-91
8 Whalin M, Halenda K, Haussen D, et al. Even small decreases in blood pressure during conscious sedation affect clinical outcome after stroke thrombectomy: an analysis of hemodynamic thresholds. *Am J Neuroradiol* 2017; **38**: 294-8
9 Johnson KB, Egan TD, Kern SE, et al. The Influence of Hemorrhagic Shock on Propofol: A Pharmacokinetic and Pharmacodynamic Analysis. *Anesthesiology* 2003; **99**: 409-20
10 Honan DM, Breen PJ, Boylan JF, McDonald NJ, Egan TD. Decrease in Bispectral Index Preceding Intraoperative Hemodynamic Crisis: Evidence of Acute Alteration of Propofol Pharmacokinetics. *Anesthesiology* 2002; **97**: 1303-5
11 April MD, Arana A, Schauer SG, et al. Ketamine Versus Etomidate and Peri-intubation Hypotension: A National Emergency Airway Registry Study. *Acad Emerg Med* 2020; **27**: 1106-15
12 Englehart MS, Allison CE, Tieu BH, et al. Ketamine-based total intravenous anesthesia versus isoflurane anesthesia in a swine model of hemorrhagic shock. *J Trauma* 2008; **65**: 901-8; discussion 8-9
13 Monagle J, Siu L, Worrell J, Goodchild CS, Serrao JM. A Phase 1c Trial Comparing the Efficacy and Safety of a New Aqueous Formulation of Alphaxalone with Propofol. *Anesth Analg* 2015; **121**: 914-24
14 Goodchild CS, Serrao JM, Sear JW, Anderson BJ. Pharmacokinetic and Pharmacodynamic Analysis of Alfaxalone Administered as a Bolus Intravenous Injection of Phaxan in a Phase 1 Randomized Trial. *Anesth Analg* 2020; **130**: 704-14
15 Hinkelbein J, Lamperti M, Akeson J, et al. European Society of Anaesthesiology and European Board of Anaesthesiology guidelines for procedural sedation and analgesia in adults. *Eur J Anaesthesiol* 2018; **35**: 6-24
16 Checketts M, Alladi R, Ferguson K, et al. Recommendations for standards of monitoring during anaesthesia and recovery 2015: Association of Anaesthetists of Great Britain and Ireland. *Anaesthesia* 2016; **71**: 85-93
17 Apfelbaum J, Gross J, Connis R, et al. Practice guidelines for moderate procedural sedation and analgesia 2018: a report by the American Society of Anesthesiologists Task Force on moderate procedural sedation and analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American dental association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. *Anesthesiology* 2018; **128**: 437-79
18 McKeating K, Bali I, Dundee J. The effects of thiopentone and propofol on upper airway integrity. *Anaesthesia* 1988; **43**: 638-40
19 Chia YY, Lee SW, Liu K. Propofol causes less postoperative pharyngeal morbidity than thiopental after the use of a laryngeal mask airway. *Anesth Analg* 2008; **106**: 123-6
20 Sengupta J, Sengupta M, Nag T. Agents for facilitation of laryngeal mask airway insertion: a comparative study between thiopentone sodium and propofol. *Ann Afr Med* 2014; **13**: 124-9

21 Sato T, Kato Y, Yamamoto M, Nishiwaki K. Novel anesthetic agent remimazolam as an alternative for the asleep-awake-asleep technique of awake craniotomy. *JA Clinical Reports* 2020; **6**: 92
22 Sneyd JR, O'Sullivan E. Tracheal intubation without neuromuscular blocking agents: is there any point? *Br J Anaesth* 2010; **104**: 535-7
23 Ing C, Jackson WM, Zaccariello MJ, et al. Prospectively assessed neurodevelopmental outcomes in studies of anaesthetic neurotoxicity in children: a systematic review and meta-analysis. *Br J Anaesth* 2021; **126**: 433-44
24 McCann ME, Soriano SG. Does general anesthesia affect neurodevelopment in infants and children? *BMJ* 2019; **367**: l6459
25 Jevtovic-Todorovic V, Absalom AR, Blomgren K, et al. Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar. *Br J Anaesth* 2013; **111**: 143-51
26 Jabre P, Combes X, Lapostolle F, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet* 2009; **374**: 293-300
27 Oddo M, Crippa IA, Mehta S, et al. Optimizing sedation in patients with acute brain injury. *Crit Care* 2016; **20**: 128
28 Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth* 2018; **121**: 1005-12
29 Curtis MS, Forman NA, Donovan AL, Whitlock EL. Postoperative delirium: why, what, and how to confront it at your institution. *Curr Opin Anesthesiol* 2020; **33**: 668-73
30 American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2019; **67**: 674-94
31 Krzych L J, Pluta MP, Putowski Z, Czok M. Investigating Association between Intraoperative Hypotension and Postoperative Neurocognitive Disorders in Non-Cardiac Surgery: A Comprehensive Review. *J Clin Med* 2020; **9**: 3183
32 Sahinovic MM, Struys MMRF, Absalom AR. Clinical Pharmacokinetics and Pharmacodynamics of Propofol. *Clin Pharmacokinet* 2018; **57**: 1539-58
33 Egan TD. Is anesthesiology going soft?: trends in fragile pharmacology. *Anesthesiology* 2009; **111**: 229-30
34 Egan TD, Obara S, Jenkins TE, et al. AZD-3043: a novel, metabolically labile sedative-hypnotic agent with rapid and predictable emergence from hypnosis. *Anesthesiology* 2012; **116**: 1267-77
35 Ball AJ, Campbell JA, Riley SA. Nitrous oxide use during colonoscopy: a national survey of English screening colonoscopists. *Frontline Gastroenterol* 2014; **5**: 254-9
36 Borrat X, Ubre M, Risco R, et al. Computerized tests to evaluate recovery of cognitive function after deep sedation with propofol and remifentanil for colonoscopy. *J Clin Monit Comput* 2019; **33**: 107-13
37 Mertens MJ, Vuyk J, Parivar K, Engbers FH, Burm AG, Bovill JG. Pharmacodynamic interaction of eltanolone and alfentanil during lower abdominal surgery in female patients. *Br J Anaesth* 1999; **83**: 250-2
38 Sneyd JR, Wright PM, Cross M, et al. Administration to humans of ORG 21465, a water soluble steroid i.v. anaesthetic agent. *Br J Anaesth* 1997; **79**: 427-32
39 Rigby-Jones AE, Sneyd JR, Vijn P, Boen P, Cross M. First administration to man of Org 25435, an intravenous anaesthetic: A Phase 1 Clinical Trial. *BMC Anesthesiol* 2010; **10**: 10
40 Norberg A, Koch P, Kanes SJ, et al. A Bolus and Bolus Followed by Infusion Study of AZD3043, an Investigational Intravenous Drug for Sedation and Anesthesia: Safety and Pharmacodynamics in Healthy Male and Female Volunteers. *Anesth Analg* 2015; **121**: 894-903
41 Valk BI, Absalom AR, Meyer P, et al. Safety and clinical effect of i.v. infusion of cyclopropyl-methoxycarbonyl etomidate (ABP-700), a soft analogue of etomidate, in healthy subjects. *Br J Anaesth* 2018; **120**: 1401-11

42 Bergese SD, Dalal P, Vandse R, et al. A double-blind, randomized, multicenter, dose-ranging study to evaluate the safety and efficacy of fospropofol disodium as an intravenous sedative for colonoscopy in high-risk populations. *Am J Ther* 2013; **20**: 163-71
43 Borgeat A, Wilder-Smith OHG, Saiah M, Rifat K. Subhypnotic Doses of Propofol Possess Direct Antiemetic Properties. *Anesth Analg* 1992; **74**: 539-41
44 Sneyd JR, Carr A, Byrom WD, Bilski AJ. A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhalational agents. *Eur J Anaesthesiol* 1998; **15**: 433-45
45 Grant MC, Kim J, Page AJ, Hobson D, Wick E, Wu CL. The Effect of Intravenous Midazolam on Postoperative Nausea and Vomiting: A Meta-Analysis. *Anesth Analg* 2016; **122**: 656-63
46 Ulsamer B, Doenicke A, Laschat M. [Propofol in comparison with etomidate for the induction of anesthesia]. *Anaesthesist* 1986; **35**: 535-42
47 Krigel A, Chen L, Wright JD, Lebwohl B. Substantial Increase in Anesthesia Assistance for Outpatient Colonoscopy and Associated Cost Nationwide. *Clin Gastroenterol Hepatol* 2019; **17**: 2489-96
48 Goudra B, Singh PM, Lichtenstein GR. Medical, Political, and Economic Considerations for the Use of MAC for Endoscopic Sedation: Big Price, Little Justification? *Dig Dis Sci* 2020; **65**: 2466-72
49 Knape JT, Adriaensen H, van Aken H, et al. Guidelines for sedation and/or analgesia by non-anaesthesiology doctors. *Eur J Anaesthesiol* 2007; **24**: 563-7
50 Barends CRM, Driesens MK, van Amsterdam K, Struys M, Absalom AR. Moderate-to-Deep Sedation Using Target-Controlled Infusions of Propofol and Remifentanil: Adverse Events and Risk Factors: A Retrospective Cohort Study of 2937 Procedures. *Anesth Analg* 2020; **131**: 1173-83
51 Sieg A, bng-Study-Group, Beck S, et al. Safety analysis of endoscopist-directed propofol sedation: a prospective, national multicenter study of 24 441 patients in German outpatient practices. *J Gastroenterol Hepatol* 2014; **29**: 517-23
52 Perel A. Non-anaesthesiologists should not be allowed to administer propofol for procedural sedation: a Consensus Statement of 21 European National Societies of Anaesthesia. *Eur J Anaesthesiol* 2011; **28**: 580-4
53 Sneyd JR. Making sense of propofol sedation for endoscopy. *Br J Anaesth* 2017; **118**: 6-7
54 Jantz MA. The Old and the New of Sedation for Bronchoscopy. *Chest* 2009; **135**: 4-6
55 Pambianco DJ, Whitten CJ, Moerman A, Struys MM, Martin JF. An Assessment of Computer-Assisted Personalized Sedation: a sedation delivery system to administer propofol for gastrointestinal endoscopy. *Gastrointest Endosc* 2008; **68**: 542-7
56 Sneyd JR, Montgomery H, Pencheon D. The anaesthetist and the environment. *Anaesthesia* 2010; **65**: 435-7
57 Yeoh CB, Lee KJ, Coric V, Tollinche LE. Simple Green Changes for Anesthesia Practices to Make a Difference. *EC Clin Med Case Rep* 2020; **3**: 1-6
58 Sherman J, Le C, Lamers V, Eckelman M. Life cycle greenhouse gas emissions of anesthetic drugs. *Anesth Analg* 2012; **114**: 1086-90
59 Shelton CL, Sutton R, White SM. Desflurane in modern anaesthetic practice: walking on thin ice(caps)? *Br J Anaesth* 2020; **125**: 852-6
60 Perry NJS, Buggy D, Ma D. Can Anesthesia Influence Cancer Outcomes After Surgery? *JAMA Surg* 2019; **154**: 279-80
61 Wigmore TJ, Mohammed K, Jhanji S. Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology* 2016; **124**: 69-79
62 Wang C, Datoo T, Zhao H, et al. Midazolam and Dexmedetomidine Affect Neuroglioma and Lung Carcinoma Cell Biology In Vitro and In Vivo. *Anesthesiology* 2018; **129**: 1000-14
63 Wall T, Sherwin A, Ma D, Buggy DJ. Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes: a narrative review. *Br J Anaesth* 2019; **123**: 135-50
64 Peacock JE, Lewis RP, Reilly CS, Nimmo WS. Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients. *Br J Anaesth* 1990; **65**: 346-52

65 Aggarwal S, Goyal VK, Chaturvedi SK, Mathur V, Baj B, Kumar A. A comparative study between propofol and etomidate in patients under general anesthesia. *Braz J Anesthesiol* 2016; **66**: 237-41
66 Baekgaard JS, Eskesen TG, Sillesen M, Rasmussen LS, Steinmetz J. Ketamine as a Rapid Sequence Induction Agent in the Trauma Population: A Systematic Review. *Anesth Analg* 2019; **128**: 504-10
67 Komatsu R, You J, Mascha EJ, Sessler DI, Kasuya Y, Turan A. Anesthetic Induction with Etomidate, Rather than Propofol, Is Associated with Increased 30-Day Mortality and Cardiovascular Morbidity After Noncardiac Surgery. *Anesth Analg* 2013; **117**: 1329-37
68 McPhee LC, Badawi O, Fraser GL, et al. Single-dose etomidate is not associated with increased mortality in ICU patients with sepsis: analysis of a large electronic ICU database. *Crit Care Med* 2013; **41**: 774-83
69 Upadhye S, Cyganik O. Is Single-Dose Etomidate Induction Safe in Emergency Intubation of Critically Ill Patients? *Ann Emerg Med* 2016; **67**: 399-400
70 Celleno D, Capogna G, Tomassetti M, Costantino P, Di Feo G, Nisini R. Neurobehavioural effects of propofol on the neonate following elective Caesarean section. *Br J Anaesth* 1989; **62**: 649-54
71 Yentis SM, Randall K. Drug errors in obstetric anaesthesia: a national survey. *Int J Obstet Anesth* 2003; **12**: 246-9
72 Fox GS, Wynands JE, Bhambhami M. A clinical comparison of diazepam and thiopentone as induction agents to general anaesthesia. *Can Anaesth Soc J* 1968; **15**: 281-90
73 McClish A. Diazepam as an intravenous induction agent for general anaesthesia. *Can Anaesth Soc J* 1966; **13**: 562-75
74 Hegarty JE, Dundee JW. Sequelae after the intravenous injection of three benzodiazepines--diazepam, lorazepam, and flunitrazepam. *Br Med J* 1977; **2**: 1384-5
75 Reves J, Corssen G, Holcomb C. Comparison of two benzodiazepines for anaesthesia induction: midazolam and diazepam. *Can Anaesth Soc J* 1978; **25**: 211-4
76 Fragen RJ, Gahl F, Caldwell N. A water-soluble benzodiazepine, RO21-3981, for induction of anesthesia. *Anesthesiology* 1978; **49**: 41-3
77 Forster A, Gardaz J-P, Suter P, Gemperle M. IV midazolam as an induction agent for anaesthesia: a study in volunteers. *Br J Anaesth* 1980; **52**: 907-11
78 Eisenkraft J, Miller R. Induction dose of midazolam. *Brit J Anaesth* 1981; **53**: 317-8
79 Kanto J, Klotz U. Intravenous benzodiazepines as anaesthetic agents: pharmacokinetics and clinical consequences. *Acta Anaesthesiol Scand* 1982; **26**: 554-69
80 Nilsson A, Persson MP. Total intravenous anaesthesia--is there a future for midazolam? *Acta Anaesthesiol Scand Suppl* 1988; **87**: 6-10
81 Nilsson A, Persson MP, Hartvig P. Effects of the benzodiazepine antagonist flumazenil on postoperative performance following total intravenous anaesthesia with midazolam and alfentanil. *J Clin Anesth* 1995; **7**: 125
82 SWARM. Sedation practice in six acute hospitals - a snapshot survey. *Anaesthesia* 2015; **70**: 407-15
83 Ong LB, Plummer JL, Waldow WC, Owen H. Timing of midazolam and propofol administration for co-induction of anaesthesia. *Anaesth Intensive Care* 2000; **28**: 527-31
84 Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. *J Anesth* 2020; **34**: 543-53
85 Aitkenhead AR, Pepperman ML, Willatts SM, et al. Comparison of propofol and midazolam for sedation in critically ill patients. *Lancet* 1989; **2**: 704-9
86 Tse AHW, Ling L, Lee A, Joynt GM. Altered Pharmacokinetics in Prolonged Infusions of Sedatives and Analgesics Among Adult Critically Ill Patients: A Systematic Review. *Clin Ther* 2018; **40**: 1598-615 e2
87 Shafer A. Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. *Crit Care Med* 1998; **26**: 947-56

88 Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012; **307**: 1151-60
89 Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. *BMJ* 1989; **298**: 1277-80
90 Cabibel R, Gerard L, Maiter D, Collin V, Hantson P. Complete Nephrogenic Diabetes Insipidus After Prolonged Sevoflurane Sedation: A Case Report of 3 Cases. *A & A Pract* 2019; **12**: 155-9
91 Merkel G, Eger EI. A Comparative Study of Halothane and Halopropane AnesthesiaIncluding Method for Determining Equipotency. *Anesthesiology* 1963; **24**: 346-57
92 Gropper MA, Miller RD, Eriksson LI, et al. *Miller's Anesthesia, 2-Volume Set E-Book. Chapter 23*. Elsevier Health Sciences, 2019
93 Barash PG, Cahalan MK, Cullen BF, et al. *Clinical Anesthesia, 8th Edition, Chapter 18*. LWW, 2017
94 Heneghan CP, Thornton C, Navaratnarajah M, Jones JG. Effect of isoflurane on the auditory evoked response in man. *Br J Anaesth* 1987; **59**: 277-82
95 Thornton C, Konieczko KM, Knight AB, et al. Effect of propofol on the auditory evoked response and oesophageal contractility. *Br J Anaesth* 1989; **63**: 411-7
96 Thornton C, Konieczko K, Jones JG, Jordan C, Dore CJ, Heneghan CP. Effect of surgical stimulation on the auditory evoked response. *Br J Anaesth* 1988; **60**: 372-8
97 Nishiyama T. Changes in the auditory evoked potentials index by induction doses of four different intravenous anesthetics. *Acta Anaesthesiol Scand* 2005; **49**: 1326-9
98 Schwender D, Klasing S, Madler C, Pöppel E, Peter K. Effects of benzodiazepines on mid-latency auditory evoked potentials. *Can J Anaesth* 1993; **40**: 1148-54
99 Schwender D, Golling W, Klasing S, Faber-Zullig E, Poppel E, Peter K. Effects of surgical stimulation on midlatency auditory evoked potentials during general anaesthesia with propofol/fentanyl, isoflurane/fentanyl and flunitrazepam/fentanyl. *Anaesthesia* 1994; **49**: 572-8
100 Russell IF. Midazolam-alfentanil: an anaesthetic? An investigation using the isolated forearm technique. *Br J Anaesth* 1993; **70**: 42-6
101 Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; **86**: 836-47
102 Miyake W, Oda Y, Ikeda Y, Hagihira S, Iwaki H, Asada A. Electroencephalographic response following midazolam-induced general anesthesia: relationship to plasma and effect-site midazolam concentrations. *J Anesth* 2010; **24**: 386-93
103 Fiset P, Lemmens HL, Egan TE, Shafer SL, Stanski DR. Pharmacodynamic modeling of the electroencephalographic effects of flumazenil in healthy volunteers sedated with midazolam. *Clin Pharmacol Ther* 1995; **58**: 567-82
104 Greenblatt DJ, Ehrenberg BL, Culm KE, et al. Kinetics and EEG effects of midazolam during and after 1-minute, 1-hour, and 3-hour intravenous infusions. *J Clin Pharmacol* 2004; **44**: 605-11
105 Mandema JW, Tukker E, Danhof M. Pharmacokinetic-pharmacodynamic modelling of the EEG effects of midazolam in individual rats: influence of rate and route of administration. *Br J Pharmacol* 1991; **102**: 663-8
106 Bruhn J, Bouillon TW, Shafer SL. Bispectral index (BIS) and burst suppression: revealing a part of the BIS algorithm. *J Clin Monit Comput* 2000; **16**: 593-6
107 Zhou J, Leonowens C, Ivaturi VD, et al. Population pharmacokinetic/pharmacodynamic modeling for remimazolam in the induction and maintenance of general anesthesia in healthy subjects and in surgical subjects. *J Clin Anesth* 2020; **66**: 109899
108 Antonik LJ, Goldwater DR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part I. Safety, efficacy, and basic pharmacokinetics. *Anesth Analg* 2012; **115**: 274-83

109 Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc* 2018; **88**: 427-37
110 Borkett KM, Riff DS, Schwartz HI, et al. A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. *Anesth Analg* 2015; **120**: 771-80
111 Pastis NJ, Yarmus LB, Schippers F, et al. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest* 2019; **155**: 137-46
112 Power S, Morgan M, Chakrabarti M. Carbon dioxide response curves following midazolam and diazepam. *Br J Anaes* 1983; **55**: 837-42
113 Arrowsmith JB, Burt Gerstman B, Fleischer DE, Benjamin SB. Results from the American Society for Gastrointestinal Endoscopy/U.S. Food and Drug Administration collaborative study on complication rates and drug use during gastrointestinal endoscopy. *Gastrointest Endosc* 1991; **37**: 421-7
114 Bailey PL, Pace NL, Ashburn MA, Moll JW, East KA, Stanley TH. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. *Anesthesiology* 1990; **73**: 826-30
115 National Patient Safety Agency. *Reducing risk of overdose with midazolam injection in adults. National Patient Safety Agency Rapid Response Report: NPSA/2008/RRR011.* London, 2008
116 Lameijer H, Sikkema YT, Pol A, et al. Propofol versus midazolam for procedural sedation in the emergency department: A study on efficacy and safety. *Am J Emerg Med* 2017; **35**: 692-6
117 Kilpatrick GJ, McIntyre MS, Lovell GG, Wiard RP, Feldman PL, Tilbrook GS. CNS 7056: A Novel Ultra-Short–Acting Benzodiazepine. *Anesthesiology* 2007; **107**: 60-6
118 Wiltshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesth Analg* 2012; **115**: 284-96
119 Scott JC, Stanski D. Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240**: 159-66
120 Shafer A, Sung ML, White PF. Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia. *Anesth Analg* 1986; **65**: 1021-8
121 Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; **86**: 10-23
122 Greenblatt DJ, Ehrenberg BL, Gunderman J, et al. Pharmacokinetic and electroencephalographic study of intravenous diazepam, midazolam, and placebo. *Clin Pharmacol Ther* 1989; **45**: 356-65
123 Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; **88**: 1170-82
124 Doi M, Hirata N, Suzuki T, Morisaki H, Morimatsu H, Sakamoto A. Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA Class III): results of a multicenter, randomized, double-blind, parallel-group comparative trial. *J Anesth* 2020; **34**: 491-501
125 Haller G, Bampoe S, Cook T, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine initiative: clinical indicators. *Br J Anaesth* 2019; **22**: 30297-1
126 Fennelly ME, Powell H, Galletly DC, Whitwam JG. Midazolam sedation reversed with flumazenil for cardioversion. *Br J Anaesth* 1992; **68**: 303
127 Penninga EI, Graudal N, Ladekarl MB, Jürgens G. Adverse Events Associated with Flumazenil Treatment for the Management of Suspected Benzodiazepine Intoxication--A Systematic Review with Meta-Analyses of Randomised Trials. *Basic Clin Pharmacol Toxicol* 2016; **118**: 37-44

128 Veiraiah A. This meta-analysis does not reflect current practice and overestimates SAEs. *Basic Clin Pharmacol Toxicol* 2015; **117**: 363
129 Steib A, Freys G, Jochum D, Ravanello J, Schaal JC, Otteni JC. Recovery from total intravenous anaesthesia. Propofol versus midazolam-flumazenil. *Acta Anaesthesiol Scand* 1990; **34**: 632-5
130 Sneyd JR. Remimazolam: new beginnings or just a me-too? *Anesth Analg* 2012; **115**: 217-9
131 Io T, Saunders R, Pesic M, Petersen KU, Stoehr T. A miniature pig model of pharmacological tolerance to long-term sedation with the intravenous benzodiazepines; midazolam and remimazolam. *Eur J Pharmacol* 2021; **896**: 173886
132 Freyer N, Knospel F, Damm G, et al. Metabolism of remimazolam in primary human hepatocytes during continuous long-term infusion in a 3-D bioreactor system. *Drug Des Devel Ther* 2019; **13**: 1033-47
133 Azeem TMA, Yosif NE, Alansary AM, Esmat IM, Mohamed AK. Dexmedetomidine vs morphine and midazolam in the prevention and treatment of delirium after adult cardiac surgery; a randomized, double-blinded clinical trial. *Saudi J Anaesth* 2018; **12**: 190-7
134 Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016; **388**: 1893-902
135 Shehabi Y, Howe BD, Bellomo R, et al. Early sedation with dexmedetomidine in critically ill patients. *N Engl J Med* 2019; **380**: 2506-17
136 Perbet S, Verdonk F, Godet T, et al. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: A randomised double-blind control trial. *Anaesth Crit Care Pain Med* 2018; **37**: 589-95
137 Anonymous. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-classFDA Drug Safety Communication. FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class. 2020
138 Warner DO, Berge K, Sun H, Harman A, Wang T. Substance Use Disorder in Physicians after Completion of Training in Anesthesiology in the United States from 1977 to 2013. *Anesthesiology* 2020; **133**: 342-9
139 Kranioti EF, Mavroforou A, Mylonakis P, Michalodimitrakis M. Lethal self administration of propofol (Diprivan). A case report and review of the literature. *Forensic Sci Int* 2007; **167**: 56-8
140 Pesic M, Schippers F, Saunders R, Webster L, Donsbach M, Stoehr T. Pharmacokinetics and pharmacodynamics of intranasal remimazolam—a randomized controlled clinical trial. *Eur J Clin Pharmacol* 2020; **76**: 1505-16
141 Pesic M, Stöhr T, Ossig J, et al. Remimazolam Has Low Oral Bioavailability and No Potential for Misuse in Drug-Facilitated Sexual Assaults, with or Without Alcohol: Results from Two Randomised Clinical Trials. *Drugs in R&D* 2020; **20**: 267-77
142 Kitch BB. Out-of-hospital ketamine: review of a growing trend in patient care. *JACEP* 2020; **1**: 183-9
143 Parks DJ, Alter SM, Shih RD, Solano JJ, Hughes PG, Clayton LM. Rescue Intubation in the Emergency Department After Prehospital Ketamine Administration for Agitation. *Prehosp Disaster Med* 2020: 1-5
144 Muir-Cochrane E, Oster C, Gerace A, Dawson S, Damarell R, Grimmer K. The effectiveness of chemical restraint in managing acute agitation and aggression: A systematic review of randomized controlled trials. *Int J Ment Health Nurs* 2020; **29**: 110-26
145 Botched executions https://deathpenaltyinfo.org/some-examples-post-furman-botched-executions. Available from https://deathpenaltyinfo.org/some-examples-post-furman-botched-executions (accessed 23rd January 2021
146 Bian Y, Zhang H, Ma S, et al. Mass balance, pharmacokinetics and pharmacodynamics of intravenous HSK3486, a novel anaesthetic, administered to healthy subjects. *Br J Clin Pharmacol* 2021; **87**: 93-105

147 Ludbrook G, Li F, Sleigh J, Liang Y. Assessments of Onset and Duration of Drug Effects and Pharmacokinetics by Dose Level of HSK3486, a New Sedative-Hypnotic Agent, in Healthy Female/Male Subjects: A Phase I Multiarm Randomized Controlled Clinical Trial. *Anesth Analg* 2021 Publish Ahead of Print
148 Li JX, Wang X, Liu J, Wang X, Zuo Y. A Phase 3 Trial Of Ciprofol For Deep Sedation During Colonoscopy Compared With Propofol. *http://wwwasaabstractscom/* 2020: A3004
149 Goodchild CS, Serrao JM, Kolosov A, Boyd BJ. Alphaxalone Reformulated: A Water-Soluble Intravenous Anesthetic Preparation in Sulfobutyl-Ether-beta-Cyclodextrin. *Anesth Analg* 2015; **120**: 1025-31
150 Goodchild CS, Serrao JM. Alfaxalone anesthesia is accompanied by better cardiovascular function compared with propofol and sevoflurane anesthesia: results from a Phase 3 pilot study of ASA II and III patients. *Anesth Analg* 2020; **130 (Supplement 5)**: 57-8

	Propofol	Thiopental	Methohexital	Etomidate	Dexmedetomidine	Ketamine	*Diazepam	Lorazepam	Midazolam	Remimazolam
Ready to use injectable presentation	✓	✘	✘	✓	✓	✓	✓	✘	✓	✘
Formulation does not support bacterial growth	✘	✓	✓	✓	✓	✓	✘	✓	✓	✓
Free from lipid accumulation with long infusions	✘	✓	✓	✓	✓	✓	✘	✓	✓	✓
Free from pain on injection	✘	✓	✘	✘	✓	✓	✓	✘	✓	✓
Rapid onset	✓	✓	✓	✓	✘	✓	✓	✘	✘	✓
Free from extraneous muscle movements	✓	✓	✘	✘	✓	✓	✓	✓	✓	✓
Airway obstruction unlikely	✘	✘	✘	✘	✓	✓	✓	✓	✓	✓
Minimal hypotension	✘	✘	✘	✓	✘	✓	✓	✓	✓	✓
No active metabolite	✓	✘	✘	✓	✓	✓	✘	✓	✘	✓
Rapid offset	✓	✘	✓	✓	✘	✘	✘	✘	✘	?
Reversal with flumazenil	✘	✘	✘	✘	✘	✘	✓	✓	✓	✓
No adrenocortical depression	✓	✓	✓	✘	✓	✓	✓	✓	✓	✓

Table 1. Characteristics of injectable hypnotics licensed for anaesthesia or sedation in the USA or Europe. Ticks and crosses indicate the presence or absence of the relevant characteristic. *Lipid emulsion formulation.

	Propofol	Thiopental	*Methohexital	Etomidate	Dexmedetomidine	Ketamine	Diazepam	Lorazepam	Midazolam	**Remimazolam
Premedication	✘	✘	✘	✘	✘	✘	✓	✓	✓	✘
Procedural sedation	✓	✘	✘	✘	✓	✓	✓	✓	✓	✓
Induction of §anaesthesia	✓	✓	✓	✓	✘	✓	✘	✘	✓	**
Maintenance of §anaesthesia	✓	✓	✓	✘	✘	✓	✘	✘	✓	**
ICU sedation	✓	✘	✘	✘	✓	✘	✘	✘	✓	✘

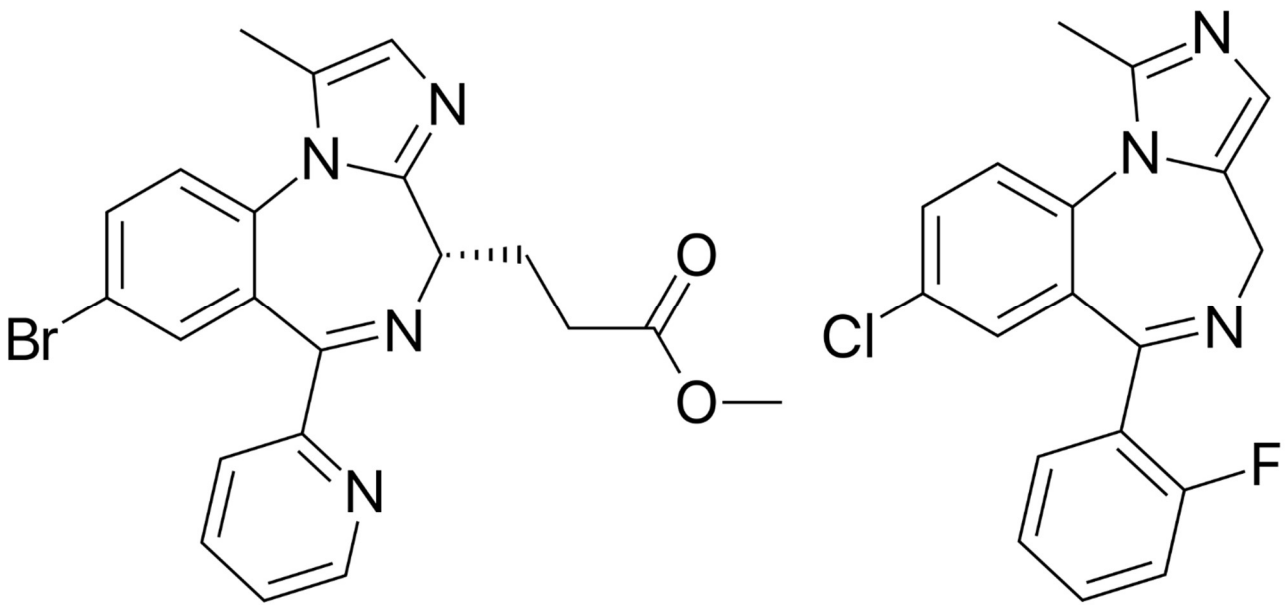
Table 2. Licensed (USA or Europe) and developmental perioperative uses of injectable hypnotics. Ticks and crosses indicate the presence or absence of a licensed indication. *USA only. **Remimazolam is licenced for procedural sedation in the USA and for general anaesthesia in Japan, Russia and Korea, a European licensing application for procedural sedation is under evaluation. §Includes use as the hypnotic component of an intravenous anaesthetic technique but not (except ketamine) as a single agent able to maintain a general anaesthetic state.

Legends for figures

Figure 1. Structures of remimazolam (left) and midazolam (right). Remimazolam undergoes hydrolysis by Carboxylesterase 1 (CES1) to an inactive metabolite. Midazolam is converted to an active metabolite alpha-1 hydroxy-midazolam.

Figure 2. Effect site opioid and hypnotic concentrations over time as a proportion of the peak effect site concentration. Midazolam[122] (heavy brown dashes), fentanyl[119] (thin blue dashes), remimazolam[107] (heavy black line), alfentanil[120] (thin dotted line), propofol[123] (large green dots) and remifentanil[121] (thin blue line). Onset and offset of remimazolam is intermediate between propofol and fentanyl and faster than midazolam. Simulated using STANPUMP. STANPUMP is freely available from the author at opentci.org/code/stanpump.

Figure 3. Context-sensitive half-times of the plasma hypnotic concentrations over time. Midazolam[122] (heavy brown dashes), remimazolam[107] (heavy black line), propofol[123] (large green dots) and remifentanil[121] (thin blue line). Offset of remimazolam is intermediate between propofol and midazolam. Simulated using PK/PD tools for Excel. PK/PD tools is freely available from pkpdtools.com.



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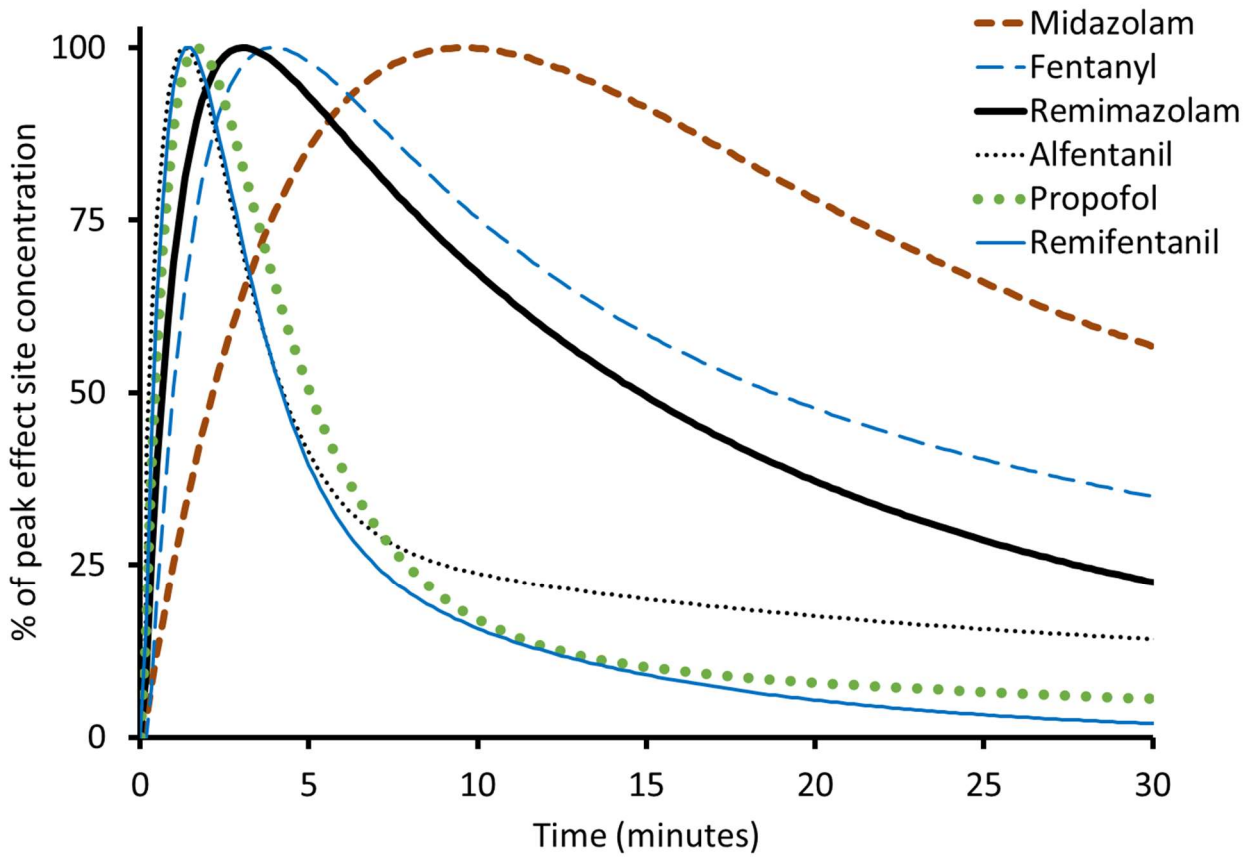

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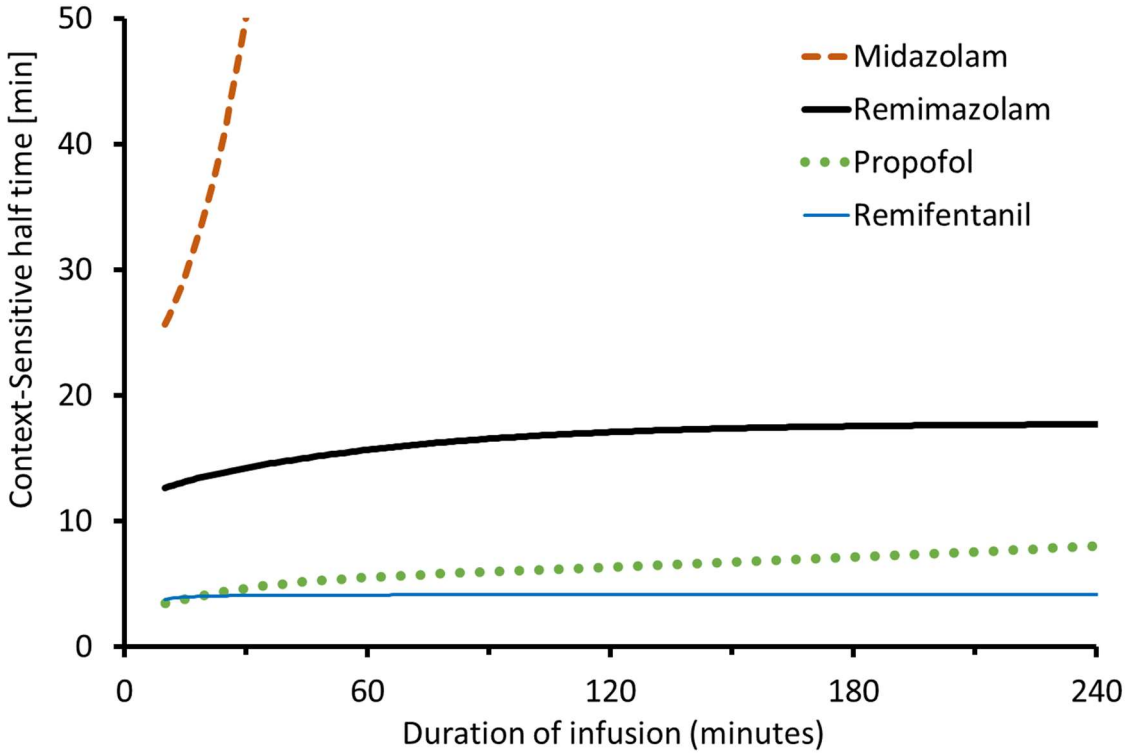

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