2016-12-12

Time to move the goalposts? Do we need new targets for developing i.v. anaesthetics?

Sneyd, John

10.1093/bja/aew330
British Journal of Anaesthesia
Elsevier BV

Authors draft of:

http://dx.doi.org/10.1093/bja/aew330

Title:

Time to move the goalposts? Do we need new targets for developing intravenous anaesthetics?

Short running title:

New targets for developing intravenous anaesthetics

Author:

J Robert Sneyd

Plymouth University Peninsula Schools of Medicine and Dentistry,

The John Bull Building, Research Way, Plymouth Science Park, Plymouth PL6 8BU, UK

robert.sneyd@pms.ac.uk (07870) 271531

PA: Deb Fox 01752 437401 deborah.fox@plymouth.ac.ukr:

Summary (abstract):

the submitted manuscript is proposed as an editorial for which no summary is required

Keywords:

Anesthetics, Intravenous

propofol

remifentanil

etomidate

ketamine

Trial registration: not applicable

Ethical approval: not applicable

Declaration of interests:

Prof Sneyd acts as a consultant to the following:

Maruishi pharmaceutical company, Japan;

The Medicines Company, USA

Altus, Canada

Funding: this editorial was written without funding

Contribution: RS conceived, planned and wrote the editorial

Acknowledgement: none

Time to move the goalposts? Do we need new targets for developing intravenous anaesthetics?

Widespread use of intravenous hypnotics for induction of anaesthesia dates from 1934 when thiopentone was introduced. Since then a handful of agents have come and gone with only propofol and ketamine enjoying common use in addition to some residual administrations of thiopentone and etomidate,

During the 30 years since propofol was introduced in 1986, number of candidate hypnotics and propofol reformulations have been evaluated but none have yet achieved commercial success or significant clinical impact. During this period developmental objectives built on the shortfalls of thiopentone listed by Dundee[1] in 1961 with additional ambitions arising from the known limitations of propofol and increasing interest in maintenance of anaesthesia by infusion. Table 1.

----------Table 1 near here----------

In addition, swift esterase hydrolysis allows the use of remifentanil to provide intense opioid effect with rapid offset thereby sharply decreasing the amount of maintenance hypnotic required. Similar thinking has proposed the use of the benzodiazepine remimazolam for maintenance of general anaesthesia.[2]

"Problems" with propofol - are they really an issue?

Although frequently cited, the well-known limitations of propofol appear to be manageable and have not materially impacted its use. Pain on injection may be reduced or abolished by addition of Lidocaine or changing the lipid used in the emulsion. Accumulation of lipids seems only to be an issue during prolonged administration in comprised patients and possibly in children. Sepsis precipitated by

bacterial contamination is diminished by addition of an antiseptic (EDTA or sodium metabisulphite) and should never happen if a flawless aseptic technique is used. Haemodynamic depression is attenuated by slow administration, careful adjustment of dose and co-administration of fluid. Finally, respiratory depression is generally easily managed by a competent anaesthetist and the suppression by propofol of laryngeal reflexes is a positive advantage facilitating laryngeal mask airway insertion.

Who needs thiopentone anyhow?

The use of thiopentone has been in decline following association with judicial execution and subsequent restriction of supply within the USA plus the withdrawal of a major manufacturer. Contemporary anaesthetic use of thiopentone is limited to induction of general anaesthesia for Caesarean section, a small number of patients for whom propofol is considered contraindicated (typically after some kind of allergic reaction) or occasional use to attempt neuro protection. Even the limited use of thiopentone on the labour ward may cease because anaesthetists are increasingly unfamiliar with the drug and sceptical about the limited literature supporting its superiority to propofol for obstetric indications.[3] Allergy to propofol is controversial and certainly infrequent. Finally, supply issues are exacerbated by limited commercial interest in a drug that hardly anybody uses.

Does anybody need etomidate?

Since its association with adrenocortical depression the use of etomidate has declined sharply. Residual use, notably in the United States is based around rapid onset, short duration of action and minimum haemodynamic and respiratory disturbance. Its continued popularity with some anaesthetists and notably non-anaesthetist emergency physicians and intensivists is defended by assertions that

single doses do not impact morbidity/mortality although this remains controversial. Novel etomidate derivatives have dealt with the adrenocortical depression issue through structural changes to form a pyrrole analogue, carboetomidate[4] with diminished binding to 11beta-hydroxylase or to a rapidly hydrolysed ester, cyclopropyl-methoxycarbonyl metomidate, ABP-700 which is currently under evaluation in man.[5]

Is intravenous anaesthesia worth the trouble?

The popularity of total intravenous anaesthesia, TIVA with propofol reflects the appreciation by patients and their anaesthetists of swift emergence from anaesthesia followed by rapid clearheaded recovery with minimal post-operative nausea and vomiting, PONV. Target Controlled Infusion, TCI facilitates TIVA by simplifying drug administration. However, swift clearheaded recovery can easily be achieved with sevoflurane or desflurane and multi-drug anti-emetic prophylaxis greatly reduces PONV after inhaled anaesthesia. Perhaps the favourable recovery profile of propofol can be achieved by other means?

The versatility and safety of propofol in the hands of anaesthetists plus a questioning approach to its alleged problems has acted as a brake on otherwise attractive novel approaches to intravenous anaesthesia. PF016 (a propofol derivative free from pain on injection),[6] (reference) and alfaxalone (superior haemodynamic stability to propofol)[7] have failed to attract sustained commercial interest, presumably because their advantages appear insufficient to justify the cost of development.

Currently only remimazolam[2] and ABP-700[8] remain in clinical development with both programs focused initially on endoscopy where an agent with superior cardiorespiratory stability and ease of administration might permit sedation by an operator-sedationist or at least a non-physician sedation provider. In each case the business case focuses on avoiding the need for an expensive anaesthetist thereby generating cost savings that in turn justify a more expensive hypnotic.

Use of anaesthetic drugs for non-anaesthetist sedation

Multiple non-anaesthetist clinicians give elective or emergency sedation to patients. Sensibly they mostly restrict themselves to midazolam plus fentanyl.[9] Nevertheless, such sedation providers often yearn for the more profound effects of anaesthetic hypnotics whilst understandably remaining cautious about cardiorespiratory depression. Although the safety of non-physician use of propofol has been demonstrated in carefully constrained circumstances (ASA physical status 1-2 patients, well-trained nurse sedationists)[10] wider deployment is considered problematic.[11] The semi-autonomous Sedasys sedation system has been withdrawn after sustained opposition by the American Society of Anesthesiologists.[12] Development of compounds to address this clinical opportunity remains a commercial interest although establishing the necessary trials may be problematic without the support of anaesthetists.

If current considerations have failed to motivate sustained commercial development against conventional criteria we should consider alternative opportunities for innovation.

Neurotoxicity

Both intravenous and inhaled anaesthetics are unquestionably neurotoxic in at least some animal models.[13] Whether these effects are relevant to human use remains controversial[14] with selected retrospective studies suggesting harm whilst the only prospective investigation has to date shown no harm at two year follow-up to neonates randomised to loco-regional or general anaesthesia for hernia repair.[15] Only time and further research will clarify whether paediatric neurotoxic effects exist in man and if so by what mechanisms it is caused. Such insights would profoundly influence drug development with immediate parent and professional pressure to focus on compounds not so implicated.

Neuro protection

Although thiopentone, propofol and etomidate have all been used in attempts to achieve neuro protection during periods of impaired cerebral perfusion, the evidence base to support such practice is sketchy.[16] In contrast, the noble gases xenon and argon[17] are profoundly neuroprotective in vitro and in some animal models leading to experimental clinical deployment of xenon after neonatal asphyxia[18], during cardiac surgery and after cardiac arrest. The requirement for complex equipment and the procurement cost of xenon may limit widespread use. However, if proven effective then additional basic science to explore in detail the molecular basis of such efficacy could offer new targets for drug development, hopefully to produce small molecules suitable for intravenous administration.

Cognitive impairment

The combination of general anaesthesia and surgery undoubtedly precipitates post-operative cognitive impairment, POCD in a minority of patients especially the elderly.[19] Whilst POCD is generally considered reversible there are also suggestions

that a subset of patients, perhaps with a predisposition, may be tipped into Alzheimer's disease by administration of general anaesthesia.[20] The epidemiology and mechanisms of these changes are under intense investigation. Insights into their mechanisms may suggest new targets for hypnotic development strategies for using existing drugs to cause least harm.

Anaesthetics and cancer

Preclinical data and retrospective studies in man suggest that choice of anaesthetic technique may influence the progression of cancer and subsequent mortality. Recently a substantial retrospective review of cancer surgery patients suggested long-term differences in mortality with a substantial effect size with an association between intravenous anaesthesia and decreased mortality.[21] Multiple drug effects and mechanisms have been postulated including promotion of angiogenesis by morphine, beneficial effects of bupivacaine and propofol and harmful effects of inhalational agents.[22] As these effects (if reproducible) and their mechanisms are clarified there will emerge opportunities for changes in anaesthetic practice and possibly new drugs designed to interact favourably with the immune system and other factors influencing outcome after cancer surgery. Pending further evidence a recent consensus statement recommends no changes in anaesthetic techniques.[23]

Intravenous anaesthesia and the difficult airway

Induction of general anaesthesia patients with difficult airway's risks lapse into the can't-intubate-can't-ventilate scenario and awake intubation may therefore be preferred. Combination of the short-acting opioid, remifentanil, a rapid onset neuromuscular blocker, rocuronium immediately reversible with sugammadex, and a rapid-onset, rapid-offset ultra short acting intravenous hypnotic might permit careful

exploration of intubation under general anaesthesia with the option of a swift bale-out.[24] Novel ultra-short acting intravenous agents may offer swift recovery of consciousness to mirror the reversal of neuromuscular block in such situations. If respiratory drive can be maintained then progressive induction with an IV agent might be an alternative to inhalation induction for patients with airway compromise.

Intravenous hypnotics with novel properties

The recent suggestion that a short-acting ketamine derivative may have analgesic properties outlasting its hypnotic effects,[25] the use of ketamine in the treatment of depression[26] and the recent demonstration of a specific and separate mechanism for this[27] suggest further scope for targeting and refinement of drug effects through better understanding of receptor and cellular mechanisms and innovative synthetic chemistry.

Widening the hunt

Advances in pertinent basic science including novel selective photo-affinity ligands [28] today permit the identification of the protein targets of anaesthetic effects and subsequently the detailed characterisation of the sites at which individual drug actions are affected. Deconstruction at a molecular level of individual anaesthetic drug effects will offer new opportunities and may merit commercial investment with goes more ambitious than simply being a little bit better than propofol.

Anaesthetists can and should demand novel intravenous anaesthetics with unique characteristics tailored to clinical need. For a profit-motivated pharmaceutical industry to deliver these at prices affordable in resource limited health systems requires wider thinking than the boundaries defined by Dundee 55 years ago.

REFERENCES

1 Barron DW, Dundee JW. The recently introduced rapidlyacting barbiturates; a review and critical appraisal in relation to thiopentone. *Br J Anaesth* 1961; **33**: 81-91

2 Sneyd JR. Remimazolam: new beginnings or just a me-too? *Anesth Analg* 2012; **115**: 217-9

3 Lucas DN, Yentis SM. Unsettled weather and the end for thiopental? Obstetric general anaesthesia after the NAP5 and MBRRACE-UK reports. *Anaesthesia* 2015; **70**: 375-9

4 Pejo E, Feng Y, Chao W, Cotten JF, Le Ge R, Raines DE. Differential effects of etomidate and its pyrrole analogue carboetomidate on the adrenocortical and cytokine responses to endotoxemia. *Crit Care Med* 2011

5 Ge R, Pejo E, Gallin H, Jeffrey S, Cotten JF, Raines DE. The pharmacology of cyclopropyl-methoxycarbonyl metomidate: a comparison with propofol. *Anesth Analg* 2014; **118**: 563-7

6 Jenkins TE. Stereoisomers propofol therapeutic compounds Patent WO/2008/141097. 2008

7 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

8 Campagna JA, Pojasek K, Grayzel D, Randle J, Raines DE. Advancing novel anesthetics: pharmacodynamic and pharmacokinetic studies of cyclopropyl-methoxycarbonyl metomidate in dogs. *Anesthesiology* 2014; **121**: 1203-16

9 South West Anaesthetic Research M, South West Anaesthetic Research Matrix S. Sedation practice in six acute hospitals - a snapshot survey. *Anaesthesia* 2015; **70**: 407-15

10 Sieg A, bng Study G, 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

11 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

12 Singh PM, Borle A, Goudra BG. Use of computer-assisted drug therapy outside the operating room. *Curr Opin Anaesthesiol* 2016; **29**: 506-11

13 Hemmings HC, Jr., Jevtovic-Todorovic V. Special issue on anaesthetic neurotoxicity and neuroplasticity. *Br J Anaesth* 2013; **110 Suppl 1**: i1-2

14 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

15 Davidson AJ, Disma N, de Graaff JC, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet* 2016; **387**: 239-50

16 Bilotta F, Gelb AW, Stazi E, Titi L, Paoloni FP, Rosa G. Pharmacological perioperative brain neuroprotection: a qualitative review of randomized clinical trials. *Br J Anaesth* 2013; **110 Suppl 1**: i113-20

17 Brucken A, Cizen A, Fera C, et al. Argon reduces neurohistopathological damage and preserves functional recovery after cardiac arrest in rats. *Br J Anaesth* 2013; **110 Suppl 1**: i106-12

18 Lobo N, Yang B, Rizvi M, Ma D. Hypothermia and xenon: novel noble guardians in hypoxic-ischemic encephalopathy? *J Neurosci Res* 2013; **91**: 473-8

19 Steinmetz J, Rasmussen LS. Peri-operative cognitive dysfunction and protection. *Anaesthesia* 2016; **71 Suppl 1**: 58-63

20 Jiang J, Jiang H. Effect of the inhaled anesthetics isoflurane, sevoflurane and desflurane on the neuropathogenesis of Alzheimer's disease (review). *Mol Med Rep* 2015; **12**: 3-12

21 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

22 Byrne K, Levins KJ, Buggy DJ. Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis? *Can J Anaesth* 2016; **63**: 184-92

23 Buggy DJ, Borgeat A, Cata J, et al. Consensus statement from the BJA Workshop on Cancer and Anaesthesia. *Br J Anaesth* 2015; **114**: 2-3

24 Sorensen MK, Bretlau C, Gatke MR, Sorensen AM, Rasmussen LS. Rapid sequence induction and intubation with rocuronium-sugammadex compared with succinylcholine: a randomized trial. *Br J Anaesth* 2012; **108**: 682-9

25 Harvey M, Sleigh J, Voss L, et al. Development of Rapidly Metabolized and Ultra-Short-Acting Ketamine Analogs. *Anesth Analg* 2015; **121**: 925-33

26 aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry* 2010; **67**: 139-45

27 Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* 2016; **533**: 481-6

28 Woll KA, Dailey WP, Brannigan G, Eckenhoff RG. Shedding Light on Anesthetic Mechanisms: Application of Photoaffinity Ligands. *Anesth Analg* 2016

Issue	**strategy**	**exemplar development candidate**
Rapid onset	Lipid solubility,	ADB-700
Rapid offset	Rapid distribution and metabolism, ester compounds	AZD3043
Haemodynamic stability	Steroid derivatives, etomidate derivatives, increased opioid effect	ORG21465, eltanolone, remimazolam, remifentanil, alfaxalone
Retention of respiratory drive	Improve on propofol	ADB-700, remimazolam, alfaxalone
Pain on injection, issues with drug delivery vehicle	Water solubility, reduce free propofol concentration	ORG 21465, ORG25435
Accumulation of lipid vehicle	Non-lipid propofol formulations, water soluble agents	Various

Table 1. Recent drivers of intravenous hypnotic development.