Esterase metabolised drugs – going beyond remifentanil or a blind alley?

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The ester linkage is a chemical grouping susceptible to enzymatic degradation allowing innovation in drug design by using enzymatic processes to accelerate elimination.

A bit of history. Until the advent of remifentanil, ester degradation of anaesthetic drugs was typified by succinyl choline and the issue of cholinesterase efficiency followed by the discovery of atracurium/cis atracurium. The advent of remifentanil brought in the concept of “soft” pharmacology[1] with new options for titrating drug concentration and effect combined with rapid recovery.

Is it possible for an intravenous hypnotic to be too short acting?[2] Esterase hydrolysis offers ultra-fast recovery from anaesthetic drug effect.[3] If translated into humans this might allow swift and clear headed recovery of consciousness and perhaps early home readiness. Recently concern has mounted about perioperative awareness due to inadequate delivery of intravenous anaesthesia.[4] Anaesthetic techniques based on ultra-short offset hypnotics will be especially vulnerable to interruptions in drug delivery and offer the alarming prospect of a patient inadvertently transitioning rapidly from the anaesthetised state to full wakefulness at an inappropriate time.

Further, ultra-short acting drugs offer a pricing challenge to the pharmaceutical industry: if a reasonable price is achieved for a single bolus injection then maintenance by infusion becomes hugely expensively. Alternatively, if such a compound is priced so that maintenance is affordable then an induction dose will be something of a bargain! One approach to contain drug costs is to use a cheap agent for induction and maintenance of anaesthesia and then switch to a more expensive short acting agent towards the end of surgery in the hope of achieving rapid recovery without excessive cost. This technique has been demonstrated for sequential use of alfentanil and remifentanil in neurosurgical anaesthesia[5] and might be applicable to new ultra-short acting hypnotics by sequential use at the end of a propofol anaesthetic.[5]

Designing a molecule susceptible to rapid breakdown entails compromises on stability and drug storage, thus remifentanil is presented as a powder which must be reconstituted before use - annoying, time-consuming and potentially a source of drug administration errors.

Where a short-acting compound is infused for a sustained period the metabolites will accumulate and attention given to whether they have any pharmacological activity.

So far only remifentanil has survived the development process with other molecules falling by the wayside before successful commercialisation could be achieved.[2, 6, 7] looking ahead, Remimazolam has potential although it's optimal applications have yet to be determined.[8]

REFERENCES

1 Egan TD. Is anesthesiology going soft?: trends in fragile pharmacology. *Anesthesiology* 2009; **111**: 229-30
2 Sneyd JR, Rigby-Jones AE. New drugs and technologies, intravenous anaesthesia is on the move (again). *Br J Anaesth* 2010; **105**: 246-54
3 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
4 Safe Anaesthesia Liaison Group. Guaranteeing Drug Delivery in Total

Intravenous Anaesthesia www.aagbi.org/news/docs/tiva_infonov09.pdf. 2009. Available from www.aagbi.org/news/docs/tiva_infonov09.pdf
5 Sneyd JR, Whaley A, Dimpel HL, Andrews CJ. An open, randomized comparison of alfentanil, remifentanil and alfentanil followed by remifentanil in anaesthesia for craniotomy. *Br J Anaesth* 1998; **81**: 361-4
6 Sneyd JR. Recent advances in intravenous anaesthesia. *BRIT J ANAESTH* 2005; **94**: 393-
7 Sear JW. Challenges of bringing a new sedative to market! *Curr Opin Anaesthesiol* 2018; **31**: 423-30
8 Sneyd JR. Remimazolam: new beginnings or just a me-too? *Anesth Analg* 2012; **115**: 217-9