New hypnotics – do we need them, is anything out there?

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Remimazolam produces rapid onset dose-related sedation which is qualitatively similar to that produced by midazolam but of substantially shorter duration.[1] The profile of adverse events suggests that the new compound is relatively "clean" and remimazolam appears (so far) to be a "typical" benzodiazepine. Remimazolam is built on a typical benzodiazepine structure and binds to benzodiazepine receptors with reversal by flumazenil.[2] Pharmacokinetic modelling reveals remimazolam to have a higher clearance and smaller volume of distribution than midazolam[3] – these explain the rapid offset of drug effect following short term administration.

Remimazolam's principal metabolite CNS7054 has "300 times lower affinity" than its parent. This sounds fine, however with "soft" drugs (those rapidly broken done by tissue esterases[4]) the metabolites accumulate rapidly[5] and further work is required to describe CNS7054 concentrations in diverse groups of patients especially those with hepatic and renal dysfunction and to whom prolonged infusions (and therefore greater quantities of CNS7054) have been given.. Future studies extending our knowledge of remimazolam should also further describe the pharmacokinetics and possibly the pharmacodynamics of CNS7054 to build confidence in its disposition and (lack of) effect.

Who should use remimazolam? Endoscopy suites have seen an unedifying 'turf' dispute about the use by non-anesthesiologists of propofol sedation. The short action of remimazolam may turn this dispute into a sideshow by offering the relative safety of benzodiazepine sedation combined with rapid clear-headed recovery. More interestingly, might remimazolam allow us to extend or enhance the therapeutic uses of benzodiazepines?

Co-induction. Pre-treatment with small doses of midazolam reduces propofol induction dose.[6] Whether this is clinically useful is questionable. Remimazolam will likely interact synergistically with opioids and propofol and experimental designs allowing these to be safely investigated whilst generating data suitable for extensive interaction monitoring have been established.[7]

Benzodiazepine anaesthesia. During the development of midazolam, attempts were made to use it as sole hypnotic, in combination with an opioid, for induction and maintenance of anaesthesia with attempts to reverse its effect after the end of surgery by administration of flumazenil.[8] Such a technique is possible but has not proved useful and giving substantial doses of midazolam risks re-sedation after flumazenil administration.[9] Remimazolam offers the opportunity to revisit this area,

with and without flumazenil reversal, to evaluate whether hemodynamic stability, intense amnestic effects or other benefits exist to make the process useful.

High intensity benzodiazepine effects. Currently we use benzodiazepines at doses sufficient to establish anxiolysis or hypnosis as required. Larger doses are avoided because of accumulation and the residual effects of active metabolites. The emergence of a truly short acting benzodiazepine might allow exploration of the top end of the dose-response curve. In the opioid domain, remifentanil has permitted routine use of intense opioid effect for short and intermediate procedures with no penalty from residual drug extending recovery. Equally, we must be mindful that protracted receptor stimulation may elicit undesired effects such as the (debated) desensitization and rebound effects which may occur after high dose remifentanil.[10, 11]

Procedural sedation. In these indications midazolam is typically administered by one or more bolus injections. Truly short acting drugs will require an infusion and the optimum strategy for Remimazolam administration will require evaluation. Detailed modelling[3] will guide the design of suitable protocols for investigation. Clinical acceptability will, in part be determined by convenience of administration. In this regard sedation by one or two bolus injections trumps schemes based on an infusion pump.

A presentation of alfaxolone[12] in sulfobutyl ether β cyclodextrin which does not cause pain on injection and offers rapid onset, rapid offset anaesthesia with minimal haemodynamic disturbance compared to propofol has so far only been described in volunteers and it is unclear whether it will command the necessary investment for full commercial moment.[13] Formulating alfaxalone in a 13% 7-sulfobutylether β-cyclodextrin solution is rational and preliminary publications confirm that in this vehicle alfaxalone maintains its characteristic of haemodynamic Sulfobutyl ether β cyclodextrin is already used as a vehicle for injectables but in very different volumes to those required for total intravenous anaesthesia and intensive care sedation.

Haemodynamic stability with alfaxalone is certainly superior to propofol,[13] however virtually any patient may be safely anaesthetised with propofol in judicious doses.[14] This formulation is now undergoing Phase 3 investigation in older patients with a view to demonstrating its potential advantages over propofol and sevoflurane.

Conflict of interest. Prof Sneyd advises Paion who are developing remimazolam.

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