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## Remimazolam - new beginnings or just a me-too?

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This edition of the journal includes two manuscripts describing the first human administration of remimazolam, a novel benzodiazepine. (1,2) Not all such Phase 1 studies have a happy ending, the drop-out rate of development drugs is high and Phase 1 studies frequently represent the last outing for candidate compounds.(3,4) Such investigations, together with early clinical studies also offer the editorialist an opportunity to pontificate (often wrongly) on the possible advantages of the new drug and to indulge in some speculation. Hence: “mivacurium may constitute a versatile new addition to anesthetic practice.”(5) “minaxolone is a most promising induction agent...” and more accurately “midazolam would appear to offer many advantages over available benzodiazepines”.(6)

Can we improve on midazolam? Midazolam replaced diazepam because it is water soluble and does not cause pain on injection. Midazolam also has rapid onset and commonly induces amnesia.(7) However, midazolam has an active metabolite alpha-hydroxy-midazolam which is a potent sedative and contributes materially to the effects of its parent.(8) Following the introduction of midazolam, there were further efforts to identify short acting benzodiazepines with rapid onset and offset.(9,10) Ro 48-6791 had a similar speed of onset and duration of action to midazolam but was 3-6 times more potent.(9) Recovery from Ro 48-8684 was faster than from midazolam.(10) Neither compound was felt to have sufficient advantages over midazolam to merit further development.

Why then bother with remimazolam? The answer is a matter of degree. Incorporation of an ester linkage into remimazolam permits hydrolysis by tissue esterases to an apparently inactive metabolite. Tissue esterases are diverse and ubiquitous – there is no deficiency condition. Further, their capacity gives a high clearance with consequent rapid diminution of drug effect when administration is ceased. This approach works well for remifentanil and the experimental compounds MOC-etomidate(11) and THRX-918661 (a propanidid derivative).(12) Preclinical investigations in sheep showed remimazolam to produce dose-dependent sedation with a faster offset than midazolam.(13,14) Remimazolam appears to be a substantial improvement on midazolam with an apparently inactive metabolite and a context-sensitive half-time plot reminiscent of that for remifentanil.(2)

What should we expect from a Phase 1 study? Regulators, such as the Food and Drug Administration, FDA require the demonstration of Safety and Efficacy. In the

world of clinical trials these carry slightly different meanings to “real world” clinical practise. Safety is quantified by Adverse Events and Serious Adverse Events at the time of drug administration and for a few days afterwards. Efficacy in Phase 1 may be no more than a simple observation that the compound has some effect in the desired indication. Recently, the increasing costs of clinical studies and pressure to accelerate development timetables (against a ticking patent clock...) motivate sponsors to bring forward into Phase 1 active comparators (in this case midazolam) and detailed attempts to compare the new drug with the old. This is not necessarily a bad thing as the science is thereby enriched although excessive measurements (end points) may over-complicate the study design. Another important objective in Phase 1 is to explore the whole of the dose-response curve ranging from a “no effect” dose to doses where adverse effects begin to occur. Failing to do this in Phase 1 may otherwise lead to surprises later in clinical development. The first human study of remimazolam appropriately explores the entire spectrum of drug effect, permits comparison with the current ‘gold standard’, midazolam and through detailed PK-PD modelling adds numbers to qualitative descriptions of differences and permits exploration through simulation of alternative schedules of remimazolam administration.

How did remimazolam fare in this investigation? Remimazolam produces rapid onset dose-related sedation which is qualitatively similar to that produced by midazolam but of substantially shorter duration.<sup>(1)</sup> The profile of adverse events suggests that the new compound is relatively “clean” and remimazolam appears (so far) to be a “typical” benzodiazepine. How is this achieved? Remimazolam is built on a typical benzodiazepine structure and binds to benzodiazepine receptors with reversal by flumazenil.<sup>(15)</sup> Pharmacokinetic modelling reveals remimazolam to have a higher

clearance and smaller volume of distribution than midazolam(2) – these explain the rapid offset of drug effect following short term administration.

An important limitation on Phase 1 volunteer studies is the gender mix (typically all male or mostly male), limited age range and prospective selection for general good health of the subjects. The population is therefore relatively homogenous and possibly resilient to cardio-respiratory depression or other dose-related side effects. In contrast, “real-world” clinical use includes patients in poor health at the extremes of weight and age who may have metabolic or physiological disturbance. Data from Phase 1 studies must therefore be evaluated carefully with caution about extrapolation to other groups.

What else do we need to know? Remimazolam’s principal metabolite CNS7054 has “300 times lower affinity” than its parent. This sounds fine, however with “soft” drugs (those rapidly broken down by tissue esterases(12)) the metabolites accumulate rapidly(16) 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. In the present study infusions were limited to one minute so we now need to see studies including repeat bolus doses and continuous infusion. 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.

Dosing by weight. The relatively heterogenous volunteer population (65 – 90 kg) studied yielded “no clear relationship between weight and systemic clearance of remimazolam” however this will likely not mean that the dose should never be

adjusted. Anesthesiologists are accustomed to dosing by body weight and whilst it may not be essential for healthy adult patients similar to the participants in this study, it will likely be safer for the small, the frail and possibly the elderly or seriously ill.

Where next for remimazolam? If future clinical trials confirm initial findings, remimazolam may usefully compete with midazolam in sedative practise. Given that new drugs cost more than old ones, the pressure to achieve value-for-money will point initial studies (and possibly initial clinical use) towards procedural sedation, particularly for ambulatory surgery patients where fitness for discharge might be accelerated. Currently unpublished clinical studies of remimazolam for sedation during endoscopy have been reported to investors and the stock market but have not been subject to peer review, see <http://www.paion.de> . PAION have conducted a Phase Ib multiple dose study in volunteers undergoing colonoscopy, a Phase IIa single dose study in Upper GI Endoscopy patients, and a Phase IIb multiple dose study in Colonoscopy patients.(17)

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.(18) 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.(19)

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.(20) Such a technique is possible but has not proved useful and giving substantial doses of midazolam risks re-sedation after flumazenil administration.(21) 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.(22,23)

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(2) 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.

Saving money. Maintaining clinical effect with very short acting drugs requires repeated re-administration or infusion and thereby the progressive administration of a large mass of drug. This generates inescapable pricing choices for the manufacturer. A drug priced attractively for single bolus injection may be ruinously expensive for maintenance of anaesthesia, let alone intensive care sedation(24). Conversely, pricing remimazolam attractively for maintenance will mean it is a “giveaway” for bolus use. These simple observations cannot be escaped but are frequently overlooked. Remifentanil is a useful and flexible peri-operative opioid whose general use is severely limited by the high cost of prolonged anaesthesia and critical care sedation. The same will apply to remimazolam. One cost-effective technique may be to maintain anaesthesia or sedation with a longer acting (and cheaper) drug then switch to a shorter acting one for emergence. This has been described with remifentanil and alfentanil(25) and will likely be attempted with midazolam and remimazolam...

Conclusion. Remimazolam is another useful extension of “soft” pharmacology(12) to medicine. If clinical trials proceed well it will likely find a place in contemporary practise, uptake will be limited by cost rather than by pharmacology.

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