2018-04

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10.1016/j.bja.2018.01.024
British Journal of Anaesthesia
Elsevier

British Journal of Anaesthesia

Editorial

Quest for new drugs: a way to solve anaesthesia neurotoxicity?

Re: Neurosteroid analogue with T-channel blocking properties is an effective hypnotic but not harmful to the young brain (BJA-2017-01265-HH450)

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The authors are not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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All contemporary general anaesthetics ~~has~~ have been convincingly shown to produce neurotoxic effects in at least some experimental animal models and many of the underlying mechanisms have been identified.[1] Whilst the human relevance of these observations is still under intense scrutiny, elaboration of protective strategies along with the development of new "non-toxic" anaesthetic drug regimens have been identified as rational research directions to alleviate potential neurotoxicity.[2] In this edition of the journal Atlury and colleagues report preliminary animal experiments with a novel neurosteroid hypnotic.[3] They describe the compound as "safe" in comparison to ketamine and suggest that a new class of hypnotic 'a distinct panselective T-channel blocker devoid of GABAergic or NMDA antagonistic properties at hypnotically-relevant brain concentrations' represents a rational route of drug development which might provide effective anaesthesia without paediatric neurotoxicity.

This work deserves particular attention since it provides us with the detailed laboratory neurotoxicity profile of a drug, 3β-OH , that can induce anaesthesia/sedation comparable to that of ketamine. Focusing on 7-day-old neonatal rat pups, the authors first showed that 3β-OH is virtually devoid of pro-apoptotic effects when compared to ketamine at equipotent concentrations. In line with these observations, they then provide us with data showing that, unlike ketamine, neonatal administration of 3β-OH will not lead to impaired spatial learning at later stages of life in this experimental model. In parallel, the authors also performed serial measurements of 3β-OH concentrations both in the plasma and the brain to obtain pharmacokinetic profiles of this drug. Finally, they performed a series of electrophysiological recordings to identify potential targets and find that 3β-OH is a potent T-channel blocker but lacks direct effects on both GABA- and NMDA-mediated-currents.

What do these new and interesting data teach us? Can we consider, as the authors suggest, that this "novel class of anaesthetic agents with different cellular targets might be safe and promising alternatives to the traditional general anesthetics currently used in pediatric medicine"? Whilst this hypothesis is definitely plausible, there is still a long way to go to reach such a conclusion with ~~sufficient~~ certainty.

From the pre-clinical perspective, the major question is what criteria should be fulfilled in order to declare drug safety as far as the neurotoxicity issue is concerned? There is obviously no appropriate answer to this question. By performing a large pallet of experimental approaches, Atlury et al., clearly raise the standards on how to describe neurotoxicity potential of new compounds.[3] Based on their observations, we have a reasonable set of arguments to consider that 3β-OH is less toxic then ketamine in this particular experimental model. However, we cannot exclude that 3β-OH induces a variety of other morpho-functional effects at this particular or at another developmental stage which, in turn, could induce neurocognitive deficits at distinct cognitive domains that are not tested with the behavioural paradigm applied in this study. To push this reflection further toward translational relevance, future experiments on the neurotoxicity profile of this drug are needed in the context of surgery and analgesia. Should the authors or other investigators perform these experiments in the future before taking 3β-OH toward clinical trials? To answer this question, it should be remembered that none of the currently used anaesthetics drugs have been undergone such detailed testing protocols. Knowing the costs associated with such experiments, especially in light of as yet dubious clinical relevance, it is difficult to envisage that such detailed preclinical work will ever be conducted on all currently used anaesthetics. Last but not least, results obtained by one research group should be reproduced by other laboratories before taking

the observations for granted. This latter point is important to emphasize especially when considering two recent studies where performing the very same experimental protocol to evaluate the neurotoxic potential of dexmedetomidine yielded largely diverg~~ing~~ent results.[4,5]

From the clinical perspective, all contemporary general anaesthetics produce neurotoxic effects in at least some animal or model system and it is this rather than convincing human data that have precipitated precautionary comments by regulators.[6] Anaesthesia providers are currently confronted by a "problem" i.e. alleged neurotoxicity risk to paediatric recipients of general anaesthesia whilst not having any robust basis on which to choose one anaesthetic against another. Nevertheless, research in this area has been identified as an international priority and outcomes from human studies are eagerly awaited.

Anaesthetic effects on cancer outcomes, paediatric neurotoxicity and propensity to post-operative cognitive dysfunction in adult patients have been recommended as new development targets for hypnotic development programs[7] and it is against this background we should consider neuroactive steroid, 3β-OH [(3β,5β,17β)-3-hydroxyandrostane-17-carbonitrile].

Are preclinical studies a useful guide to neurotoxic propensity in children and neonates? Quite clearly the answer is that we currently have no idea. Given the uncertain relevance of preclinical data to humans then the conduct of additional animal experiments ~~as~~ is unlikely to take us any further forward. What we need to know is whether a drug is safe in humans. Easy to say but difficult to do. If the only valid model for demonstration of anaesthetic neurotoxicity in humans is the demonstration of anaesthetic neurotoxicity in humans then

we are not going to make much progress except through lengthy, expensive and hard to conduct randomised controlled trials.

From a practical standpoint, the "elephant in the room" affecting the development of new hypnotics is the ubiquitous availability of low-cost and safe intravenous anaesthesia using generic propofol formulations. Although there are well known issues with propofol (specifically, the lipid formulation, the risks of bacterial contamination and subsequent sepsis, pain on injection and cardiorespiratory depression), the reality is that virtually every patient may be safely anaesthetised using propofol subject to judicious choice of dosing and appropriate use of fluid and pressors.[8] Any new hypnotic therefore has its business case substantially undermined by the presence in the marketplace of an excellent low-cost generic competitor. For a development project to make progress in the harsh commercial world the compound concerned will need to have a distinct "edge" over its competitors.

In order for a putative non-neurotoxic hypnotic to complete development and approval followed by successful commercialisation and deployment several conditions need to be satisfied. Firstly, the clinical community need to be convinced that paediatric anaesthetic induced neurotoxicity is a reality.[9] At present the data appears to suggest the opposite.[10] Whilst historic data offer some signals that early exposure to general anaesthesia might be associated with neurodevelopmental delay, autism or other markers of impaired brain function the evidence can best be summarised as equivocal and all-parties stress the importance of prospective randomised controlled trials.[11]–To date, the nonrandomised PANDA trial [12] has a negative outcome and we await the five year data from the randomised GAS study knowing as we wait that the two-year planned interim analysis showed no difference between patients receiving general anaesthesia and those who did not.[13] Other

high quality clinical data can be anticipated (including the TREX trial comparing sevoflurane anaesthesia with a technique based mainly upon dexmedetomidine and remifentanil (albeit with a small amount of sevoflurane), ClinicalTrials.gov identifier: NCT02353182. Nevertheless it now seems very likely that none of the current limited portfolio of prospective clinical trials are going to show a convincing anaesthetic effect. What we do then? Would we propose to continue using agents known to be neurotoxic in a range of animal models? In the absence of an alternative the answer can easily become yes. Once we've identified a convincingly non-neurotoxic (at least in animals…) hypnotic the dialogue may change, possibly in a non-rational manner. As scientists we could argue that is logical to continue using understood hypnotics that are known to be neurotoxic in animal models but appear to be harmless in humans. As parents we might think about it differently, preferring compounds which are not neurotoxic even if the known neurotoxicity either doesn't matter to humans or doesn't exist in them. Good luck to the anaesthesiologist attempting to have that conversation with anxious parents shortly before taking their child to the operating room!

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