Article type : Correspondence

The use of intravenous lidocaine for postoperative pain and recovery

As clinicians and research leads for two relevant studies, we read with interest the recently published recommendations on the use of intravenous lidocaine for postoperative pain and recovery [1] and the accompanying editorial [2]. Whilst we agree wholeheartedly with the axiom “primum non nocere” and that intravenous lidocaine must be administered in a safe and controlled manner in the peri-operative setting, we wish to address some concerns regarding the methodology employed in the development of the document and the potential impact on clinical practice and research.

Firstly, the recommendations are labelled as ‘international consensus guidelines’. ‘Consensus’ suggests general agreement with the content of the guidelines; however, this document was written by a panel of seven members from the UK and a single Canadian co-author. This does not constitute 'consensus' and is far from 'international consensus’ [3]. The WHO guidelines state that potential members of a guideline development group are identified by the steering group and are selected to encompass the technical skills, diverse perspectives and geographic representation needed. A group of 10–20 is usually feasible and effective, although some guideline development groups are larger if the scope of the guideline is broad. Furthermore, recommendations on the development of consensus statements include formal and transparent methodology for derivation of guidelines, and peer review [4]. The document does not provide details of the processes employed in the formation of the panel, nor explicit detail as to the methodology used to generate the recommendations in the document, nor evidence of peer review as part of the process. To avoid confusion and, perhaps misleadingly, deterring anaesthetists from using intravenous lidocaine in appropriate and safe settings, these recommendations would be better reclassified as an opinion piece or systematic review. Whilst we understand and respect the editorial independence of the journal, we believe that the journal may have erred in permitting the use of this over-reaching title. This gives the reader the impression of authority of the content of the article, which we believe not to be the case.

Secondly, the document highlights the enduring uncertainty surrounding the dosing strategy of peri-operative intravenous lidocaine and the balance of efficacy and safety in diverse clinical settings. Surely this can now only be addressed by the conduct of large, reliable, multi-centre randomised controlled trials, yet the message of this 'consensus' document may deter investigators from performing such trials. We are aware of four large clinical trials, each recruiting over 500 patients, that are either underway or imminent (Table 1). The dosing strategies in these trials take into account patient weight, the impact of anaesthesia on hepatic blood flow, variations in protein binding, exposure to interacting medications and non-linear pharmacokinetics associated with prolonged infusion [5]. By contrast, and in our opinion, the 'consensus' statement places too much emphasis on absolute upper dose limits for the bolus and infusion phases irrespective of the clinical circumstances. Indeed, data from studies summarised by the authors of these consensus guidelines in their Table 1 and Figure 1 suggest little difference between reported mean lidocaine plasma levels during infusions rates between 1.5 and 3.0 $mg.kg^{-1}.h^{-1}$, with < 5 $mcg.ml^{-1}$ (and upper range 3SD [95%CI] < 10 $mcg.ml^{-1}$) in all but one patient [6].

Lastly, an important omission from the document is whether lidocaine infusions are being used exclusively in the theatre environment or are being continued into the postoperative period. When used intra-operatively, the attending anaesthetist takes responsibility for the safety of the patient during a lidocaine infusion, as they do for all other drugs administered, and the risks of serious adverse events are mitigated by a high level of clinician monitoring and responsiveness. It is appropriate that the 'consensus' statement and the linked editorial have highlighted that individual anaesthetists using lidocaine off-license in this fashion without specific consent are fully accountable, and it is likely that many will continue to do so.

In conclusion, lidocaine is a drug with properties (anti-inflammatory, analgesic, anti-neoplastic) that warrant further phase 3 trials. Such studies are underway, or imminent, and will provide reliable information on the safety and efficacy of lidocaine infusions in patients undergoing colorectal, lung and breast cancer surgery. If these studies report efficacy with acceptable safety then it is possible that the licensed indications for intravenous lidocaine will expand. We do not believe that the document warrants the label “consensus statement” and we do not believe that all the assertions within the document are supported by evidence. The impact of such erroneous assertions may adversely impact much needed clinical trials. Safety is, of course, paramount and this initiative by the authors to raise awareness of the risks of lidocaine infusions is laudable.

J. Dubowitz
Peter MacCallum Cancer Centre
Melbourne, Australia
Email: Julia.dubowitz@petermac.org

A. Toner
Royal Perth Hospital, Perth
Australia

B. Riedel
Peter MacCallum Cancer Centre
Melbourne, Australia

T. Corcoran
Royal Perth Hospital
Perth, Western Australia

No competing interests declared.

References

1. Foo I, Macfarlane AJR, Srivastava D, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. *Anaesthesia* 2020. Epub 3 November. https://doi.org/10.1111/anae.15270
2. Pandit JJ, McGuire N. Unlicensed intravenous lidocaine for postoperative pain: always a safer 'licence to stop' than to start. *Anaesthesia* 2020. Epub 3 November. https://doi.org/10.1111/anae.15286
3. World Health Organization. WHO handbook for guideline development. 2nd edn, 2014. https://www.who.int/publications/guidelines/handbook_2nd_ed.pdf?ua=1 (accessed 09/12/2020).
4. Rycroft-Malone J. Formal consensus: the development of a national clinical guideline. *British Medical Journal Quality and Safety* 2001; **10**: 238-244.
5. Bauer LA, Brown T, Gibaldi M, et al. Influence of long-term infusions on lidocaine kinetics. *Clinical Pharmacology and Therapeutics* 1982; **31**: 433-7.

6. Herroeder S, Pecher S, Schonherr ME, et al. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Annals of Surgery* 2007; **246**: 192-200.

Table 1. Current clinical trials on intravenous lidocaine

Trial name	Trial registration	Location	Sample size	Study design
ALLEGRO	EudraCT 2017-003835-12	UK	562	1.5 $mg.kg^{-1}$ (ideal body weight) bolus over 20 min followed by 1.5 $mg.kg^{-1}.h^{-1}$ infusion for a minimum of 6 and maximum of 12 h
VAPOR-C	NCT04316013	Australia and international	5736	1.5 $mg.kg^{-1}$ (adjusted body weight) bolus over 20 min then 2 $mg.kg^{-1}.h^{-1}$ for 4 h, then 1.5 $mg.kg^{-1}.h^{-1}$ thereafter until the end of surgery
LOLIPOP	Pending	Australia and international	4600	Intra-operative intravenous lidocaine and postoperative subcutaneous lidocaine for up to 24 h postoperatively (ideal body weight) *(ethics pending)*
PLAN	Pending	Canada and international	1144	1.5 $mg.kg^{-1}$ bolus followed by an infusion of 2 $mg.kg^{-1}.h^{-1}$ for the duration of surgery