Format for ANSWERING REVIEWERS

December 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in word format (file name: ESPS Manuscript NO: 14980-review.doc).

Title: Pharmacokinetics and pharmacodynamics of lignocaine: A review

Name of Journal: *World Journal of Anesthesiology*

ESPS Manuscript NO: 14980

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer:

(1) **Reviewer comments**: There are several concerns that I have regarding this paper. A reader with a relatively superficial knowledge of lidocaine can learn a great deal from it. However, there are a few organizational issues. The section entitled "Mechanism of action" is appropriately divided into subsections that clarify the wide variety of pharmacodynamics of lidocaine. One the other hand, the section entitled, "Pharmacokinetics" is lengthy and rambling, making it difficult for the reader to find particular areas of interest. Its organization would benefit greatly by inserting appropriate subheadings in this section. The content of this section appears to be arranged as follows: 1. bolus effects, 2. protein binding, 3. metabolism and excretion, 4. maximum doses, and 5. infusion kinetics. It would serve the paper well to have such headings made explicit.

Authors' response: Thank you for this valuable comment. The manuscript has been reconstructed and divided into organised subheadings to improve the organisational and readability of the text. Specifically, the pharmacodynamic section is divided into subheadings and the pharmacokinetics section has now been divided into the following sections outlined below:

1. History
2. Absorption
3. Protein binding
4. Metabolism and elimination
5. Maximum doses
6. Infusion kinetics
7. Adverse reactions and toxicity

(2) **Reviewer comments:** The end of the paper is rather abrupt. There is no conclusion, little if any mention about future areas of study and no summary. Please expand briefly on providing thoughts about new developments regarding lidocaine, and suggest where research in the field

may be heading. I think that a paragraph or two to summarize would be relatively easy to insert and would greatly improve the flow and continuity for the reader.

Authors' response: Thank you for this constructive comment. The following paragraphs have now been inserted as part of the conclusion:

Lignocaine is a local anesthetic of the amide type and a Class 1b antiarrhythmic with ubiquitous use in medicine for a variety of clinical indications. Its use as a local and regional anesthetic agent and for the treatment and prophylaxis of life-threatening ventricular arrhythmias is well-known. However, accumulating data suggests that in addition to its sodium channels properties, lignocaine possesses a wide range of in vitro and in vivo anti-inflammatory, immunomodulating and anti-cancer effects that show immense promise in a variety of other clinical applications. These effects result from lignocaine interacting with other cellular systems, often exerting effects at concentrations much lower than those required for sodium channel blockade[16,17,34].

The clinical applications of utilising lignocaine in the pharmacological armament for treating inflammatory conditions such as inflammatory bowel disease, acute lung injury, sepsis, burns, peritonitis, infections, myocardial infarction and reperfusion injury, and cancer recurrence continue to be areas of intense clinical research. In the context of anesthesia, patients where perioperative epidural analgesia is contraindicated, intravenous infusion of lignocaine could also be considered as an alternative intervention to modulate the postoperative inflammatory responses[17,34]. Modulation of such responses is therefore relevant to the practice of perioperative medicine and lignocaine may play a critical role in this regard. Finally, defining the roles of lignocaine in these clinical areas are imperative in order to gain more detailed understanding on the mechanism of action of lignocaine on the inflammatory system. Maximizing lignocaines's clinical benefits with its risks of toxicity and harm must be of paramount importance at all times. Well-designed large scale clinical studies are awaited to assess whether the immunomodulating, anti-inflammatory, analgesic, and anticancer effects of lignocaine observed in vivo and in vitro experiments and small clinical trials can be safely applied to routine clinical practice[17].

(3) **Reviewer comments:** Whereas it is interesting that the term "lign" originates from "wood", it would help to suggest a reason for this unusual association.

Authors' response: We were unable to find a reason for this association despite an extensive literature search and contact with senior clinicians and a medical historian. We would like to retain this information for its historical interest.

(4) **Reviewer comments:** Under "pharmacologic considerations" it would be helpful in a review paper to clarify what a type 1b antiarrhythmic is. On reviewing this, I think this statement is OK-spinal, epidural, regional nerve block all have relatively rapid onset of action Under "antiarrhythmic effects", it would helpful to clarify for which arrhythmia lidocaine is useful, i.e. ventricular arrhythmias.

Authors' response: The type of arrhythmia i.e. ventricular arrhythmias, has been included in the text. We have also stated in the "Pharmacological composition" section that "A Class 1b antiarrhythmic agent binds to open sodium channels during phase 0 of the action potential, therefore blocking many of the channels when the action potential peaks".

Under the section "Antiarrhythmic Effects" we have also stated that "lignocaine is indicated for the treatment or prophylaxis of life-threatening ventricular arrhythmias."

(5) **Reviewer comments:** Also, please insert several sentences on how its anti-arrhythmic properties were discovered (initial off-label use, then was adopted as a standard treatment).

Authors' response: Interestingly, the antiarrhythmic effects of lignocaine were discovered accidentally by cardiologists during the course of surgical procedures for which their anesthetic applications were needed. Previouspharmacologiac screening for novel cardiovascular drugs led to the discovery of antiarrythmic and local anesthetic activity of local anesthetic agents. In this context it was demonstrated that local anesthetic agents were effective in suppressing ventricular arrhythmias, a property now common to all Class 1 antiarrhythmic agents.

(6) **Reviewer comments:** Under "antinociceptive effects", (The antinociceptive effects of lignocaine are thought to be due to the blockade of neuronal sodium channels and potassium currents, and the blockade of presynaptic muscarinic and dopamine receptors) please clarify if you are referring to peripheral or central effects of lidocaine here. Be more precise in defining sites of action with muscarinic and dopamine receptors.

Authors' response: This has been clarified. Under the section "Antinociceptive Effects" we have added in the following:

"The antinociceptive effects of lignocaine are thought to be due to the blockade of neuronal sodium channels and potassium currents1[12, 13], and the blockade of presynaptic muscarinic and dopamine receptors[14,15]. Whilst it is generally accepted that local anesthetics suppress transmission of pain by blocking voltage-gated sodium channels of peripheral nerves, local anesthetics also have been shown to block sodium and potassium currents centrally, specifically targeting the spinal dorsal horn neurons[13]. The molecular mechanisms of these actions are complex and further characterization is an important central step in understanding the complexity of local anesthetic mechanism of action during central neuaxial blockade with spinal and epidural anesthesia. The exact nature of these mechanisms requires further characterisation."

(7) **Reviewer comments:** It is not clear what route of administration is required for lidocaine to help treat edema. Is this in use clinically? Therefore, the anti-inflammatory effects of lignocaine are thought to be due to the inhibition of the release of several critical inflammatory mediators, in addition to its direct effects on polymorphonuclear granulocytes and macrophage function. Please comment on how clinically important this effect is.
Authors' response: We have now stated in the manuscript that "Whilst lignocaine's antinociceptive effects are thought to be due to the blockade of neuronal sodium channels and potassium currents[12,13], and the blockade of presynaptic muscarinic and dopamine receptors[14,15], its anti-inflammatory effects are complex and multifactorial. In vitro pre-incubation of human polymorphonuclear granulocytes or monocytes with varying concentrations of lignocaine have been reported to inhibit leukotriene B4 release[18], Leukotriene B4 in combination with prostaglandin E2 can induce oedema formation; therefore blockade of these cells may explain lignocaine's beneficial effects on oedema prevention[19]. In these studies, the treatment of the peritoneum with intravenous local anesthetic solutions resulted in a reduction of the amount of Evans blue-albumen extravasated from areas of inflammation, with histological examinations supporting these clinical findings. However, in the perioperative

setting, development of edema is complex and multifactorial. Further clinical studies are needed to evaluate the effects of intravenous lignocaine on the development of edema in this setting.

(8) **Reviewer comments:** Is lidocaine commonly used as an anti-inflammatory agent? If so, in what clinical context? If not, why not?

Authors' response: Under the section "Anti-inflammatory Effects" the following has paragraph has now been included:

"Lignocaine has potential utility as a powerful anti-inflammatory agent, although to date there is a lack of well-designed studies to support its use in most clinical settings. A variety of lignocaine's actions on inflammatory cells have also been described, many of which suggest that lignocaine plays an important role in modulating the inflammatory response. Accumulating data suggest that the potent anti-inflammatory properties of lignocaine may be superior in several aspects to the traditional anti-inflammatory agents of the NSAIDS and steroids[16], however lignocaine is not approved for this specific indication and potential risks of toxicity (see below), particularly in unmonitored patients, may negate its beneficial antiflammatory effects. However, Cclear evidence exists, in vitro as well as in vivo, for anti-inflammatory properties of local anaesthetic solutions[16,17]. Effects on polymorphonuclear granulocytes and free radical release, as well as migration to the site of action, appear most important. Unfortunately, little is known about the specific molecular mechanisms involved in these effects. In many instances, sodium channel blockade can be excluded, either because in vitro sodium channels are not detectable in the cells under study, or because in vivo local anaesthetic solutions induce effects at concentrations much lower than those required for sodium channel blockade[17].

(9) **Reviewer comments:** Since the degree of plasma protein binding in the foetus is less than that in the mother, the total plasma concentration will be greater in the mother, although free lignocaine concentrations will be the same. It would be useful to review the concept of ion-trapping at this point, and how the ionization of lidocaine effect its solubility, movement across membranes, and clinical effects.

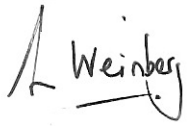
Authors' response: This section has been modified accordingly. The following section has been included under the "protein binding section":

"Foetal lignocaine concentration may be increased by transmembrane pH gradients, such as foetal acidosis, and associated ion trapping[9]. Lignocaine may exist in ionised or unionised form depending on the pH of the environment. As a weak basic drug, lignocaine tends to be more un-ionised and apt able to cross cell membranes in basic media[10]. In foetal acidosis lignocaine crosses the placenta in unionised form, becomes ionised given the acidic environment of the foetal circulation and becomes 'trapped', thus increasing foetal lignocaine concentration."

Thank you again for publishing our manuscript in the *World Journal of Anesthesiology*.

With warm regards,

A/Prof Laurence Weinberg (BSc, MBBCh, MRCP, DipCritCareEcho, FANZCA, MD)



Anaesthetist, Department of Anaesthesia, Austin Hospital, and Principal Fellow, Department of Surgery, and Anaesthesia Perioperative Pain Unit, University of Melbourne, Victoria, Australia

Address for correspondence
Department of Anaesthesia
145 Studley Rd, Heidelberg, Victoria, 3084, Australia
Email: Laurence.Weinberg@austin.org.au
Telephone: +0061 39496 5000, Facsimile: +0061 3 9459 6421