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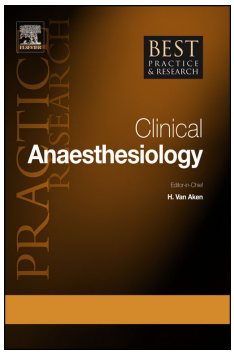

Intravenous lidocaine

Jean-Pierre Estebe, MD, PhD

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Intravenous lidocaine

Jean-Pierre Estebe MD, PhD

Corresponding author: Jean-Pierre Estebe

Department of Anesthesiology, intensive Care, and Pain Medicine

University of Rennes

CHU of Rennes

Rue H Le Guilloux, 35033, Rennes, Cedex 9, France

Phone: + 33 2 99 28 93 76

Email: jean-pierre.estebe@chu-rennes.fr

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Abstract: Lidocaine has analgesic effect, anti-hyperalgesic and anti-inflammatory properties, which makes it use as a general anesthetic adjuvant. Lidocaine is capable of reducing nociception and/or cardiovascular responses to the surgical stress, and postoperative pain and/or analgesic requirements. However, its mechanisms of action remain unclear, despite its different known properties. If the exact mechanism of action remains not fully explained; bolus then continuous lidocaine infusion has clear analgesic benefits. Lidocaine is one of major drug for opioid reduced anesthesia (ORA) or opioid free anesthesia (OFA) procedures. It clearly improves the postoperative outcomes with increased patient satisfaction. Such procedure takes place wisely in the enhanced recovery after surgery (ERAS) protocols. With recommended protocols, safety will be as great as his efficacy.

Keywords: lidocaine, analgesia, pharmacokinetic and pharmacodynamics, safety, opioid free anesthesia

Practice points:

- A: Lidocaine with initial bolus and continuous infusion has clear analgesic benefits, particularly for sparing opioids (opioid reduced anesthesia) or to avoid opioids (opioid free anesthesia).

- B: Based on various meta-analysis, recommended lidocaine doses in the perioperative period are 1-2 mg/kg as an initial bolus followed by a continuous infusion of 1-2 mg/kg/h. In case of long surgical procedures, it could be wise to recommend decreasing progressively the rate of lidocaine continuous infusion (approximately a reduction of half every 6 h). Because there is no clear benefit to prolong the infusion, it could be recommended to stop the infusion of lidocaine at the end of the post anesthesia care unit stay.

Research agenda:

- A: Further research is warranted to evaluate the safety in terms of pharmacokinetic particularly when lidocaine is used in continuous infusion and with different possible interactions (drug-drug interactions, metabolic or genetic interactions).

- B: To evaluate the pharmacodynamics. The mechanism of action remains unclear and probably not only resume to blocking the voltage-gated sodium channels.

- C: When the mechanism of action will be clarified, it would be interesting to develop some tools for the monitoring of "pain" before, during and after surgery.

- D: Dose-ranging studies could be useful to understand which was the best protocol of administration for a specific patient during a specific surgery.

Introduction:

Lidocaine (or 2-(diethylamino)-N-(2.6-dimethylphenyl) acetamide) is the main prototype of amino-amide local anesthetics (LA). It has analgesic effect, anti-hyperalgesic and anti-inflammatory properties, which makes it use as a general anesthetic adjuvant. Lidocaine is capable of reducing nociception and/or cardiovascular responses to the surgical stress, and postoperative pain and/or analgesic requirements. However, its mechanisms of action remain unclear, despite its different known properties.

1. Efficacy

1.a: Perioperative pain.

From earliest randomized trials for abdominal surgery (from Rimbäck to de Oliviera)[1, 2], various meta-analysis confirmed the efficacy of the intravenous (i.v.) lidocaine administration. From the earliest systematic review and meta-analysis [3-5] to the latest [6, 7], it is interesting to note that existing reviews found similar results. These reviews demonstrate that patients undergoing any elective surgery under general anesthesia had a significant reduction of pain and/or opioid requirements during the 24 postoperative hours.

Subgroup analysis suggested that the best benefit is for abdominal surgery (laparoscopic or open surgery)[6, 7]. The effects on gastrointestinal tract (decrease postoperative ileus, shortens both the time to first flatus and the time to first bowel movement, decrease of postoperative nausea and vomiting) are probably one of the major effects of lidocaine. Although it still debated, it has been reported that lidocaine could shorten the length of hospital stay (LOS) after abdominal surgery [8] or radical retropubic prostatectomy [9].

The analgesic effect of lidocaine has been already mentioned in some other aspects of anesthesia. The efficacy of lidocaine was described decreasing pain on the injection of propofol [10], to decrease the cardiovascular reaction to the tracheal intubation and to decrease postoperative sore throat [11].

1.b Comparison to the gold standard: the epidural

Epidural analgesia has been proposed as the criterion-standard analgesic for major abdominal surgery. Recent reviews have failed to find a significant difference between epidural and lidocaine infusion [12]. Because of its similar mechanisms of action, some authors called lidocaine infusion "the poor man's epidural" [13] despite the fact that the results of the continuous lidocaine i.v. infusion show, more or less, the same efficacy of epidural for abdominal surgery [14-16].

1.c Chronic pain:

Lidocaine has several properties, particularly in the treatment of central and peripheral neuropathic pain [17, 18]. In a neuropathic model (spinal nerve ligation), it has been reported three phases in the analgesic efficacy of lidocaine infusion [19]. The first is described during the infusion with returning to the pre-infusion level within 30-60 min, an intermediate phase with a transient improvement slightly later (360 min in this rat model), and a last phase of efficacy observed from 24 h after infusion, and sustained over the next 21 days. A recent review confirms the efficacy of lidocaine on the neuroinflammation response in perioperative pain and chronic neuropathic pain [20). For the record, a long time ago lidocaine was also proposed for the treatment of pancreatitis pain [21]. Its efficacy was reported on some opioid-refractory pain [22].

Although it is not yet clearly demonstrated, lidocaine can make a potentially useful drug for the prevention of persistent postoperative pain (or chronic postoperative pain) [23, 24].

2. Safety

2.a Pharmacokinetic:

Lidocaine is a weak base (cationic molecule with ionization constant pKa 7.9) and poorly hydrosoluble. After i.v. administration, lidocaine is initially distributed to highly vascularized organs (i.e. brain, kidneys, and heart), and then to less vascularized tissue (i.e. skin, skeletal muscle, and adipose tissue). The volume of distribution is around 91 L.kg-1.

Up to 60 to 80 % of lidocaine is bound to plasma protein (albumin, mostly with α-1 acid glycoprotein which increases postoperatively and in elderly patients, and

lipoprotein). It is interesting to point out that is has been reported experimentally that albumin administration could decrease brain extraction of lidocaine [25].

Interestingly, after i.v. lidocaine administration, 40% is temporarily extracted during first pass through the lung [26]. This is partially due to the lowest lung *pH* than that of the plasma, but mainly due to metabolization by cytochrome P 450 (CYP) (particularly for CYP2D subfamily CYP2B1, CYP1A2, and/or other enzymes). This is why this lung trapping reduces the risk of intoxication in cases of accidental i.v. administration compared to the intra-arterial administration.

Then, 90 % of lidocaine undergo hepatic metabolism (CYP 3A4) with active metabolites like monoethylglycine xylidine (MEGX), N-ethylglycine (EG) or glycinexylidide (GX) [27]. During lidocaine continuous infusion the accumulation of theses metabolites may inhibit the biotransformation of lidocaine [28] and might have been implicated in some cases of intoxication. The clearance rate of lidocaine is around 0.85L/Kg/h.

Finally, lidocaine is eliminated by the kidney (10% of lidocaine is eliminated unchanged in the urine). The half-life of lidocaine is 1.5-2h after a bolus lidocaine administration. The half-life could be prolonged around 3h in obese patients. After continuous lidocaine infusion, the half-life could be prolonged more than 3h after 24h administration to 6.9h after 48h of lidocaine administration [29]. So, it is important to remember the risk of accumulation during a continuous administration and to decrease the rate of lidocaine infusion with the time [30].

2.b Drug-drug interactions:

Ketamine usually used in association with lidocaine for opioid reduced (ORA) or opioid free anesthesia (OFA), could prevent lidocaine induced convulsion state. However, ketamine could impair cognitive function due to enhancing neuro-toxicity of lidocaine (particularly at the level of hippocampus and amygdale)[31]. General anesthesia, probably by numerous drug-drug interactions, could increase the lidocaine plasma concentration and the amount of lidocaine into the brain [32]. This drug-drug interaction was experimentally reported when beta-blocker [33] or clonidine [34] were co-administered with lidocaine. The pharmacokinetic interactions could have considerable implications for clinical practice (i.e. decrease in the effective analgesic dose of lidocaine avoiding any undesirable effects). Conversely, depth of anesthesia

requires lower minimum alveolar concentration (MAC) of volatile anesthetics or rate of propofol target-controlled infusion.

2.c Receptors

2.c.1 Sodium channels:

Like all local anesthetics, lidocaine has little or no selectivity among different types of sodium (Na^+) channels [for review see 35]. Typically, lidocaine produces blocking voltage-gated sodium channels (VGSC or Nav) that induce the inhibition of action potential propagation and of the neuronal excitability. This mechanism is established for regional anesthesia. However, the underlying mechanism of i.v. lidocaine may be more complex than simply the blockade of peripheral impulses to the nerve.

Function of the mechanisms of pain involved, it has been reported that tetrodotoxin (TTX)-sensitive Na^+ channels (Nav1.3 and Nav1.7) are activated after nerve injuries or inflammation. It has also been suggested that TTX-resistant Na^+channels (Nav1.8 and Nav1.9) are especially important in neuropathy. In the case of naïve patients (or animal) with normal pain thresholds, the analgesic mechanisms of i.v. lidocaine have not yet clearly been described.

VGSC are undoubtedly one of sites of action of lidocaine. They are heteromeric integral membrane glycoproteins formed with association with α-subunits and regulatory β-subunits (β1- β4). Ten different mammalian α-subunits (Nav1.1-Nav1.9 and Nax)[see for review 36] are described. Briefly; Nav1.1, Nav1.2, Nav1.3, and Nav1.6 isoforms are mainly expressed in the central nervous system (CNS) (target of the antiepileptic drugs), genetic deficiency induces seizures or decrease of LAs efficacy [37]. In contrast, Nav1.7, Nav1.8, and Nav1.9 are predominantly located in the peripheral nervous system (target of lidocaine and all LAs, genetic deficiency induces pain or insensitivity).

Nav1.4 isoform is mainly expressed in skeletal muscle (genetic deficiency induces myotonia), while Nav1.5 is the specific cardiac isoform (genetic deficiency induces arrhythmia). Interestingly it has been recently described a Nav1.5 isoform reported into the gastrointestinal tract [38]. This could be one explanation for the efficiency of the lidocaine in the quick recovery of intestinal transit. Indirectly, it is interesting to note

that in the irritable bowel syndrome due to mutations on the Nav1.5 isoform; the treatment with mexiletine, which exerts its pharmacological action through the blockade of VGSC, increases the bowel movements as similar results observed with lidocaine administration [39].

The affinity of lidocaine for VGSC varies according to the conformation of the channels, being greater when the channel is open (i.e. active or inactive) and lower when it is closed (i.e. deactivated or at rest). However, it should be noted that at low concentrations lidocaine induced only 50 % of inhibition of the VGSC is observed [40], which suggest another mechanism of action.

2.c.2 Other receptors:

Moreover, increasing evidence has indicated that lidocaine affects other channels such as calcium (Ca^{2+}) channels, potassium (K^{+}) channels, and transient receptor potential channels. These other receptor sites are not located in the periphery, but in the brain or in the spinal cord.

Recently, the hyperpolarization-activated cyclic nucleotide (HCN) channels has been identified as one of the central nervous system (SNC) targets of analgesics action of lidocaine (i.e. thalamus, hippocampus, spinal cord, and dorsal root ganglion) [41]. Inhibition of HCN currents may down regulate the spinal cord excitability prolonging the lidocaine efficacy largely more than it could be explained by its pharmacokinetics.

Lidocaine decreases post-synaptic depolarization mediated by N-methyl-D-aspartate (NMDA) receptors by inhibiting protein kinase C (PKC)[42, 43]. Lidocaine, and probably all ester-type LAs, inhibits the NMDA receptor (one of the major receptor channels for rapid excitatory neurotransmission) by various mechanisms [44, 45]. Experimental data suggested that the site-of-action might be in close proximity, but is not identical to, that for magnesium (Mg^{2+}) and ketamine blockade [44, 46].

The effects of lidocaine on G protein-coupled receptors (GPCR) have been described explaining its anti-inflammatory and anti-thrombotic actions [47]. These effects seem to be time dependent [48].

Lidocaine interacts with different K^{+} channels [49]. At low concentrations lidocaine suppresses the tonic firing pattern of tonic firing neurons by an interaction with voltage-gated K^{+} channels (whereas adapting firing neurons block was explained by the interaction with the VGSC) [40]. Lidocaine also acts on postsynaptic neurons to

hyperpolarize the membrane. This mechanism could be explained by a facilitating effect on descending inhibitor system and increase the release of noradrenaline or serotonin, which causes hyperpolarization by opening K+ channels [46].

Like cocaine, lidocaine increases the intracellular calcium (Ca^{2+}) concentration in sensory cortex [50]. It has been reported that modulation of Ca^{2+} currents in somatosensory neurons is one of the mechanisms underlying neuropathic pain [51]. Low voltage-activated T-type calcium channels (Ca*v*3.1, Ca*v*3.2, and Cav3.3) are involved in pain signaling. The Ca*v*3.2 subtype seems to be particularly involved in somatic neuropathic pain (nerve injuries, diabetes, toxic chemotherapy) and in visceral pain (colonic hypersensitivity) [52].

2.d Pharmacodynamic:

Although the underlying mechanisms of action of i.v. lidocaine remains unclear, its pharmacodynamics efficacy is demonstrated. The optimal plasma concentration of lidocaine observed after i.v. administration (1-2 mg/kg) is largely under (below 5µ/mL) the optimal concentration required to block peripheral nerve fiber impulses (i.e. 4 to 20 µM vs. 300 to 800 µM)[46]. This is why the lidocaine analgesic effect could be explained by another mechanism (as described above) than that of the main theory of the Na^+ channels blockade.

Similar discussion could be made about the risk of tumor recurrence and metastasis. It must separate the local efficacy of lidocaine at high doses (i.e. direct cells toxicity) and the potential systemic effects at very low concentrations [53-56].

2.d.1 Systemic

Lidocaine is a class 1b antiarrhythmic drug with little pro-arrhythmic effects. This effect is due to the blockade of VGSC. Because it reduces intracellular Na^+ and prevents Ca^{2+} overload; it has been recently reported experimentally protective effect on cardiac function after myocardial ischemia [57] and could be involved in the reduction of infarct size [58].

2.d.2 Inflammation

We must separate the antimicrobial effect reported only for the local administration of lidocaine (therefore at high tissue lidocaine concentrations) to the

systemic effects at low concentrations. Lidocaine has significant anti-inflammatory properties, reducing the *in vitro* and *in vivo* release of pro-inflammatory cytokines (e.g. interleukin-1β, TNF-α, nuclear factor κB, monocyte chemo-attractant protein-1) by reducing neutrophil activation [see for reviews 59-61]. The inhibitory effects of lidocaine on the priming process of poly morpho nuclear neutrophils are more relevant than those observed with the amide local anesthetic (LA)s class [47]. This action does not seem to impair the healing process, as reported experimentally [62]. Any interaction in the healing process was never described in the clinical review as a potential adverse effect [3-7].

In addition to its anti-inflammatory properties, it has been reported that lidocaine could increase the Natural Killer (NK) T cell activity [55]. Lidocaine may have therapeutic benefit by attenuating vascular inflammation, which would minimize microvascular endothelium injury and inflammatory hyperpermeability [63]. Therefore it isn't surprising to find that this complex mechanism on the inflammatory cascade and the immune system of lidocaine infusion, has beneficial effects as it was recently reported in retrospective evaluation of medical records of dogs with septic peritonitis underwent laparotomy [64]. Systemic administration of lidocaine exerted a protective effect cell-mediated immunity could reduce the occurrence of postoperative septic complications and tumor metastasis formation [65, 66].

2.d.3 Blood-brain barrier

As described above, the main target of lidocaine is the CNS (i.e. brain and the spinal cord); so it must cross the pharmacologic blood-brain barrier (BBB, blood spinal cord barrier, and blood-nerve barrier for the peripheral nerves). Molecules must be transported by active system in either direction through the BBB (as an example, GLUT-1 transporter is an active transporter from plasma to brain, and P-glycoprotein is highly active in extruding multitude of molecules). Therefore, it makes sense to think that there is some delay between the i.v. lidocaine administration and its action into the brain, spinal cord, and nerve [67]. Experimentally, it has been reported a delay around 15 min to observe an equilibrium between plasma and extracellular brain space [68]. This similar delay was recently confirmed in humans study [69].

In some pathological situations, like nerve injury (which might contribute to the development of neuropathic pain), it was reported a modification in the permeability of

the BBB [70]. It is possible to imagine, though it has never yet been studied, that the potential modification of the BBB permeability could modify the diffusion of the lidocaine. Similarly, some drugs like the one used under general anesthesia, could also interfere with the BBB permeability to lidocaine [71].

3. Toxicity:

Perioral paresthesia, metallic taste, slurred speech, diplopia, light headedness, tinnitus, confusion, agitation, muscular spasms and seizures have been reported when the lidocaine plasma concentration was higher than 5-8 μg/mL.

Under general anesthesia, cardiovascular toxicity could the only detectable signs (bradycardia, increase intervals, and widening QRS complex) of intoxication. This cardiac toxicity may be increased in cases of hypercapnia. However, at clinical doses of lidocaine infusion, more than cardiac toxicity, the cardio-protective effect of lidocaine has been confirmed in prospective randomized study with patients scheduled for coronary artery bypass graft [72].

Similarly, whereas at lower doses of lidocaine it has been reported an increase of brain inspiratory activity; at very high doses it was observed a ventilator depression [73].

Lidocaine induced convulsions could be provoked by the activation of limbic structures such as hippocampus and amygdala 6 or from decreasing the cortical inhibitory neurons. At usual clinical concentrations, more than anticonvulsant action, it has been reported that lidocaine may be an effective neuro-protective agent in treating early postoperative cognitive dysfunction (POCD)[74]. This cerebral protection could be explained via many mechanisms (reducing cerebral metabolic rate, reducing ischemic excite-otoxin release, and decelerating the ischemic trans-membrane ion shift) but probably overall by its anti-inflammatory and anti apoptotic properties. Clinically, lidocaine alone has very few effects on the bispectral index (BIS)[75].

4. Protocol of administration:

The recommended lidocaine doses in the perioperative period are 1-2 mg/kg as an initial bolus (earlier as possible to anticipate the onset of action and as prevention of propofol injection) followed by a continuous infusion of 1-2 mg/kg/h. In case of long surgical

procedures, it could be wise to recommend decreasing progressively the rate of lidocaine continuous infusion (approximately a reduction of half every 6 h). Clinically, based on his safety and efficacy, it was usually recommended to prolong the infusion of lidocaine for 24 to 48 hours. However, in two recent reviews and meta-analysis [7, 76], it was reported that there is no clear benefit to prolong the infusion beyond post anesthesia care unit (PACU). This prolonged effect could probably be due to the prolongation of the half-life of the lidocaine and its metabolites as described above. So, it could be recommended to stop the infusion of lidocaine at the end of the PACU stay. It is probably not recommended to add another LAs administration (infiltration or regional anesthesia) due to the risk of cumulative LAs toxicity.

In opioid free anesthesia (OFA) protocol, and because many of the drugs used in continuous infusion (anti-NMDA receptors, α-2 agonists receptors, anti-inflammatory drugs, magnesium sulfate, etc.), have a similar mechanism of action, or at least, a very close target; the doses may be slightly reduced. Similarly, because all these analgesic molecules have a sedative action, the target dose of the drugs used for anesthesia must be reduced (i.e. propofol or volatile agents) particularly in case of close monitoring of depth of anesthesia and cardiovascular response.

Conclusion

If the exact mechanism of action remains not fully explained; continuous lidocaine infusion has clear analgesic benefits, particularly into OFA or ORA procedures. It clearly improves the postoperative outcomes with increased patient satisfaction. Such procedure takes place wisely in the enhanced recovery after surgery (ERAS) protocols.

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