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REVIEW

Pharmacokinetics and pharmacodynamics of lignocaine: A review

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Abstract

Lignocaine is an essential drug on World Health Organisation essential drug list, considered efficacious, safe and cost-effective for any health-care system. Despite its ubiquitous use in medicine and surgery, there are few detailed reviews of its pharmacokinetics and pharmacodynamics. Being an amide-type local anesthetic and Class 1b antiarrhythmic, lignocaine is most frequently used clinically for its anesthetic and antiarrhythmic benefits. However, lignocaine has important antinociceptive, immuno-modulating, and anti-inflammatory properties. Information pertaining to the pharmacokinetics and pharmacodynamics of lignocaine was examined by performing a literature search of PubMed, Embase and MEDLINE (*via* Ovid), pharmacology textbooks and online sources. We present a focused synopsis of lignocaine's pharmacological composition, indications for use and mechanisms of action, focusing on its anti-inflammatory, immuno-modulating and analgesia effects. In addition we review the dosing regimes and infusion kinetics of lignocaine in the clinical setting. Finally, we review the evidence for ligocaine's modulation of the inflammatory response during major surgery and its specific effects on cancer recurrence. These indirect effects of local anesthetics in tumor development may stem from the reduction of neuroendocrine responses to the stress response elicited by major surgery and tissue damage, enhanced preservation of immune-competence, in addition to opioid-sparing effects of modulating tumor growth.

Key words: Lignocaine; Humans; Pharmacokinetics; Pharmacodynamics; Adult

Core tip: Lignocaine is a widely used amide-type local anesthetic and Class 1b antiarrhythmic. In addition to its anesthetic and antiarrhythmic effects, lignocaine has

important analgesic, antinociceptive, immuno-modulating, and anti-inflammatory properties. Understanding the pharmacokinetics and pharmacodynamics of lignocaine will enable clinicians to safely prescribe lignocaine in a variety of clinical settings.

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INTRODUCTION

Lignocaine, commonly referred to as "Lidocaine", is an amide local anesthetic agent and a Class 1b antiarrhythmic. Lignocaine is an essential drug on World Health Organisation essential drug list, considered efficacious, safe and cost-effective for any health-care system. Despite its ubiquitous use in medicine and surgery, there are few detailed reviews of its pharmacokinetics and pharmacodynamics. We present a focused synopsis of lignocaine's pharmacological composition, indications for use and mechanisms of action, focusing on its anti-inflammatory, immuno-modulating and analgesia effects.

SEARCH

Search strategy

Information pertaining to the pharmacokinetics and pharmacodynamics of lignocaine was examined by performing a literature search of PubMed, Embase and MEDLINE (*via* Ovid), pharmacology textbooks and online sources. Only articles in the English language and human studies were considered. There were no date restrictions applied to the MEDLINE and Central searches. The last search update was in November 2014. The online databases were searched for the following terms: "lidocaine", "lignocaine", "humans", "pharmacokinetics", "pharmacodynamics", "adult". Specifically, clinical information relevant to the pharmacokinetics and pharmacodynamics of lignocaine was included in this literature review.

Search results

Using a combined search strategy, a total of 7311 articles were revealed. A further search confining the results to "humans" and "English language" revealed 216 information sources and titles, of which 81 references were examined for analysis. A detailed review was undertaken that included the screening of manuscript or abstract titles against the key search criterion. A total of 120 articles were included in this review.

BACKGOUND

Nils Löfgren, Bengt Lundqvist, and Holger Erdtman were the three pioneers who were instrumental in the development of LL30, later developed into the solution known today as "lignocaine". Lignocaine, as detailed by Professor Wildsmith[1-3], was first synthesized in 1942, approved for use in humans and launched in 1948 in Sweden, patented in United States in 1948, and launched in 1949 after Food and Drug Administration approval. Lidocain and Xylocain were the original proprietary and trade names chosen for LL30: Lidocain because it is an acetanilide, and Xylocain because m-xylidide is the major reagent in its synthesis. In the United States the "e" was added to each, hence the names Xylocaine and Lignocaine. Lignocaine was the generic name in the United Kingdom from 1950 until Recommended International Non-proprietary Names were required by European law. The name was derived from the Greek "xylo", or the Latin, "ligno", both meaning "wood" originally[4].

Interestingly, cardiologists discovered the antiarrhythmic effects of lignocaine accidentally during surgical procedures requiring the local anesthetic's use. Previous pharmacologic screening for novel cardiovascular drugs led to the discovery of anti-arrythmic 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 common to all Class 1 antiarrhythmic agents.

PHARMACOLOGICAL COMPOSITION

Lignocaine, 2-diethylaminoaceto-2',6'-xylidide ($C_{14}H_{22}N_2O$), is a amide local anesthetic and a Class 1b antiarrhythmic agent according to the Vaughn Williams classification[5]. 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. Lignocaine is a stable, crystalline, colourless solid whose hydrochloride salt is water soluble[6]. Solutions for injection are available with or without adrenaline. All lignocaine solutions should be protected from light and maintained at a room temperature of approximately 25 degree Celcius or 77 degree Fahrenheit[7].

INDICATIONS

The indications of lignocaine include the requirement for local, neuraxial, regional or peripheral anesthesia by infiltration, block or topical application, or the prophylaxis or treatment of life-threatening ventricular arrhythmias. It has also been extensively used for chronic and neuropathic pain management, and more recently as an intravenous infusion for the management of postoperative analgesia and surgical recovery.

MECHANISM OF ACTION

Local anesthetic blockade

Similar to other local anesthetics, the mechanism of action of lignocaine for local or regional anesthesia is by

reversible blockade of nerve fibre impulse propagation[7]. Some local anesthetic is removed by tissue binding and circulation when lignocaine is infiltrated near a nerve[8]. The remaining anesthetic enters the nerve cells by diffusion through membranes. Lignocaine then binds to sodium channels, causing a conformational change that prevents the transient influx of sodium, therefore depolarisation[9]. All potentially excitable membranes are affected, however sensory fibres are blocked preferentially because they are thinner, unmyelinated and more easily penetrated[10]. Lignocaine's onset of action is rapid, and blockade, whilst dependent of dose given, concentration used, nerves blocked and status of the patient, may last for up to 5 h when administered as a peripheral nerve block[7].

Antiarrhythmic effects

An important indication for lignocaine is prophylaxis or treatment of life-threatening ventricular arrhythmias. The mechanism of action of lignocaine for its antiarrhythmic action is by direct effect on mammalian Purkinje fibres. By decreasing the slope of phase 4 and changing the excitability threshold, lignocaine reduces automaticity[9]. This results in a decrease of both the action potential length and the refractory period duration of the Purkinje fibres[11]. The PR interval, QRS and QT durations are not commonly effected by lignocaine[9]. There is no evidence of any important interactions between lignocaine and the autonomic nervous system, thus lignocaine has minimal effect on autonomic tone[11].

Antinociceptive effects

The antinociceptive effects of lignocaine are thought to be attributable to the blockade of neuronal sodium channels and potassium currents[12,13], and the blockade of presynaptic muscarinic and dopamine receptors[14,15]. Local anesthetics have also been shown to block sodium and potassium currents centrally at a spinal cord level, specifically targeting the spinal dorsal horn neurons, in addition to their generally accepted peripheral nerve blockade[13]. The mechanisms of these actions at the molecular level are complex and further characterization will be integral in our understanding of central neuraxial anesthesia.

Anti-inflammatory effects

Lignocaine has potential utility as a potent anti-inflammatory agent, although to date well-designed studies are lacking to substantiate its use in most clinical settings. A variety of lignocaine's actions on inflammatory cells have been described. Accumulating data suggests that lignocaine's powerful anti-inflammatory properties may be superior in many ways to nonsteroidal anti-inflammatory drugs and steroids, the traditional anti-inflammatory agents[16,17]. 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. Unfortunately, the specific molecular mechanisms involved in the migration of polymorphonuclear granulocytes and free radicals are not well known. Sodium channel blockade can be however excluded. Firstly, because *in vivo* local anesthetic solutions are active at lower concentrations than those required for blockade of the sodium channel, and secondly because sodium channels *in vitro* are often not even detectable in the cell lines that are being investigated[17].

Whilst lignocaine's antinociceptive effects are thought to be secondary 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], Both leukotriene B4 and prostaglandin E2 can induce edema; therefore the blockade of these cells may explain lignocaine's beneficial effects on tissue inflammation and edema 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. To evaluate the effects of intravenous lignocaine on the development of edema in this setting, further clinical studies are required.

Lignocaine has been documented to block the release of interleukin-1 (IL-1), an inflammatory mediator acting on polymorphonuclear granulocytes, which in turn activates phagocytosis, respiratory burst, degranulation and chemotaxis[16,17]. This reduction in the release of interleukins may also contribute to lignocaine's anti-inflammatory effects. *In vitro*, lignocaine, at concentrations of 0.2-20.0 mmol/L, has been shown to inhibit IL-1 production in peripheral blood mononuclear cells[18]. *In vivo* studies have shown that at high micromolar concentrations, lignocaine can inhibit histamine release from human leukocytes, mast cells, and cultured basophils[20]. Accordingly, the anti-inflammatory actions of lignocaine are thought to be attributable to lignocaine's direct effects on macrophage and polymorphonuclear granulocyte function, in addition to its inhibition of the release of several critical markers of the inflammation cascade.

Arachidonic acid (released from phospholipids) and the subsequent generation of bioactive eicosanoids have a critical function in the regulation of tissue preservation and the patho-physiological response to organ injury and ischemia[21]. This critical sequence of biological processes is modified by lignocaine's action on the enzymes phospholipase A2, cyclooxygenase and lipoxygenase. Lignocaine interacts in a dual manner with phospholipase A2; causing inhibition of its activity at high concentrations and stimulating activity at lower concentrations[22,23]. Lignocaine has been shown to inhibit

spontaneous prostaglandin biosynthesis, in early *in vitro* studies[24,25]. Lignocaine administration significantly inhibited prostanoid release and biosynthesis from human gastric mucosa in response to experimental damage[26-28]. In dogs with cardiac arrhythmias the release of prostaglandin was seen to be inhibited during systemic administration of lignocaine[29]. Lastly, topical lignocaine has been shown to inhibit prostaglandin release when used clinically for the treatment of burns in an animal model[30], confirming other studies that report reduced prostaglandin release from gastric mucosa as a result of lignocaine intervention[26]. These inhibitory effects on prostaglandin release may explain some of the powerful antinociceptive and anti-inflammatory effects of intravenous lignocaine described in patients with severe burns[31,32].

Numerous *in vivo* and *in vitro* studies demonstrate the effects that lignocaine have on thromboxane B2 release[26,28,33]. Lignocaine has an inhibitory effect on thromboxane induced platelet aggregation, which may contribute to reduced incidence of venous thrombosis[34,35]. In addition, early studies demonstrate that lignocaine at low concentrations can powerfully inhibit the release of histamine from activated mast cells[36,37]. Lignocaine also has important effects on oxygen free radical production. The inhibition of free oxygen radical formation (such as superoxide anions) by lignocaine has been eloquently demonstrated in clinical trials[38,39]. The mechanism of action of this direct scavenging effect is due to lignocaine's interaction with protein and phospholipid membranes, the interference with mitochondrial radical formation[40], and the prevention of free radical production[41].

Antibacterial activity

Lignocaine has also been shown to possess antibacterial activity[16]. The potent effects of lignocaine on antimicrobial activity are related to lignocaine's concentration and pharmacological structure. Structure is of lesser importance as both amide and ester type local anaesthetics can inhibit bacteria in high enough concentrations[42]. Lignocaine has been shown to have important inhibitory actions on various strains of bacterium, including important Gram-positive cocci such as *Staphylococcus aureus* and *Streptococcus pneumonia*, and Gram-negative bacteria such as *Haemophilus influenza* and *Pseudomonas aeruginosa*[16,43-46]. Lignocaine's anti-bactericidal effects are poorly understood, however complex interactions between the local anesthetic solutions and the bacterial wall[47] or with macromolecules at the surface of the bacterium[44] have been implicated. Functional changes, which include the alterations in the membrane proteins and reductions of membrane fluidity that may be induced by electrostatic interactions between anionic membrane components and cationic local anesthetics, have been implicated mechanisms[45,48,49]. Consequently, various cell and membrane functions such as the DNA binding properties of the cell and membrane-bound ATPase activity may be inhibited[50,51]. The immunomodulating and anti-inflammatory effects of lignocaine are summarized in Table 1.

PHARMACOKINETICS

History

One of the earliest studies evaluating the pharmacokinetic properties of lignocaine was by Friden[52] in 1965. It was observed that lignocaine displayed a rapid onset of action, but of very short duration (between 10-20 min) after the intravenous administration of either 50 or 100 mg boluses doses. In the same year, Beckett *et al*[53,54] reported that lignocaine had a half-life of approximately 10 to 20 min one hour after the administration of an intravenous bolus. Two years later, Gianelly *et al*[55] reported that patients with occlusive coronary artery disease who were administered a continuous intravenous lignocaine infusion, without an initial loading dose, achieved acceptable plateau plasma concentrations within a 30 to 60 min period, suggestive of a 10 to 20 min half-life. Rowland *et al*[56] studied the ability of intravenous lignocaine to control ventricular arrhythmias in order to understand its disposition kinetics, and thus was able to establish safe and effective dosage regimens. Rowland reported a rapid early fall in lignocaine plasma levels after the administration a 50 mg bolus dose. The mean half-life was 7 min. However, they also reported a significantly slower phase (a mean half-life of 108 min), related to the drug's elimination. After a 4-h lignocaine infusion, the average elimination time of 108 min was similar to the elimination half-life of 96 to 108 min reported by Beckett *et al*[54]. Rowland found that lignocaine was primarily eliminated by metabolism, since urine collected 24 h after the bolus contained less than 4% of unchanged lignocaine. The range of elimination half-life was relatively narrow (73 to 133 min) among the subjects evaluated[56]. Beckett *et al*[54] also put forward that de-ethylation of lignocaine to monoethylglycine xylidide was the drug's primary metabolic pathway.

Absorption

Lignocaine's pharmacokinetics have been studied in a variety of clinical models, which include healthy volunteers, subjects with chronic pain syndromes, and patients with cardiac failure[56-59]. The speed of onset of lignocaine is 1 to 5 min after local infiltration, and 5 to 15 min after peripheral nerve blockade. Lignocaine's absorption is dependent upon the total dose administered, the route by which it is delivered, and blood supply to the site of injection[7]. In 1972, Scott *et al*[57] found that upon injection of lignocaine 400 mg, serum levels were highest following infiltration of vaginal mucosa and lowest following subcutaneous abdominal infiltration. Major nerve blocks and epidurals result in intermediate peak plasma levels. Irrespective of the administration site, peak serum levels occurred 20 to 30 min following injection. The addition of adrenalin (1:200000) to the local anesthetic solution reduced peak levels and delayed the rate of absorption.

Table 1 Immuno-modulating and anti-inflammatory effects of lignocaine

Effects	Immuno-modulating and inflammatory actions
Anti-nociceptive and analgesic effects[12,16,17,34,101]	Interaction with nociceptive pathways
	Blockade of neuronal sodium channels
	Blockade of potassium currents
	Muscarinic receptor antagonist
	Blockade of dopamine receptors
	Glycine inhibitor
	Reduction in excitatory amino acids
	Reduction in thromboxane
	Release of endogenous opioid peptides
	Reduction in neurokinins
	Release of ATP-adenosine triphosphate
Wound healing effects[19,38, 39,102-104]	Retardation by reduction of mucopolysaccharide and collagen synthesis
	Reduction in recruitment and metabolic response of
	Inhibition of thrombus formation
	Antithrombotic activity
	Inhibition of platelet aggregation *via* blockade of calcium influx
	Mobilization of intracellular calcium stores
	Inhibition of oxygen free radical production
	Inhibition of inflammatory cytokines
	Inhibition of vascular permeability
	Inhibition of edema formation
Inhibition of immune cell mediators from monocytes[18,105]	Inhibition of interleukin 1α
	Inhibition of interleukin β
	Inhibition of interleukin 8
	Inhibition of tumor necrosis factor
Inhibition of immune cell mediators from neutrophils[18,24-26,28,33,102,106]	Inhibition of prostaglandins
	Inhibition of thromboxanes
	Inhibition of leukotrienes
	Inhibition of lysosomal enzymes
	Inhibition of free radicals
Inhibition of immune cell mediators from mast cells[36]	Inhibition of histamine release
Anti-bactericidal effects[16-18,43-46,107]	Inhibitory actions on *Pseudomonas aeruginosa*
	Inhibitory actions on *Escherichia coli*
	Inhibitory actions on *Staphylococcus aureus*
	Inhibitory actions on *Haemophilus influenza*
	Inhibitory actions on *Mycobacterium tuberculosis*
Anti-viral and anti-fungal effects[16,17,108]	Inhibitory actions on Herpes simplex virus
	Inhibitory actions on *Candida albicans*
Clinical effects in inflammation-related disease[109-117]	Protective effects in acute lung injury
	Protective effects in septic shock
	Protective effects in cardiac ischemia
	Beneficial effects in ischemia-reperfusion injuries
	Protective effects in interstitial cystitis
	Protective effects in ulcerative colitis
	Protective effects in ulcerative proctitis
	Protective effects in burn injuries
	Accelerated return of bowel function in major surgery
	Blockade of airway hyperactivity in asthma
	Treatment of intractable hiccups
	Beneficial effects in traumatic brain injury

Protein binding

When lignocaine is given intravenously to normal subjects, the volume of distribution is 0.6-4.5 L/kg[60]. The plasma binding of lignocaine is inversely proportional to the drug concentration. It is 60% to 80% protein-bound at concentrations of between 1 and 4 mcg/mL[7]. Binding fraction also depends on the plasma levels of the acute phase reactant alpha-1-glycoprotein[9]. Lignocaine has been shown to cross the placenta and blood-brain barrier by simple passive diffusion. Given that proportion of maternal protein binding is greater than that foetal protein binding, the maternal total plasma concentration will be higher, however free lignocaine concentrations will remain the similar in both mother and fetus[7]. Fetal lignocaine concentration may be increased by transmembrane pH gradients, such as fetal 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 unionised and able to cross cell membranes in basic media[10]. In fetal acidosis lignocaine crosses the placenta in unionised form, becomes ionised given the acidic environment of the fetal circulation and becomes "trapped", thus increasing fetal lignocaine concentration.

Metabolism and elimination

Lignocaine is dealkylated in the liver by the cytochrome P450 system forming numerous metabolites. Monoethylglycine xylidide and glycine xylidide are the key active metabolites, both of which have reduced potency but have comparable pharmacologic activity to lignocaine[9]. The only reported metabolite of lignocaine found to be carcinogenic in a rat model is 2, 6-xylidine[61]. Its pharmacologic activity is unknown. After the intravenous administration of lignocaine, monoethylglycine xylidide and glycine xylidide concentrations equate to approximate 11% to 36%, and 5% to 11%, respectively, of the total plasma lignocaine concentrations[62].

Hepatic blood flow appears to be a limiting factor in lignocaine's metabolism. The rate of metabolism is slower reduced in patients with congestive cardiac failure, chronic liver disease and hepatic insufficiency, and after acute myocardial infarction[63]. Lignocaine and its metabolites are predominantly renally excreted. Less than 10% of lignocaine is excreted without being metabolised[53,64].

The total body plasma clearance of lignocaine in healthy volunteers has been reported to be approximately 10-20 mL/min per kilogram[62]. The majority of lignocaine elimination occurs in the liver, and since the total body plasma clearance of lignocaine is about 800 mL/min and hepatic blood flow is about 1.38 L/min[65,66], up to 60% of an oral dose is metabolised before entry into the systemic circulation. This accounts for the low plasma lignocaine concentrations observed following a the oral administration of 500 mg lignocaine hydrochloride[67].

Elimination half-life is defined as the rate at which a local anesthetic is removed from the blood. Therefore, the time necessary for 50% reduction in lignocaine blood level is one half-life; two half-lives equates to a 75% reduction, three half-lives to an 87.5% reduction, four half-lives to a 94% reduction, five half-lives to a 97% reduction and six half-lives to a 98.5% reduction. The half-life of lignocaine has been shown to be approximately 100 min following either an infusion lasting less than 12 h or a bolus injection. In this setting lignocaine demonstrates linear pharmacokinetics[56]. However, following an intravenous infusion greater than 12 h, lignocaine exhibits nonlinear, or time-dependent pharmacokinetics. Patients who received prolonged lignocaine infusions following a myocardial infarction, were found to have lignocaine concentrations that continued to rise for approximately 48 h, with the half-life extending up to 4 h[68].

Maximum doses

The maximum doses for lignocaine is based primarily on manufacturer recommendations and animal studies. Animal studies are frequently used to calculate a drug's therapeutic index. This is derived or calculated from the median toxic dose and median effective dose ratio. It is important to note that the complexities found within human populations are not replicated in animal studies. General recommendations based on site of administration, use of vasoconstrictors, and patient factors such as age, hepatic, renal, cardiac diseases, and pregnancy have been attempted. However due to the lack of quality data, specific recommendations regarding generic maximum doses cannot be definitively made. Furthermore, recommended doses from manufacturers vary between countries. The intrathecal ED50 of lignocaine for a motor block (defined as the development any motor block in either leg within a five-minute-period) has been shown to be approximately 13.7 mg (95%CI: 13.1-14.4 mg)[69]. According to most manufacturers recommendations, the maximum dose of lignocaine for infiltration and regional nerve block techniques is 300 mg (approximately 4.5 mg/kg) or 500 mg (7 mg/kg) with 1:200000 adrenalin (based on a 70 kg patient). However, for neuropathic pain treatment in human subjects, the ED50 and ED90 of lignocaine has been reported as 372 mg and 416 mg respectively, although the resulting plasma levels were not evaluated[70]. Generally, however, from animal data, the ED50 of intravenous lignocaine for CNS toxicity is approximately 19.5 mg/kg (95%CI: 17.7-21.3 mg/kg) and 21 mg/kg (95%CI: 19.0-23.4 mg/kg) for electrocardiographic evidence of cardiac toxicity[71].

Infusion kinetics

As discussed above, plasma concentrations of lignocaine differ widely, depending on the total dose administered, the method and route of delivery, and the vascularity of the site where it is injected. Plasma levels of between 0.5 and 5.0 mcg/mL (2-20 μmol/L) are required for many of reported clinical effects after both intravenous or subcutaneous administration[72]. A infusion of intravenous lignocaine administered at a dose of 2 to 4 mg/min results in plasma levels of between 1 and 3 mcg/mL after 150 min[73]. After 15 min of the same infusion, a 2 mg/kg intravenous bolus of lignocaine leads to peak plasma levels of 1.5 to 1.9 mcg/mL[74]. Subcutaneous lignocaine infusions may be advantageous over intravenous drug delivery methods because plasma levels are more stable, and therapeutic benefit may be achieved whilst avoiding the toxic effects of peaks and troughs associated with episodic drug administration or a prolonged continuous intravenous infusion[75].

The aim of an intravenous lignocaine infusion is to achieve a therapeutic steady-state concentration while minimising systemic toxicity. The pharmacokinetic implication of using a lignocaine bolus dose prior to a continuous infusion is important. This technique increases plasma concentrations allowing therapeutic ranges to be achieved more quickly. Hsu *et al*[59] evaluated the lignocaine's pharmacokinetics during 2-d infusion in patients who underwent cardiac surgery. These researchers concluded that lignocaine plasma concentrations are more accurately described using a two-compartment pharmacokinetic model, and advocated that lignocaine infusions should be dosed by body weight, with the infusion dose reduced after 24 h to avoid toxicity. The authors advocated that the ideal lignocaine continuous infusion protocol is a bolus/loading dose of 1 mg/kg, then an infusion at 50 mcg/kg per minute

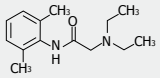
Systematic name	2-(diethylamino)-N-(2, 6-dimethylphenyl)acetamide (International Union of Pure and Applied Chemistry nomenclature)
Class	Amide
Vaughan Williams classification	Class IB antiarrhythmic agent
Molecular formula	$C_{14}H_{22}N_2O,HCl,H_2O$
Structural formula	
pKa	7.86
Molecular mass	234.34 g/mol
Pregnancy Class	Australia: Class A United States: Class B
Trade names	Xylocaine
Preparation	Clear and colorless Sterile and preservative-free Isotonic
Mechanism of action and effects	Myocardial depolarization: decreases Myocardial automaticity: decreases Ventricular excitability during diastole: decreases (by a direct action on Purkinje network) Autonomic system: no effect Contractility: no effect Blood pressure: no effect Atrioventricular conduction: no effect Absolute refractory period: no effect[9,118]
Distribution	Intravenous route: volume of distribution: 0.6 to 4.5 L/kg Transdermal route: lignocaine 5% patch[119] Approximately 70% bound alpha-1 glycoprotein Absorption: depends on duration of application and the surface area When 2100 mg (3 × lignocaine 5% patches) applied over intact skin for 12 h: dose absorbed: 64 ± 32 mg; C_{max}: 0.13 ± 0.06 mcg/mL; T_{max}: 11 h
Protein binding	60% to 80% protein bound
Biotransformation	90% hepatic Metabolites: monoethylglycinexylidide and glycinexylidide (less potent toxic effects[120]) Following intravenous dosing, monoethylglycinexylidide and glycinexylidide in plasma range from 11% to 36%, and from 5% to 11% of lignocaine concentrations Transdermal application (lignocaine 5% patch): negligible metabolite concentrations[119]
Half-life	60 to 120 min Dose-dependent Biphasic distribution phase (7 to 9 min after intravenous loading dose) During prolonged (approximately 24 h) intravenous infusions: > 3 h Time to steady-state plasma concentration Limited data regarding subcutaneous infusion.
Therapeutic plasma concentration	1.5 to 5 mcg/mL > 5 mcg/mL: toxic effects described
Duration of action	Intravenous route: 10 to 20 min
Elimination	Renal excretion: 10% unchanged Not reliably removable by dialysis Systemic clearance: 10-20 mL/min per kilogram

Figure 1 Summary of the pharmacokinetics of lignocaine.

infusion for the first hour, then 25 mcg/kg per minute for the second hour, then 12 mcg/kg per minute for the following 22 h, and finally 10 mcg/kg per minute for the remaining 24 h. The pharmacokinetics of lignocaine are summarised in Figure 1.

ADVERSE REACTIONS AND TOXICITY

Generally, lignocaine toxicity can result when either the correct dose of lignocaine is inadvertently administered or delivered *via* the intravascular route, or when doses, even if given by the correct route, are excessive[76]. There are a number of factors that influence or directly affect the severity of lignocaine toxicity. These include the vascularity of the site of injection, speed of the injection, acid base status, and underlying hepatic or renal impairment. Lignocaine is metabolised by the liver, therefore severe hepatic dysfunction will significantly increase the both the risk and severity of toxicity[9]. In addition, given that lignocaine is protein bound, severe hypoalbuminemia may also predispose to toxicity risk[9]. Acidosis increases the risk of toxicity because due to lignocaine dissociating from plasma proteins[7]. Lignocaine's pharmacokinetics and antiarrhythmic effects may be potentiated or altered by beta-blockers, ciprofloxacin, cimetidine, clonidine, and phenytoin[6]. Beta-blockers such as propranolol and metoprolol can reduce lignocaine's metabolism, whilst cimetidine and amiodarone reduce its clearance. Lignocaine's interactions with phenytoin and ciprofloxacin are thro-

Table 2 Adverse effects of lignocaine toxicity

System	Effects
CNS	Biphasic effects
	Early: CNS excitation with seizures
	Late: CNS depression, termination of convulsions, reduced level of consciousness, leading to respiratory depression and/or arrest
	Mechanism: Local inhibition of inhibitory CNS pathways (CNS stimulation), then inhibition of inhibitory and excitatory pathways (CNS inhibition)
	Symptoms and signs
	Anxiety
	Dizziness or light headed
	Confusion
	Euphoria
	Tinnitus
	Blurring of vision or diplopia
	Nausea and vomiting
	Twitching and tremors
	Seizures with reduced consciousness
Cardiovascular	General effects
	Conduction block of neural impulses
	Prevention of passage of sodium through sodium channels
	Stabilization of excitable membranes
	Prevention of the initiation and transmission of nerve impulses
	Attenuation of phase 4 diastolic depolarization
	Reduction in automaticity
	Reduction in absolute refractory period
	Increase in the ratio of effective refractory period: action potential duration
	Decrease in action potential duration
	Ventricular fibrillation threshold: raised
	Higher serum concentrations
	Blockage of sodium channels
	Depression of rate of depolarization during phase 0 of the cardiac action potential
	Re-entrant arrhythmias
	Suppression of conduction through the sinus and atrioventricular nodes
	Symptoms and signs
	Bradycardia
	Hypotension
	Cardiovascular depression
	Cardiac arrest
Respiratory	Symptoms and signs
	Tachypnea
	Respiratory depression
	Respiratory arrest
Allergic reactions	Extremely rare
	Symptoms and signs
	Cutaneous lesions: urticaria, edema
	Anaphylaxis

CNS: Central nervous system.

ugh their effects on the liver's cytochrome system.

Adverse effects of lignocaine and other amide local anesthetic agents are similar in nature[7]. These are summarised in Table 2. Low plasma concentrations of lignocaine (less than 5 mcg/mL) are used in the clinical setting to suppress cardiac ventricular arrhythmias and status seizures, but seizure activity may be induced at higher concentrations. Seizures result from selective depression of central nervous system inhibitory tracts. As plasma lignocaine levels increase, all pathways are suppressed, resulting in respiratory arrest, cardiovascular collapse and coma[76]. Lignocaine toxicity may commence at concentrations greater than 5 mcg/mL, although convulsive seizures most often occur at concentrations greater than 10 mcg/mL. The adverse systemic effects of lignocaine toxicity are summarised in Table 2.

CARCINOGENICITY AND MUTAGENICITY

Toxicity studies of 2, 6-xylidine, a lignocaine metabolite, have documented the development of nasal cavity adenomas and carcinomas in rats[6,77]. Nasal tumors were reported with daily doses of 900 mg/m^2 (150 mg/kg) 2, 6-xylidine, but not with low dose (15 mg/kg) or control animals.

LIGNOCAINE AND CANCER OCCURRENCE

Whilst clear *in vitro* and *in vivo* evidence exists for

the anti-inflammatory properties of lignocaine and its modulation of the inflammatory response during major surgery, the question of whether lignocaine can influence cancer outcomes following cancer surgery is a debatable topic. The indirect effects of local anesthetics in tumor development may stem from the reduction of neuroendocrine responses to the stress response elicited by major surgery and tissue damage, enhanced preservation of immune-competence, in addition to opioid-sparing effects of modulating tumor growth[78]. The plasma concentrations of local anesthetic agents, even when administered as part of a regional anesthetic technique or from infiltration around neoplastic tissue, are frequently in the millimolar range. These concentrations have been shown to have cytotoxic properties *in vitro*[79]. Other actions of local anesthetic agents on cancer cells may be through direct sensitisation of chemotherapy[80]. Protection against tumor cell invasion and suppression of tumor proliferation has been found with the infiltration of local anesthetic agents[79]. Furthermore, local anesthetics can modulate tumor biology[81], and lignocaine has been suggested to be a potent demethylating agent with cancer treatment potential[81].

A retrospective study in patients with breast cancer who received paravertebral anesthesia with local anesthetic solutions during mastectomy showed considerable benefit with regard to metastatic spread[82]. These promising finding could not however be replicated in abdominal cancer patients[83-85]. When epidural anesthesia with a local anesthetic solution was utilized as part of a standardised anesthetic, Gupta *et al*[86] reported a reduction in all-cause mortality after resection of rectal cancer; but not after resection of cancer of the colon. Intraoperative epidural analgesia has been linked to increased three and five-year survivals, and increased recurrence-free interval in patients with from ovarian malignancy[87]. Patients with cervical cancer showed no significant survival effect associated with epidural anesthesia during brachytherapy[88], however the use of epidural anesthesia in patients hepatocellular carcinoma undergoing percutaneous radiofrequency ablation was not associated with a significant decrease in survival[89]. The equivocal results of these small observational studies indicate that there is distinct biological heterogeneity of the cancers being investigated, or that regional anesthesia with local anesthesia has no effect.

Multiple factors can hamper perioperative immune competence. Surgery itself can result in significant cytokine and neuroendocrine responses, which can impair several immune functions and attenuate the adverse effects of natural killer cell function. Natural killer cells play an important role in preventing tumor spread[90]. Lignocaine may reduce the stress response to surgery; hence enhance natural killer cell response[91]. Perioperative immune competence may also be influenced by opioids, which have been shown to suppress multiple immune functions, including both humoral and cellular immune function[92-95]. If lignocaine is used as part of a patient's anesthesia regime, less opioid may be required, resulting in less immune compromise. Appropriate analgesia may also reduce metastatic spread of cancer through preservation of natural killer cell function[96]. Finally, morphine is pro-angiogenic and may promote the release of factors that enhance tumor growth[97]. Lignocaine, therefore, may help to maintain immune function in the perioperative period by minimising the need for postoperative opioids and reducing general anesthesia requirements.

The use of lignocaine in patients with prostate cancer remains equivocal[98-100]. Wuethrich *et al*[98] performed a retrospective study examining prostate cancer-related outcomes and the effects of the anesthesia technique in patients undergoing open radical retropubic prostatectomy. The authors reported a reduction in the risk of clinical cancer progression in a cohort of patients receiving epidural analgesia. However, there were no statistical differences in overall survival, cancer-specific survival, and biochemical recurrence-free survival. Similarly Biki *et al*[99] investigated recurrence of cancer of the prostate in men who underwent open prostatectomy under a general anesthetic with postoperative opioid for analgesia, or general anesthetic with epidural anesthesia/analgesia. They observed a significantly reduced risk of biochemical cancer recurrence when open prostatectomy surgery was performed with general anesthesia in combination with epidural analgesia. In contrast to these two retrospective analyses, more recently Tsui *et al*[100] performed an observational study investigating disease free-survival in patients undergoing open radical retropubic radical prostatectomy. There was no difference in clinically evident or biochemical occurrence of prostate cancer when comparing epidural and control groups. In summary, the question of whether lignocaine can modulate cancer recurrence has not yet been answered unequivocally. It is probable that only specific cancer types may be affected by the tumor-suppressive effects of lignocaine[81].

CONCLUSION

Lignocaine is a unique amide local anesthetic and a Class 1b antiarrhythmic agent with ubiquitous use in medicine and surgery. 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* immunomodulating, anti-inflammatory and anti-cancer effects that show immense promise in a variety of other clinical applications. These effects are often exerted at lower concentrations than needed for sodium channel blockade, and result from lignocaine's complex interactions with other cellular systems[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]. Lignocaine may be an important pharmacological agent in the influence and modulation of these responses in the practice of modern perioperative medicine. Finally, defining the roles of lignocaine in these clinical settings are necessary to obtain a more detailed appreciation of the complex mechanisms of lignocaine's clinical utility. 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 trials are awaited to assess whether the immuno-modulating, anti-inflammatory, analgesic, and anticancer effects of lignocaine observed in both *in vitro* and *in vivo* experiments and small clinical trials can be safely applied to routine clinical practice[17].

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