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Review Article

Neuroprotective effect of lidocaine: is there clinical potential?

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Abstract: Local anesthetic lidocaine has been shown to be protective in animal models of focal and global ischemia as well as in *in vitro* hypoxic models. Lidocaine has been tested in patients for its potential protective effect on postoperative cognitive dysfunction. This mini-review summarizes the laboratory and clinical evidences and discusses its clinical applications as neuroprotective agent.

Keywords: Lidocaine, neuroprotection, stroke, postoperative cognitive dysfunction

Introduction

This goal of mini-review is to offer a concise overview of laboratory and clinical evidence for the use of lidocaine to protect neurons against injury or preserve neurological function. Lidocaine, first synthesized in 1943, is one of the most widely used local anesthetics in clinical practice. The primary mechanism for local anesthesia is block of voltage-gated sodium channels. The anti-arrhythmia effect of lidocaine was described in 1950 and it is still used by anesthesiologists to treat arrhythmia during cardiac surgery [1]. It has a fast onset, an intermediate duration of action and a relatively high safety profile. In addition, lidocaine is the only local anesthetic that is approved by FDA to be administered intravenously. It is routinely given in anesthesia practice as an intravenous bolus prior to induction to reduce the irritating effect of propofol [2] and also to suppress the sympathetic response of tracheal intubation [3].

Because of the safety profile, availability and systemic applicability of lidocaine, other potential clinical applications including neuroprotection, decompression sickness/cerebral air embolism and postoperative ileus have been explored. Lidocaine has a systemic anti-inflammatory effect [4]. It has been shown that lidocaine shortens hospital stays, spares opioid use and is effective in acute primary chamber closure glaucoma [5].

Perhaps the most important, but unanswered, question is whether there is any potential for lidocaine as a neuroprotectant in clinical practice? A neuroprotectant is to protect neurons from injury or degeneration. Injury to neurons can be due to interruption of blood or oxygen supply, direct trauma, harmful endogenous metabolites or exogenous toxins. Neuronal degenerative disease is typically a chronic and progressive process that is typically concomitant with irreversible neuronal injury or loss once it is initiated.

In evaluating the neuroprotective effects of lidocaine, we distinguish between well-defined injury and ill-defined injury. The interruption of blood supply to the brain causes tissue and cell death, a pathological process commonly named stroke. This is a well-defined insult. Stroke is the second leading cause of death in the United States and results in most devastating disability. Current therapy relies on the timely restoration of blood supply with thrombolysis [6]. Understanding of excitatory amino acid neurotoxicity/excitotoxicity led to the hope of im-

proved patient outcome in stroke by suppression of excitotoxicity. However, multicenter trials have revealed no benefit of such treatment. This expensive failure has discouraged clinical trials for neuroprotection in stroke [7]. Currently, there are no effective neuroprotective drugs for stroke patients.

Postoperative cognitive dysfunction or postoperative cognitive decline (POCD) occurs following surgery. POCD is an ill-defined injury with no clear etiology. The incidence of POCD varies with age, type and duration of surgery and comorbidity. Age is a risk factor. In elderly populations, the incidence of POCD could be as high as 26% one week after surgery, and decreases to 10% three months after surgery [8]. Subtle reduction in brain cognitive function can be measured only by employing a battery of tests before and after surgery. Cardiac surgery is associated with the highest incidence of POCD and thus most trials regarding lidocaine on POCD were conducted in patients undergoing cardiac surgery [9]. The etiology of POCD is complex and multifactorial, with contributions from hypoxemia, arterial hypotension, surgery induced stress, endocrine dysfunction and systemic inflammation, brain thrombosis, air micro emboli associated with cardiopulmonary by pass, effects of anesthesia and unmasked or exacerbation of pre-existing dementia [8, 10]. In the case of POCD the insults could be multiple, making it difficult to determine a specific cause.

Neuroprotection by lidocaine against ischemic insults

Laboratory evidence

Evans et al. found that both pre- and post-treatment with systemic lidocaine reduced changes in somatosensory evoked potential amplitude, systemic hypertension and intracranial pressure induced by air embolism in cats [11, 12]. They also reported similar beneficial effects in protecting the spinal cord from injury induced by epidural inflated balloon in cats [13]. The method of administration was 1.5 mg/kg over the first 5 minutes, 3.0 mg/kg over the next 25 minutes, and 1.0 mg/kg every 30 minutes thereafter. A blood concentration of 3 to 4 μg/ml (13-17 μM) was reported. A similar dose was found to be effective in reducing cortical edema and maintaining electrophysiological activity in an experimental model exposing a cat's cerebral surface to air [14].

Reduction of infarct size by lidocaine was reported in a cat focal ischemia model in which the left middle cerebral artery (MCA) was occluded [15]. This finding, however, was not confirmed by another study, in which lidocaine transiently preserved the somatosensory evoked potentials but did not significantly affect the infarction size [16]. Lei et al. demonstrated a significant effect of 2-7 μg/ml lidocaine (8.5-30 μM), at reducing infarct sizes and improving neurologic outcome in rats with focal ischemia [17]. When lidocaine was given after an ischemic event, the infarct size was not changed but the number of intact neurons was increased. This suggests it may even be beneficial to administer lidocaine after the onset of focal ischemia [18]. Later, Lei et al. reported that lidocaine suppressed apoptosis in the penumbra; this is thought to contribute to the reduction in infarct size [19]. Lidocaine was also found to inhibit cytokine production from mouse microglial cells so that reduction of neuroinflammation may contribute to neuroprotection [20].

Rasool et al. used graded carotid occlusion to induce incomplete global ischemia in rabbits and found that a low infusion dose of 0.2 mg/kg/min lidocaine expedited the return of electroencephalographic and evoked-potential amplitudes [21]. Zhou et al. reported that lidocaine given at 4 mg/kg before cardiac arrest and 2 mg/kg before rewarming reduced the neurological deficits in cardiac arrest in deep hypothermia dogs [22].

Lidocaine concentrations of 2-200 μM protected CA1 pyramidal cells from ischemic damage in rat hippocampal slices deprived of oxygen and glucose [23]. In this study, lidocaine did not interfere with electrical signaling within and between cells. Lidocaine at 10-100 μM promoted the recovery of evoked population spikes recorded from the CA1 pyramidal cell layer after anoxic treatment in rat hippocampal slices [24]. The underlying mechanism was thought to be associated with a reduction of both sodium influx and ATP consumption. In another report, 10 μM lidocaine reduced intracellular sodium levels, while 100 μM lidocaine suppressed changes in membrane potential, sodium, potassium, ATP, and calcium during hypoxia [25]. Lidocaine, but not procaine, was found to preserve mitochondrial structure after ischemia in CA1 pyramidal cells [26].

In a transient global cerebral ischemia rat model induced by bilateral occlusion of common carotid arteries combined with hypotension, Popp et al. examined the neuroprotective effect of lidocaine at two anti-arrhythmia doses 2 and 4 mg/kg, corresponding to blood plasma concentrations of about 3 and 8 μM respectively [27]. In this study, both doses of lidocaine attenuated the predominant loss of intact CA-1 neurons induced by ischemic events. Importantly, the authors included behavioral tests and found that lidocaine improved cognitive function after ischemia. This is probably the most thorough pre-clinical animal study to date. It strongly suggests a role for lidocaine in neuroprotection in humans.

In spite of this *in vitro* and *in vivo* animal model evidence, we have not found any studies of lidocaine used in human subjects with ischemic stroke. The reason for this is not clear. One factor may be concerns about adverse effects and/or the uncertainty of drug concentrations in stroke patients whose blood-brain barrier is disrupted. In addition, the low cost of lidocaine offers no financial incentive to pharmaceutical companies. The ineffectiveness of lidocaine in cardioprotection may also be a factor. An early meta-analysis suggested that prophylactic lidocaine is ineffective at preventing ventricular arrhythmia [28]. A recent review failed to show any benefit to using lidocaine in all-cause mortality and ventricular fibrillation in patients with myocardial infarction undergoing heart surgery [29].

Neuroprotection by lidocaine in POCD

Lidocaine has been studied in humans as a means of reducing postoperative cognitive dysfunction in patients undergoing cardiac and non-cardiac surgery. POCD is one of many profound medical problems associated with a huge economic burden and diminished quality of life. It is hoped that the neuroprotective effect of lidocaine in well-controlled laboratory settings can be extended to clinical application for protecting the patients from numerous insults associated with surgery.

In a small, randomized clinical trial, Mitchell et al reported improved postoperative neuropsychological function in 65 patients undergoing left heart valve procedures [30]. Lidocaine was infused to achieve a serum concentration of 6-12 μM for 48 hours. The left side valve procedure is associated with a high incidence of brain injury [31]. Neuropsychological function was evaluated preoperatively and postoperatively at 10 days, 10 weeks and 10 months. Significant improvement was indicated at 10 days and 10 weeks. Wang et al. performed a randomized clinical trial of 118 patients undergoing elective coronary artery bypass with cardiopulmonary bypass [32]. Neuropsychological function was tested preoperatively and 9 days after surgery. Lidocaine, given during surgery only, significantly reduced the incidence of POCD.

Unfortunately, this beneficial effect was not confirmed in a follow up study by Mitchell et al [33]. Lidocaine was administered for 12 hours instead of 24 as in their previous study. The patient population underwent a wide variety of surgical procedures including coronary artery bypass. Postoperative neuropsychological function at 10 or 25 weeks was not significantly improved by lidocaine. The authors speculated that this lack of effect might be attributed to the shorter administration period or that the protective effect of lidocaine is limited to open chamber heart surgery. In another randomized study involving 241 patients undergoing cardiac surgery, lidocaine was given for 48 hours postoperatively and no protective effect was observed [34]. Further discouragement comes from a recent randomized study showing lidocaine did not improve the cognitive outcome at 6 months after supratentorial tumor surgery [35].

Summary

In vitro and animal studies have demonstrated that lidocaine is neuroprotective against hypoxia and ischemia. The underlying mechanism is not clear and may be multifactorial, including inhibition of sodium influx, preservation of cellular mitochondria and ATP and reduction of neuroinflammation. Lidocaine at higher concentrations (>300 μM) inhibits acid sensing ion channels [36] and TRPM7 channels [37]. Although both of these channels are involved in mediating ischemic injury [38, 39], only a local injection of lidocaine would achieve a high enough concentration to provide significant, transient inhibition. High concentrations of local anesthetics induce neuronal cell death; the LD50 for lidocaine on human SH-SY5Y neuroblastoma cells is 15 mM [40].

In trying to translate the demonstrated protective effect of lidocaine in animal models to humans, we must recognize a significant limitation in the animal studies done so far. Protection was observed only when lidocaine was given before the ischemic event or very shortly afterwards. This treatment regimen is relevant to planned ischemia but not to patients who have had an acute stroke. Future studies on animals should be designed with a realistic and specific clinical scenario in mind.

POCD is a complex clinical problem associated with multiple causes. Lidocaine may be effective in certain subpopulations of surgical patients. Currently, there is a large ongoing randomized clinical trial evaluating neuroprotection of a 48-hour pretreatment with lidocaine in cardiac patients (https://clinicaltrials.gov/ct2/show/NCT00938964?term=Mathew%2C+lidocaine&rank=2). If this trial is successful, we may be able to add "clinical neuroprotection" to the list of beneficial effects of the inexpensive, versatile drug, lidocaine.

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