PERIODICUM BIOLOGORUM
VOL. 115, No 2, 113–117, 2013

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Leading article

Non anesthetic action of local anesthetics

ALAIN BORGEAT

Department of Anesthesiology
Balgrist University Hospital
Forchstrasse 340
CH-8008 Zurich / Switzerland
E-mail: alain.borgeat@balgrist.ch

Key words: Local anesthetics; neuroprotection; chronic pain; intrathecal administration; antimicrobial properties; cancer recurrence; myotoxicity; chondrotoxicity

Summary

Local anesthetics are not only used as drugs to block the sodium channel to provide analgesia and anti-arrhythmic action. The purpose of this review is to highlight the new indications and limitations of this class of drugs. Recent research has focused on the use of i.v. local anesthetics to improve bowel function after surgery or trauma, to protect the central nervous system, to find new clues of local anesthetic effects in chronic neuropathic pain and to investigate the long-term effect of anesthesia / analgesia provided by local anesthetics on cancer recurrence. Recent facts dealing with myo- and chondrotoxicity are presented. There is growing evidence that local anesthetics have a broad spectrum of indications aside analgesia and anti-arrhythmic effect. Most of them are still insufficiently known and investigated. These new indications will no doubt be intensively studied in the coming years.

Received May 15, 2013.

INTRODUCTION

The use of local anesthetics has long been focused on the treatment of pain and cardiac arrhythmias. During the last decades several studies have demonstrated that local anesthetics are able to interfere with other receptors *(1)*. This has led to the administration of local anesthetics in different settings including postoperative ileus, neuroprotection, decompression sickness, cerebral air embolism, cancer recurrence and various types of inflammation. On the other hand some concerns including chondrotoxicity have been the focus of different investigations. The aim of this review is to provide an overview of recent progress in terms of new indications and limitations of local anesthetic application.

Recovery of bowel function

Postsurgical ileus is a common occurrence after abdominal surgery, and is one of the major reasons to delay patient's discharge. Previous studies have shown that continuous infusion of lidocaine has positive effects in this setting *(2, 3)*. These preliminary results have been confirmed by Harvey *et al (4)*. The authors examined in a prospective, randomized and double-blinded study whether systemic infusion of lidocaine (1 mg/min for 24h) compared to a placebo could reduce postoperative pain, duration of postsurgical ileus and time to discharge. Patients receiving lidocaine had less postoperative pain, the return of bowel movement was fastened and they were discharged home one day earlier than the others. Paralytic ileus is a major concern in the acute phase of spinal cord injury. The effect of i.v. lidocaine infusion (2–3 mg/min) was investigated in seven patients with severe traumatic spinal cord injury resistant to the administration of i.v. neostigmine. In five patients

bowel function recovered 10–20 h after lidocaine initiation[5]. Among the possible hypothesis to explain the salutary effects of i.v. lidocaine, a reduction of the inflammatory reaction secondary to peritoneal distension and / or reduction of post-traumatic – post-surgical stress have been suggested *(6, 7)*.

Beaussier *et al (8)*. investigated the effects of parietal analgesia on postoperative diaphragm dysfunction after major open colorectal surgery. Patient received ropivacaine 0.2% given at a rate of 10ml/h during 48 h through a preperitoneal wound catheter. PCA-morphine was used in the treatment and control group. Diaphragmatic function was assessed by the sniff inspiratory pressure test. It was shown that patients receiving preperitoneal ropivacaine had a significant lower decrease in the sniff inspiratory pressure compared to the control group at 24h – 24% vs – 58% and at 48h – 11% vs – 44%, respectively. It was hypothesized that the beneficial effect could be attributed not only to analgesia, but also to the blockade of peritoneal afferents involved in the reflex diaphragmatic dysfunction induced by intra-abdominal surgery *(9)*.

Neuroprotection / chronic pain

Several studies have previously shown that lidocaine at antiarrhythmic doses *(10)* or lower doses *(11)* demonstrates neuroprotective effects. These potential properties are of great importance since the severity of neurologic sequelae and the relatively limited therapeutic interventions make this an important area of research. Postoperative neurocognitive decline is detected in more than 50% of patients after cardiac surgery and is still present 6 months later in 30%. Mathew *et al (12)* investigated in a prospective, randomized double-blinded, placebo controlled study whether a continuous infusion of lidocaine (bolus 1mg/kg followed by 1mg/min for the next 48h) would reduce postoperative cognitive dysfunction after cardiac surgery using cardiopulmonary bypass. This work demonstrated that lidocaine did not reduce the incidence of cognitive dysfunction, but in non-diabetic patients a secondary analysis did show a protective effect, which was still present 1 year after surgery. This study suggests that certain patients, but not all, may benefit from this treatment.

Neuropathic pain is a chronic condition characterized by spontaneous pain, allodynia, hyperalgesia, and sensory deficits in the painful area. Treatment is still often inadequate. Gormen *et al (13)* were able to show that both AMPA/GluR5 antagonist (NS 1209) and lidocaine reduced significantly brush – evoked allodynia and cold allodynia in a small group of patients with well-defined neuropathic pain symptoms. These are key elements of neuropathic pain suggesting that AMPA receptor ligands may be involved in pain modulation and also that lidocaine may interfere with this receptor. In order to elucidate the question whether lidocaine analgesic effects are mediated through central rather than peripheral nervous system action, Luo *et al (14)* performed fMRI in anesthetized rats to quantify brain activation patterns in response to innocuous and noxious forepaw stimulation before and after i.v. administration of lidocaine. The authors found in this animal model that lidocaine when administered intravenously, did not abolish or diminish the brain's response as measured by functional magnetic resonance imaging using the blood-oxygen-level dependent activation to innocuous or acute noxious electrical stimulation of the forepaw in normal rats. Moreover, this investigation showed that lidocaine enhanced the somatosensory cortical response to acute noxious stimulation. This is in contrast to what has been observed previously for opioid analgesics *(15)*. These findings raised several challenging questions regarding the mode of action of lidocaine in the setting of neuropathic pain. The efficacy of lidocaine application to relieve neuropathic pain was further confirmed by Kanai *et al (16)*. They compared the metered-dose 8% lidocaine pump spray to saline placebo pump in patients having posttraumatic peripheral neuropathy. The pump sprays were applied directly to painful skin areas. The results demonstrated that the lidocaine pump spray, but not the placebo one, significantly decreased the intensity of the continuing pain and tactile allodynia. Compared to patch this system has the advantages to have a more rapid onset of action and the possibility to increase the dose when necessary.

There is growing evidence that local anesthetics modulate a wide range of ion channels other than sodium channels. How systemic application of lidocaine exerts its analgesic effect is not entirely clear. In order to better document this effect Muth-Selbach *et al (17)* administered intrathecally on rats l-serine (an agonist at the glycine-binding site at the NMDA receptor), its inactive isomer I-serine CGP 78608 (antagonist at the glycineB--site of the NMDA receptor) and strychnine (antagonist at inhibitory glycine receptor) after the animals received i.v. lidocaine and formalin s.c. in the paw. The results indicated a modulatory effect of lidocaine on the NMDA receptor and since lidocaine-induced antinociception was antagonized by both glycineB-site modulators and strychnine, this would favour the hypothesis of a general glycine-like action on inhibitory strychnine-sensitive receptors and on strychnine-insensitive glycine receptors. This is one new possible mechanism to explain lidocaine effect. However, chronic / neuropatic pain is such a complex process that research is still needed to have a better understanding.

MDMA (3.4 methylene-dioxy-methamphetamine) is commonly consumed by many teenagers and young adults. MDMA is more and more frequently consumed with a local anesthetic, cocaine. The influence of this "cocktail" on motor activity, anxiety, memory and brain monoamines in adolescent mice has been assessed**18.** This investigation showed that both drugs, administered alone or concurrently, produced hyperactivity and decrease in social contacts. However, an anxiolytic effect assessed by means of elevated plus maze and expressed as an increase in the time on the open arms, was observed only in those animals treated with both MDMA and cocaine. Mice treated with MDMA did not present significant changes in brain monoamines, while those receiving both drugs

showed a decrease in dopamine in the striatum, which was accompanied by an increase in the serotonin concentration in the striatum and cortex 30min after administration. It is known that acute activation of neurons by cocaine induces long-term changes in behaviour by activating transcriptional complexes and that young adolescent male rats have greater locomotor responses than adults after acute low dose cocaine administration.

The purpose of Caster's investigation *(19)* was to correlate cocaine-induced locomotor activity with neuronal activation in different regions in the brain by acute cocaine in young adolescents and adult rats by measuring the induction of the plasticity-associated immediate early genes c-fos and zif268. It was found that low dose cocaine induced more locomotor activity and striatal c-fos expression in adolescents than adults whereas high dose cocaine induced more locomotor activity, striatal c-fos and striatal zif268 expression in adults. Locomotor activity correlated with the expression of both genes in adults but correlated with striatal c-fos only in adolescents. There was also a significant correlation between the expression of c-fos and zif 268 in the adult striatum but not in adolescents. These interesting results suggest that the coordinated expression of transcription factors by cocaine continues to develop during adolescence. The immature regulation of transcription factors by cocaine could explain why adolescents show unique sensitivity to specific long-term behavioural alterations following cocaine treatment.

Intrathecal administration

Local anesthetics are frequently administered intrathecally for various procedures or pathologies. Tian *et al (20)* investigated the best dosage of lidocaine administered intrathecally in a rat model of established thermal hyperalgesia and tactile allodynia. The following dosages were compared: 2, 6.5, 15 and 35mg/kg. Behavioural tests indicated that 6.5, 15 and 35mg/kg showed different degrees of reversal of thermal hyperalgesia lasting 2–8 days, while 2mg/kg did not. The inhibition of tactile allodynia was only observed in rats receiving 15 and 35mg/kg. Considering the ratio benefits/side-effects, the dosage of 15 mg/kg was the most suitable for this indication. However, the mechanisms of action remain to be elucidated.

Ambulatory surgical procedures are more and more commonly used worldwide. Spinal anesthesia is a good and reliable technique in this setting. However, lidocaine, which has been frequently used in this indication, has been reported to be neurotoxic. In order to look for more suitable alternative Takenami *et al (21)* compared the clinical course and toxicity of different local anesthetics administered intrathecally in rats. Different concentrations of prilocaine, mepivacaine, procaine or bupivacaine were compared. Among the 4 local anesthetics tested, procaine has the mildest neurotoxicity and the fastest recovery time to ambulation.

Lidocaine has been implicated in the occurrence of TNS *(22)*. However, the exact mechanism explaining TNS is still unknown. In order to have a better understanding of the possible neurotoxicity of lidocaine, freely moving rats received either saline, 400 or 1000ug of lidocaine intrathecally *(23)*. The impact of a pre-treatment with an NMDA glutamate antagonist and a COX2 inhibitor was also assessed. Cerebrospinal PGE_2 levels increased to 400% of baseline and remained elevated for 90–120min after intrathecal lidocaine at both doses. Pretreatment with both inhibitors attenuated this increase. A 40 min period of enhanced pain after von Frey filament stimulation – temporary state of spinal cord sensitization – was observed during and after sensory and motor block recovery. This work showed that intrathecal lidocaine provokes a transient period of hyperalgesia. Yet, the link with the PGE2 increase and the occurrence of hyperalgesia (TNS?) needs to be further investigated.

Despite adequate needle placement, application of the right local anesthetic at the adequate concentration, 2–3 % of spinals still fail. Steiner *et al (24)* assessed bupivacaine cerebrospinal fluid (CSF) concentration in all patients with inadequate block, after intrathecal application of bupivacaine 0,5%. In this investigation 2600 spinals were considered. The failure rate was 2.7%. A CSF concentration of bupivacaine of 73ug ml^{-1} was considered adequate for a successful spinal. In the failure group the CSF concentration was between 3.36 and 1020 $ug.ml^{-1}$. A large number of failures had a concentration below $73ug.ml^{-1}$, but some of them were above, suggesting maldistribution of local anesthetic to explain the failure. This work highlights the fact that inadequate CSF local anesthetic concentration may explain some cases, but not all, of spinal failure in the absence of technical problem. Other issue like drug maldistribution should be considered.

Antimicrobial properties

Local anesthetics have long been known to inhibit the growth of different species in vitro *(25)*. Infiltration of surgical wound with 2ml lidocaine 2% prior to inoculation was associated with an average decrease in bacterial count of >70%[26]. Epidural abscess is an uncommon yet serious complication of epidural catheterisation. Coghlan *et al (27)* investigated the antibacterial activity of various local anesthetics and additives used in epidural infusions, against a range of micro-organisms associated with epidural abscess. Different concentrations of bupivacaine, ropivacaine and levobupivacaine with or without fentanyl, adrenaline or clonidine were tested. Bupivacaine was shown to have the most efficient activity against micro-organisms. It showed antibacterial activity against staphylococcus aureus, enterococcus faecalis and escherichia coli with minimum inhibitory concentrations between 0.125% and 0.25%. However, bupivacaine did not inhibit the growth of pseudomonas aeruginosa. Levobupivacaine and ropivacaine had no activity against any of the micro organisms tested. The presence of fentanyl, adrenaline and clonidine had no additional effect on the antimicrobial activity of any of the local anesthetic tested. While the clinical implications of this in vitro

study are not known, consideration should be given to use higher concentration of LA (bupivacaine 0.25% has a greater antimicrobial activity than 0.125%) in epidural infusion in order to take advantage of this property.

The application of EMLA® cream is indicated for topical anesthesia of the skin in connection with i.v. cannulation, as vascular access is often linked with nosocomial infection. The impact of EMLA® cream (an eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) on the skin flora was investigated by Batai *et al (28)*. They compared the bacteriostatic / bactericidal effect of EMLA® with Skinsept Pur® (alcohol based disinfectant) disinfection. Samples were taken from 0 to 12h after treatment. EMLA® cream was shown to have a similar bactericidal effect than Skinsept Pur® and a longer bacteriostatic effect. This difference was significant after 4h. Whether this finding may have clinical relevance in terms of reducing nosocomial infection need further studies.

Cancer recurrence

Surgery still remains a cornerstone in the management of cancer patients. However, surgery inevitably induces a profound neuroendocrine, metabolic, and cytokine response. A retrospective analysis has suggested that paravertebral anesthesia and analgesia for breast cancer surgery reduced the risk of recurrence of metastasis during the initial years of follow-up *(29)*. Biki *et al (30)* performed a similar retrospective review of cancer patients after radical prostatectomy. They compared outcome between a group having general anesthesia with either opioid analgesia or epidural analgesia. This analysis showed that open prostatectomy surgery with general anesthesia, substituting epidural analgesia for postoperative opioids, was associated with substantially less risk of biochemical cancer recurrence. These exciting perspectives warrant prospective, randomized trials to evaluate this association. General anesthesia, pain, sympathetic blockade, all are involved in the modulation of the immune system. The natural killer cells (NK) are an important part of non-specific cellular-mediated and antitumoral immunity. Forget and De Kock *(31)* performed a systematic review to recapitulate data over NK activity during the perioperative period and the influence of anesthesia, analgesia and modulation of sympathetic system. It came out from this review that local anesthetics, contrary to opioids, stimulate the activity of NK cells during the perioperative period. However, it is important to keep in mind that the long term consequences of each technique on patient's outcome warrant further investigations. Yardeni *et al (32)* assessed pain intensity and immune reactivity in two groups of female patients scheduled for transabdominal surgery assigned either to i.v. lidocaine started 20min before surgery or a placebo. All patients had patient-controlled epidural analgesia. In the lidocaine group postoperative pain at rest and during coughing was less in the first 8 postoperative hours. The in vivo production of IL-1ra and IL-6 was significantly reduced, whereas the lymphocyte proliferation response to phytohemmaglutinin-M was better maintained in the control group. This study indicates that i.v. lidocaine reduces surgery-induced immune alterations. The long-term clinical implications of these findings are unknown and warrant future investigations.

CONCLUSIONS

It is fascinating that more than decades after the introduction of local anesthetics for perioperative analgesia, we may still discover new properties and anticipate new applications of this class of drugs. Various types of inflammation including neuroprotection, acute lung injury, bowel function recovery and maybe cancer recurrence may be positively influenced by the application of local anesthetics. These issues are without any doubt the challenges of the coming years.

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