CKJ REVIEW

Local anesthetics for the Nephrologist

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ABSTRACT

Several specialists in medicine use local anesthetics. In patients with kidney disease, these agents are used during catheter insertions for hemodialysis and peritoneal dialysis, arteriovenous fistula and graft procedures, kidney transplantation, parathyroidectomy, kidney biopsies, and dental and skin procedures. Patients on chronic hemodialysis use a topical application prior to use of needles for arteriovenous fistula cannulation before starting dialysis. They are also used to manage acute and chronic pain conditions, in regional nerve blockade and in multi-modal enhanced recovery protocols. Despite their frequent use by both physicians and patients, data on the use of local anesthetics in patients with kidney impairment are not well reported. This review will summarize the use of local anesthetics in chronic kidney disease, describe their pharmacology and the impact of lower estimated glomerular filtration rate on their pharmacokinetics, and suggest dose regulation in those with kidney dysfunction.

Keywords: chronic kidney disease, local anesthetics, pharmacology

INTRODUCTION

Local anesthetics (LAs) are ubiquitous in healthcare, having been in use for more than a century by medical specialists in diverse locations including physician offices, ambulatory surgical centers and hospitals. They are widely used in patients with kidney disease, particularly in those with advanced chronic kidney disease for central and peritoneal dialysis (PD) catheter placement, weekly arteriovenous fistula (AVF) anesthesia, and other surgeries including kidney transplantation and parathyroidectomy. Additionally, they are also used for numerous local procedures including skin and dental procedures, and kidney biopsies, and for pain management in this population.

LAs are grouped by their chemical structure into ester and amide anesthetics (Figure 1). Routes of administration include neuraxial, perineural, intravenous, infiltrative, topical and transdermal (Table1) [1–3]. The primary mechanism of action is reversible blockade of voltage-gated sodium channels after diffusion across the neuronal cell membrane. They also interact with other channels and receptors such as potassium and calcium channels, ligand-gated channels and G-protein-coupled receptors [1–3].

The variation in individual patient's response to LAs is probably larger than previously assumed. LA systemic toxicity (LAST) can result in serious patient harm and fatality. Accordingly, educating providers in all relevant specialties about the safe use of LAs is essential [3]. Herein, this brief
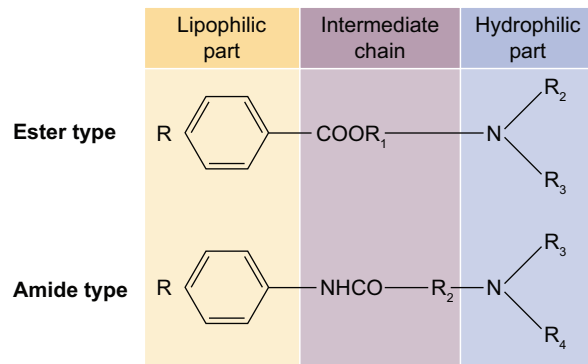
FIGURE 1: Typical local anesthetic. Top: ester type; bottom: amide type. Figure created using biorender.com.

review summarizes the use of LAs in practice for the Nephrologist.

CHEMICAL AND PHARMACOLOGIC PROPERTIES OF LAs

LAs have different pharmacokinetics that depend on a multitude of chemical properties, however most of them have fundamental mechanistic features in common. Chemically they consist of a lipophilic group, joined to a carbon chain and hydrophilic group by either an amide or ester linkage. This bond distinguishes LAs into the two classes of esters and amides [4] (Table 1). See Table 1 for classification of common LA agents. Tables 2 and 3 describe different characteristics of LAs (ester and amide anesthetics).

The speed of onset, potency and duration of LAs is dependent on the pKa, lipid solubility and protein binding, respectively. Most LAs have a rapid onset when administered parenterally for infiltrative anesthesia, the fastest being lidocaine (0.5–1 min) followed by prilocaine (1–2 min). The average onset of action for the remaining agents is between 3 and 5 min. As rate of diffusion across the nerve sheath and nerve membrane is related to the proportion of non-ionized drug, LAs with low pKa have a rapid onset of action, and those with higher pKa have a slower onset of action. If the pH of the tissue is decreased, as may occur in sites of infection, the onset of action may be further prolonged or the drug rendered ineffective. Nerve morphology is another factor, given that the relatively thin pain fibers are usually anesthetized readily. Within limits, higher concentration and greater lipid solubility improve onset to a small degree. The duration of action depends on the length of time that the drug can stay in the nerve to block the sodium channels [5].

Pharmacokinetic parameters of absorption, distribution, metabolism and elimination define how the LA will act (Table 2). In addition, the effects of LAs on various ion channels and intracellular pathways also affect their action. Molecular weight and lipid solubility of these agents are important as they determine the rapidity with which molecules diffuse through membranes. The smaller molecular weight and more lipid-soluble agents have more rapid diffusion through lipid membranes and reach their site of action more quickly, influencing the speed of onset. Lipid solubility is directly related to potency. The lipid solubility of LAs is expressed as the partition coefficient, which is defined as the ratio of the concentration when LA is dissolved in a mixture of lipid and aqueous solvents. Higher lipid solubility gives a greater volume of distribution of LA, which is associated with higher potency. Furthermore, LAs with high protein binding to α_1-acid glycoprotein (AAG) have a longer duration of action and lower bioavailability for metabolism. Hypoxia, hypercarbia and tissue acidosis decrease protein binding, which can further compromise the activity of LAs. Vasoconstriction can prolong the effects of the anesthetic by reducing systemic distribution. Table 2 summarizes the factors affecting pharmacology of various LAs [1–3].

LAs act on ion channels. Blockade of sodium (Na+) channels by LAs prevents the generation of action potentials at nerve endings during an infiltration block, blocks action potential conduction along axons for peripheral nerve blocks, and inhibits the depolarization-dependent release of transmitters and neuropeptides at presynaptic terminals, where LAs penetrate into the spinal cord during neuraxial blocks. The action potentials in nociceptive fibers are inhibited, which leads to blockade of transmission of pain impulses. Inhibition of potassium (K+) channels potentiates the impulse blocking action that occurs via the blockade of Na+ channels. Hyperpolarization-activated cyclic nucleotide-gated channels blockade by LAs is what leads

Table 1. Types of LAs, and indications for their use

Molecule	Indication
Amide structure LAs	
Articaine	Odontology
Lidocaine	Infiltration, nerve block, ophthalmic, epidural, intrathecal, IVRA, topical use (i.e., gels, ointment, liquid, cream, spray, patch)
Levobupivacaine	Infiltration, nerve block, epidural, intrathecal
Bupivacaine	Infiltration, nerve block, epidural, intrathecal
Mépivacaine	Infiltration, epidural, intrathecal, nerve block
Prilocaine	Infiltration, IVRA, topical (used in eutectic mixture with lignocaine) Local on healthy skin, spinal anesthesia
Ropivacaine	Infiltration, nerve block, epidural, intrathecal, wound infusion, phantom limb pain, herpes zoster pain
Ester structure LAs	
Oxybuprocaine	
Procaine/chloroprocaine	Infiltration, epidural, intrathecal, nerve block
Tetracaine	Mucosal, ophthalmic

IVRA, intravenous regional anesthesia.

Table 2. Pharmacokinetic parameters influencing the pharmacology, pharmacokinetics of LAs

Pharmacokinetic parameters	Action via or dependent on
Absorption	– Properties: lipid solubility, protein binding, pKa
	– Vascularization of the injection site
	– Concentration
	– Additives
Distribution	– Tissue vascularization
	– Amides: good diffusion in the lungs, spleen, kidneys
	– Placental barrier passage
Metabolism	–Esters: hydrolysis into para-amino benzoic acid causing allergies
	–Amides: Hepatic metabolism
Elimination	–Liver and kidney
	–Function of pH, protein binding and fat solubility

Table 3. Characteristics of amide and ester LAs

Characteristic	Amide LAs	Ester LAs
Metabolism	Hepatic, slow	Pseudocholinesterase to PABA, rapid
Stability	More stable	Can break down in heat, ampules and sun
Allergic reactions	Rare	Possible due to PABA derivative
Systemic toxicity	More common	Less likely

PABA, para-aminobenzoic acid.

to the antiarrhythmic ability of systemic lidocaine and anti-hyperalgesic actions of lidocaine to treat chronic pain. Finally, LAs have effects on calcium channels as well [6, 7]. Additionally, LAs can alter the cell membrane's surface electrical charge and affect lipid dynamics [8].

LAs' PHARMACOKINETICS AND DOSING IN KIDNEY DISEASE

Both acute and/or chronic kidney insufficiency can alter the 4 phases of drug pharmacokinetics: absorption, distribution, metabolism and elimination. Impairment in kidney function can be responsible for pathophysiological variations that can have repercussions on the absorption of drugs, independently of its action on elimination [9]. Patients with kidney dysfunction have enhanced initial absorption of LAs at the injection site [10, 11], perhaps due to a relative alkalinization of LA. In a hyperdynamic circulation, the increased blood flow coupled with increased uptake can result in high peak plasma concentrations that may be achieved earlier compared with patients with normal kidney function. Additionally, impaired kidney function also leads to a decrease in the clearance of metabolites of LAs that are eliminated by the kidneys [12, 13]. Thus, the LA peak effect, and their metabolites may accumulate during prolonged infusion [14]. Taken together, this may result in rapid attainment and maintenance of high peak concentrations, and accumulation of metabolites especially with continuous infusions. This may predispose to a higher side-effect risk profile [15], warranting consideration to use reduced dosage and avoid extended infusion use in patients with kidney dysfunction.

The amide-type LAs, which include bupivacaine, levobupivacaine and ropivacaine, undergo primarily liver metabolism to inactive metabolites prior to excretion [15], and thereby may be better suited for use in patients with kidney failure. Articaine is currently the LA of choice for chronic kidney disease (CKD)

patients undergoing dental procedures [16]. It is recommended that close monitoring of the response to treatment with LAs should be instituted [17]. LAs are not dialyzable, however it is advisable to avoid using the drug during hemodialysis sessions as the active metabolites may undergo dialysis. Tsuchiya *et al.* have suggested to decrease the dose of LA by approximately 25% in the acidotic patient [18].

A decrease in protein expression and activity of several drug-modifying enzymes (Cyp1a1, Cyp2c11, Cyp3a1, Cyp3a2, Nat1, Nat2) has been observed in experimental models of end-stage kidney disease (ESKD), which in turn has been shown to affect the pharmacokinetics of lidocaine [19]. On the contrary, patients with advanced CKD also have increased levels of AAG. Binding of LAs to AAG can lead to a decrease in free fraction of the drug available for hepatic metabolism and also a reduced volume of distribution. This may result in an apparent 'ineffectiveness' of anesthesia, and thereby lead to an increase in LAs' dosage and subsequent side effects.

Pere *et al.* reported that the pharmacokinetics of ropivacaine are not altered in patients with impaired renal function. Although unconjugated plasma concentrations of 3-OH-ropivacaine were relatively high [similar to those of 2′,6′-pipecoloxylidide (PPX)], the toxic potential of this metabolite is negligible. While a substantial part of the active metabolite PPX is renally excreted, there is also clinically relevant non-renal elimination of PPX in patients with impaired renal function [11].

Based on available recommendation, it is not necessary to adjust the dosage of lidocaine in patients with renal insufficiency. It is reported that lidocaine infusion in uremic patients is safe, with no abnormal accumulation of lidocaine or its metabolite monoethylglycinexylidide. However, its main metabolite glycinexylidide may increase progressively, even after 12 h [20], and induce neurological adverse effects. While lidocaine pharmacokinetics are not significantly altered in CKD, its clearance has been shown to be reduced in proportion to the degree

of impairment in kidney function in patients not receiving hemodialysis [17]. Lidocaine is not significantly dialyzable [17, 21].

Articaine is the most widely used LA agent for outpatient dental surgery in a number of European countries [22]. It produces sensory and motor blockade shorter than bupivacaine and has lower neurotoxicity than lidocaine. It is metabolized by nonspecific plasma esterases both in blood and tissues, leading to rapid clearance. Also, the rapid breakdown of articaine to the inactive metabolite articainic acid is related to a very low systemic toxicity and consequently to the possibility of repeated injections [23]. Additionally, epinephrine is present in low concentration in articaine solutions. Due to its favorable pharmacological characters, articaine seems to be the LA of first choice in patients with impairment in kidney function [16].

Animal models have shown that acidosis can decrease the protein binding of bupivacaine, thereby leading to an increase in free fraction of the drug, and associated increased risk of toxicity. Acidosis has also been reported to decrease the central nervous system (CNS) threshold to the toxic adverse effects of LAs [18]. Additionally, patients with advanced kidney disease have uremic platelet dysfunction, and those on hemodialysis also ususaly receive heparin during treatment sessions. This increases the risk of bleeding, which is an important factor to be considered when using spinal anesthesia in this patient population.

Epinephrine is usually given along with LA, to slow down the absorption of LA, and increase the length of anesthetic action and intensification of the block [10]. Patients with kidney dysfunction are at higher risk of adverse responses, as this may lead to increase in side effects due to LA, and a lower than usual dose may be adequate to produce similar anesthetic effect.

OTHER PATHOLOGIC AND PHYSIOLOGIC STATES IN KIDNEY DISEASE

Patients with chronic or ESKD often have concomitant liver and cardiac disease. Elston *et al.* proposed several mechanisms by which CKD can impair hepatic drug metabolism. These include modification of plasma protein binding, alteration in liver blood flow, inhibition of biotransformation reactions by metabolites normally excreted by the kidney, and inhibition of hepatic drug metabolism or uptake by circulating inhibitors present in uremic plasma [24]. In some patients, renal failure may lead to major changes in metabolism due to the slowing of hepatic enzyme reactions such as reductions, acetylations and oxidations [25]. Thus, a drug with strictly hepatic metabolism may have altered pharmacokinetics in patients with renal impairment [26]. Hepatic disease generally does not increase the risk of LA-associated systemic toxicity in single-dose administrations. However, uremia may impair metabolic functions of both liver and the kidneys, which may lead to an enhancement in the accumulation of renally excreted metabolites of LAs [27].

Cardiac disease with associated heart failure can lead to LA-associated systemic toxicities. It is unclear whether this effect is due to reduced clearance associated with kidney disease or hepatic congestion, or reduced elimination due to cardiac disease itself. Heart failure reduces local absorption of these medications due to low tissue perfusion. The 'safe dose' and toxicity profile for an LA is unique to the particular drug. These safe dosages are available for most commonly used LAs. Most toxicity manifests as paresthesia, perioral tingling and other peripheral neural symptomatology. Early systemic toxicity for certain LA agents can be CNS in nature, while others demonstrate early cardiotoxicity. Greater toxicity risk is seen in those on either continuous infusions or with repeated dosing of LA [14].

In pregnant patients with CKD or ESKD, most LA agents can be used during epidural anesthesia. They can be systemically absorbed and cross the placenta, depending on the local pH, degree of protein binding and the pKa of the molecule. They are also excreted at low concentrations into breast milk, however both lidocaine and bupivacaine have been reported to be safe for use in lactating mothers [28].

LA infiltration or regional anesthesia blocks are often performed in the elderly as a means of reducing the necessary doses of systemic sedative and opioid medication in order to achieve anesthesia. Local anesthesia sensitivity is increased in the elderly due to decreased neural density, nerve conduction velocity and the physiological changes in the elderly. Additionally, in the elderly population with kidney disease, clearance of LAs may be slowed due to reduced systemic blood flow and hepatic function. Lower doses of LA can often be sufficient to achieve adequate block in elderly, as compared with younger individuals [29].

LA USE IN PATIENTS WITH KIDNEY DISEASE

There are several surgical procedures that patients with CKD and ESKD will likely need to undergo. All patients requiring kidney replacement therapy either have access creation for hemodialysis or catheter insertion for PD, and/or undergo kidney transplant. Parathyroidectomy is another surgery performed commonly in this patient population. Use of LA for the surgeries may have various clinical implications. Additionally, a role of LA has also been suggested in treatment of CKD associated pruritus.

One of the most common surgical interventions in the CKD population is the creation of AVF. The success of AVF has been studied comparing regional versus local anesthesia using bupivacaine and lidocaine mixtures. The most recent study appears to show the benefit of regional anesthesia over LA for AVF patency [30]. Regional anesthesia has been associated with improved outcomes, presumably as a result of vasodilation by blockade of sympathetic nerves, improved blood flow and decreased vasospasm, in the perioperative and postoperative periods [31].

Brachial plexus block is an ideal technique for the provision of anesthesia of the arm for the formation of AVF [32]. There is, however, a clinical suspicion that brachial plexus block is less effective in patients with CKD than in those with normal renal function. This is supported by a study that showed a decreased duration (38%) of brachial plexus anesthesia in CKD [33]. The authors suggested that it might reflect a faster systemic uptake of drug because of an increased cardiac output in renal failure [34]. In addition, reports of toxicity in CKD [35, 36] have led to suggestions that the pharmacokinetics of LAs may be altered unfavorably in this condition, although conclusive data in this area are lacking.

Cannulating the AVF induces pain in the ESKD population and requires topical anesthetics to minimize discomfort. A recent review article indicates that eutectic mixture of local anesthetic (EMLA) cream, which is a combination of lidocaine and prilocaine, is more effective in pain management compared with lidocaine and piroxicam gel or spray [37]. EMLA is a mixture of 2.5% lidocaine

and 2.5% prilocaine. Local side effects with the use of EMLA include edema, erythema and pallor of skin. However, one review showed that more serious reactions can occur, which include methemoglobinemia, CNS toxicity and cardiotoxicity. Contributing factors for systemic toxicity include excessive application of EMLA, inflamed or diseased skin, and pediatric age. Use of EMLA with caution is advised in the pediatric group [38].

PD catheter placement has also successfully utilized LAs in regional anesthesia blocks using ultrasound guidance [39]. The transversus abdominis plane (TAP) block is a technique whereby LA is injected between the transversus abdominis and internal oblique muscles, and diffusion of drug causes anesthesia of the nerves that supply cutaneous innervation to the abdominal wall. This technique has decreased the need for opioids in the postoperative period and decreased the postoperative nausea and vomiting patients have experienced. In the study by Li *et al.*, there were no adverse effects using 40 mL of 0.25% ropivacaine for TAP block [39]. A Japanese case study using 1.8 mg/kg ropivacaine (120 mg) provided adequate analgesia in a patient undergoing PD catheter placement TAP block with cardiac and renal dysfunction. The patient reached a maximum 2.5 μg/mL after 15 min and did not develop significant LAST, except for drowsiness. Based on this existing literature, we would consider 100–120 mg ropivacaine dosing to be the upper limit and would avoid exceeding this upper limit to avoid LAST, especially in patients with renal and cardiac dysfunction [40].

There has been no causal or associative relationship defined between the type of anesthesia and kidney outcomes after transplantation, but the use of the drug propofol has been suggested as beneficial in mitigating ischemia–reperfusion injury. Conduction anesthesia using epidural administration of LAs has been shown to reduce the incidence of AKI, but likely as a result of the anesthetic technique rather than the LA itself [41]. When investigated in 13 healthy individuals, there was no alteration of renal blood flow seen after administration of 2% lidocaine with epinephrine for epidural analgesia [42]. Additionally, lidocaine and bupivacaine are associated with low toxicity and excellent graft outcomes when used for epidural anesthesia during kidney transplantation [43].

Though kidney transplantation is usually performed under general anesthesia (GA), combined spinal and epidural anesthesia (CSEA) can also be used. A small ($n = 50$) randomized control trial that compared use of regional and GA during kidney transplantation did not shown any significant difference between total anesthesia time, surgical time or hemodynamic parameters [43], followed by a subsequent case series that revealed 92% success rates with CSEA, without any significant intra-operative changes [44]. GA may be associated with higher risk of hemodynamic instability in patients with underlying cardiovascular or respiratory compromise. One such condition could be ESKD secondary to Alport's syndrome. A case report using CSEA during kidney transplantation in a patient with Alport's syndrome suggests that a low dose of LA along with a continuous epidural infusion is beneficial in providing adequate anesthesia without the risks associated with GA, and may aid with successful recovery of the transplanted graft [45].

The neuraxial route for LA administration may be ideal in patients with kidney disease, as it can provide better postoperative pain control when nonsteroidal anti-inflammatory drugs are contraindicated, and dose of opioids is limited due to risk of respiratory depression [46].

Secondary hyperparathyroidism is a complication of kidney failure, and patients who fail medical therapy require parathyroidectomy. Patients may have benefits if the surgery is performed under LA, as compared with GA. Both total [47] and focused parathyroidectomy [48] for primary hyperparathyroidism, when performed under LA, have been associated with minimal postoperative pain and minimal postoperative analgesic requirement, and with decrease in postoperative nausea and vomiting. The agents used were 1% lidocaine and a combination of 0.2% bupivacaine and 2% lignocaine in a 1:1 ratio for total and focused parathyroidectomy, respectively [47, 48].

Pramoxine hydrochloride is a morphine derivative that can be used as a topical LA for management of pruritus associated with advanced CKD and ESKD. Young *et al.* conducted a randomized, double-blinded study in patients on hemodialysis, which showed statistically significant effectiveness with use of 1% pramoxine when used twice daily for 4 weeks [49].

LA TOXICITY

Usually, kidney dysfunction does not increase the risk of LA toxicity, unless metabolic derangements including acidosis, hypoxia or hypercarbia are present. The hyperdynamic circulation in uremic patients causes a rapid rise in LAs plasma levels after large volume nerve block, however the levels of free drug in circulation are low, due to greater protein binding to AAG, which is an acute-phase reactant and is increased in this subset of patients [12]. Therefore, the overall risk of LA systemic toxicity remains low.

Table 4 describes the various local and systemic toxicities seen with LAs. Initial management of LA toxicity should be focused on airway management, circulatory support and reduction of systemic side effects. Management of LA-induced cardiac arrest is based upon the advanced cardiovascular life support (ACLS) guidelines, with a few adjustments. Epinephrine (less than 1 μg/kg) is recommended for initial treatment. If ventricular arrhythmias occur, amiodarone is the preferred pharmacotherapy, as lidocaine and procainamide can exacerbate the existing LA toxicity [50]. Immediate administration of benzodiazepines is recommended in the event of seizure occurrence.

Recent case studies support the use of lipid emulsion therapy as soon as prolonged seizure activity or LA-induced arrhythmias are suspected. Theories suggest that lipid emulsion works by acting as a 'lipid sink', drawing the lipid-soluble LA out of the tissue. Treatment has been documented to be effective in systemic CNS and cardiac toxicity. Use of lipid emulsion in LA cardiac toxicity improves cardiac conduction, contractility and coronary perfusion. A bolus of 1.5 mL/kg of 20% lipid emulsion and subsequent infusion of 0.25 mL/kg/min should be given. The infusion should be continued for 10 min after hemodynamic stability is attained. An additional bolus and an increase of the infusion rate to 0.5 mL/kg/min can be administered if stability is not achieved. The maximum recommended dose for initial administration is approximately 10 mL/kg for 30 min [50]. If cardiac stability has not been achieved following the modified ACLS guidelines, and subsequent lipid emulsion therapy, then cardiopulmonary bypass is recommended until the LA has cleared.

The American Society of Regional Anesthesia and Pain Medicine has developed a checklist and electronic decision support tool for LA systemic toxicity, the ASRA LAST smartphone app, available from https://www.asra.com/page/150/asra-apps, the Apple App Store or Google Play [51, 52]. The clearance rates of LAs with hemodialysis have not been well described. Remote data by Thomson *et al.* demonstrated the disposition kinetics of lidocaine did not differ between healthy individuals and those

Table 4. Toxicity and controversies in clinical use (for all classical LAs)

Allergy: rare, <1% (ester LA more prone to elicit allergic reactions than amides)
Resistance: related to mutations in ion channels and/or metabolic disturbances
Tachyphylaxis: unclear mechanisms and clinical relevance
Injection complications:
Needle trauma, hematoma, abscess formation, paraesthesia, necrosis
Injury to muscles, connective tissue and cartilage
Local neurotoxicity

Systemic toxicity
Minor CNS symptoms: e.g. perioral tingling, metallic taste, tinnitus, dysarthria, dysphoria, dizziness, drowsiness, dysgeusia, tremors, logor-
    rhea, visual disturbances
Major CNS symptoms: agitation, seizures, coma, respiratory distress
Cardiovascular symptoms: arrhythmias (bradycardia, tachycardia, ventricular ectopy/tachycardia/fibrillation), hypotension or hypertension,
    conduction disturbances (e.g., widened QRS complex)
*Lidocaine and mepivacaine predominantly affect myocardial contractility
*Ropivacaine, levobupivacaine and bupivacaine are negatively inotropic, and highly arrhythmogenic
Hematologic symptoms: methemoglobinemia
*Can lead to cyanosis, tachypnea, exercise intolerance, fatigue, dizziness, syncope and weakness
*Seen with the use of prilocaine, articaine and benzocaine

Table 5. Research essentials for LA use in patients with kidney disease

Dose adjustments in CKD and ESKD patients

Incidence of LA toxicity in CKD and ESKD patients
Potential role and underlying mechanisms leading to renal protection with use of specific LAs
Safety and drug interaction data in organ transplant patients
Safety and toxicity profile in use of LAs in kidney biopsies
Quality of life studies for improved pain management in ESKD patients using EMLA cream
Prescription patterns of Nephrologists doing procedures and using LAs

on hemodialysis [14], and a subsequent study conducted on a hemodialysis patient showed removal of lidocaine with hemodialysis to be negligible [21]. Therefore, there is no role of dialysis in treatment of LA toxicities. However, lipid emulsion has been used successfully to treat both cardiovascular and neurologic systemic toxicity in patients with renal failure.

CONCLUSION

Conventionally, dose adjustment in kidney failure is considered imperative only for drugs that are renally excreted, however active metabolites of LAs may get accumulated and can cause toxicity despite renal excretion not being the predominant mode of excretion for these agents. Most LAs can be safely administered in CKD and ESKD patients. Amide-type LAs may be preferred over ester-type LAs, as they are converted to inactive metabolites in the liver prior to excretion. Patients with advanced kidney dysfunction can have an increase in the absorption of LAs, quicker attainment of peak concentration and sustained high concentrations for a longer duration. Therefore, physicians should consider dose reduction, with use of minimal amount of drug to achieve adequate anesthesia and avoidance of continuous infusions when using these agents for this subset of individuals. When repeated doses are required, an increase in dosing interval should be contemplated. Since the dose reduction is not well described in the literature, specific estimates of dose reduction are not recommended in this paper.

Clinicians also need to be mindful of greater neurological and cardiac toxicities, and increased risk of uremic neuropathy with use of LAs in patients with renal impairment, and thus need to closely monitor tolerance to LAs' effects. Additionally, dose of the LA should be individualized based on patient factors including age, weight and presence of comorbidities. The paucity of available literature on use of LAs in the CKD population warrants the need for more refined studies to determine the optimal dosing to make them most efficacious, while minimizing known toxicities. Table 5 delineates future perspectives and research opportunities in this field.

CONFLICT OF INTEREST STATEMENT

K.D.J. serves as a consultant for Astex Pharmaceuticals and Natera and is a paid contributor to Uptodate.com.

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