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Intravenous Therapies in the Management of Neuropathic Pain: A Review on the Use of Ketamine and Lidocaine in Chronic Pain Management

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1. Introduction

Neuropathic Pain is a term referred to "pain arising as a direct consequence of a lesion affecting the somatosensory system". As a first line option, oral medications are mostly used, as they are easily available, relatively safe, and do not need much resources. They include antidepressants in the form of tricyclics, newer selective reuptake inhibitors of serotonin and norepinephrine, gabapentin, pregabalin etc. Although neuropathic pain conditions do share some common clinical features, they are quite diverse when considered individually according to their etiology and pathogenesis. Hence not all patients and not all types of neuropathic pain respond to such oral therapy. In practice patients are given a form of such neuropathic pain medication along with or without an opioid, depending upon the extent of pain that the patient suffers. Opioids are potent analgesics but are not a good choice for neuropathic pain conditions. With time the clinician is left with fewer alternatives and furthermore, with the the increasing knowledge that escalation of opioid therapy will perhaps lead to hyperalgesia and tolerance, it becomes necessary to explore other options. Among the other options one can always consider to explore treatment with intravenous medication such as Ketamine, Lidocaine, and Magnesium etc. This chapter would highlight the use of ketamine and lidocaine in the form of drug profile, the pharmacological basis behind its use, strategies to use, important side effects and limitations and available evidence base, including a review of randomised controlled studies. Both are considered separately in two different parts. References for both the parts are given at the end, in separate sections.

Part A: Ketamine

1. Ketamine is a potent anesthetic and analgesic compound with unique actions. It is a phencyclidine (PCP), anesthetic compound with its chemical name being 2-O-chlorophenyl-2-methylamino- cyclohexanone. It contains an asymmetric carbon atom and exists as 2 isomers {(R) and (S)}, of which the (S) isomer is the more potent general anesthetic and NMDA antagonist. Commercially available ketamine formulations are a racemic mixture of S (+) and R (-) preserved in benzethonium chloride (Orser, 1997; Ben Ari, 2007). Animal

studies has shown that the affinity at the phencyclidine binding site of S (+) ketamine at the NMDA receptor is four fold that of R(-). Studies in rats and mice have demonstrated that the S (+) form is five times more hypnotic and three times more analgesic than the R (-) raceme (White, 1985). The incidence of side effects is although similar, overall it is theoretically less, as you need less S ketamine for a therapeutic action and the side effects are observed to be proportional to their blood levels.

Ketamine is unique because no other drug combines the property of anesthetic, analgesic and amnesic properties. The search for a PCP compound with less hallucinogenic side effects led to ketamine (CI-581), first synthezised in 1962 by Calvin Stevens at Parke-Davis and Co, and introduced into clinical practice during 1970 after investigation from Corssen and Domino in 1964 on human volunteers (Sinner & Graf, Sabia, 2011). Apart from the property of dissociative anesthesia, its analgesic effects have been widely investigated, in both experimental and human studies. The analgesic properties of ketamine primarily exist because of its property to block NMDA receptor in a non-competitive fashion. Other clinically known NMDA-receptor blockers include dextromethorphan, dextrorphan, memantine, and amantadine. There are other mechanisms of analgesia which could be partly responsible for the actions of ketamine. Ketamine is also active at opioid, norepinephrine, serotonin, and muscarinic cholinergic receptors; it acts by inhibiting serotonin and dopamine reuptake and inhibits voltage-gated Na+ and K+ channels (Okon, 2007). Indeed, some studies suggest that analgesic effects of Ketamine are actually due to its activation of monoaminergic descending inhibitory pathways, rather than NMDA receptor (Okon, 2007). To understand its mechanism one has to also understand the role of NMDA receptors, at least briefly, as related to pain mechanisms.

2. NMDA receptor, central sensitization and chronic pain

1. NMDA receptors are known to be involved in the development of wind up phenomenon and generation of central sensitization and hence chronic pain.
2. There is increasing evidence that NMDA receptors are also involved in peripheral sensitization and visceral pain.
3. Evidence shows that Ketamine primarily acts at NMDA receptors but also has actions at other sites.

2.1 Pain is mediated through C (unmyelinated) and A-delta (thinly myelinated) fibres

The primary excitatory neurotransmitter released via C fibres is Glutamate. This is the major excitatory neurotransmitter in the mammalian nervous system and modulates several functions through subtypes of glutaminergic receptor: the *N*-methyl-D-aspartate (NMDA) subtype, the kainite, the AMPA (l-amino-3-hydroxy-5-methylsoxasole-propionic acid) subtype, and the metabotropic subtype (Bennett, 2000). NMDA receptor is also called "coincidence detector", as several events must combine to activate it. Apart from glutamate, glycine is also needed as a co-agonist (Carpenter, 1999). NMDARs display a number of unique properties that distinguish them from other ligand-gated ion channels. First, the receptor controls a cation channel that is highly permeable to monovalent ions and calcium. Second, simultaneous binding of glutamate and glycine, the co-agonist, is required for efficient activation of NMDAR. Third, at resting membrane potential the NMDAR channels are blocked by extracellular magnesium and open only on simultaneous depolarization and

agonist binding, thus both depolarization of the postsynaptic neuron and presynaptic release of glutamate and glycine are required for maximum current flow through the NMDAR channel. The response of ionotropic glutamate receptors to agonists is usually potentiated after phosphorylation.

Wind-up is a progressive, frequency-dependent facilitation or increase in the magnitude of C-fiber evoked responses, of the responses of a neurone observed on the application of repetitive (usually electrical) stimuli of constant intensity. **Central sensitization** refers to enhanced excitability of dorsal horn neurons and is characterized by increased spontaneous activity, decrease in response threshold, enlarged receptive field (RF) areas, and an increase in responses evoked by large and small caliber primary afferent fibers (Jun Li, 1999; Cook, 1987). Sensitization of dorsal horn neurons often occurs following tissue injury and inflammation and is believed to contribute to hyperalgesia.

2.2 NMDA activation

Because it is a transmembrane protein, it spans the electric field generated by the membrane potential. The magnesium binding site within the receptor is physically located within this electric field. As the cell is depolarized, the negative field effect weakens and in this phase, when the magnesium is absent, Ca^{2+}, Na^{+} and K^{+} -ions flow through the channel. Magnesium ions are rapidly substituted by next set of magnesium ions during repolarization. The Ca^{2+} influx is crucial for the induction of the NMDA receptor-dependent long-term potentiation (LTP), which is thought to underlie neuronal plasticity, including development of central sensitization, learning and memory. The activation of the NMDA receptor leads to a Ca^{2+} /calmodulin-mediated activation of NO synthetase, which plays a crucial role in nociception and neurotoxicity. The primary endogenous neurotransmitter active at NMDA-R is glutamate, the main EAA. It is likely that glutamate facilitates the activation of NMDAR, by causing the intracellular elevation of calcium, leading to a cascade of excitatory events. The sequence of these intracellular signaling events is complex. However, they seem to result in the activation of protein kinase C and elevation of levels of nitrous oxide, which in turn, leads to enhanced release of other EAAs (Sinner & Graf, 2008; Petrenko, 2003; Zhou, 2011).

2.3 Peripheral NMDA receptors and their involvement

Several studies have demonstrated the presence of peripheral NMDA receptors which are involved with pain. Local injections of glutamate or NMDA agonists result in nociceptive behaviors that can be decreased by peripheral administration of NMDAR antagonists (Zhou, 1996). Pederson found that ketamine infiltration had only brief local analgesic effects, but several measures of pain and hyperalgesia were unaffected. Therefore, a clinically relevant effect of peripheral ketamine in acute pain seems unlikely. The local anesthetic action of ketamine can also result from its blocking of cations, and it has been demonstrated that it enhances the local anesthetic and analgesic actions of bupivacaine used for infiltration anesthesia in a postoperative setting (Tverskoy, 1996) and also the development of primary and secondary hyperalgesia after an experimental burn injury (Warnke, 1997). Topical application of ketamine ointment has been recently reported to reduce pain intensity and to attenuate allodynia in patients with an acute early dystrophic stage of complex regional pain syndrome type I (Ushida, 2002).

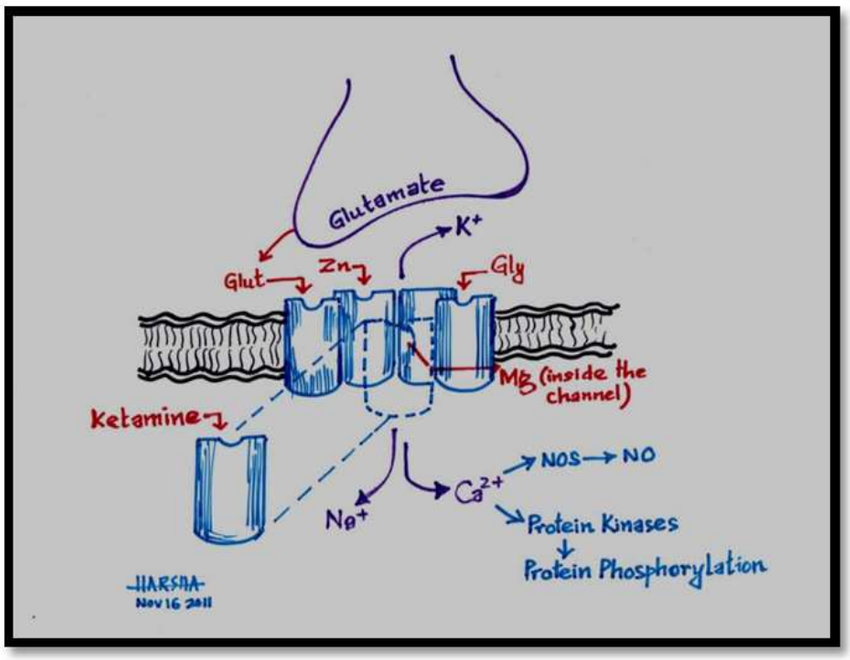


Fig. 1. NMDA Receptor and Mediators involved

3. Pharmacokinetics and pharmacodynamics

The bioavailability after IV administration is about 90%, whereas bioavailability after oral and rectum administrations is 16%, indicating significant first-pass effect by the liver. Particularly, oral administration of ketamine is accompanied by extensive first-pass metabolism, and the plasma levels of (R and S)-norketamine are about three times higher than the levels produced by IV or IM administration (Yanagihara 2003). Nor Ketamine, which is excreted in urine, is thought to have about 30% of the analgesic potency of the parent drug (Sinner & Graf, 2008). Ketamine is soluble in both water and lipids. Because of its high lipid solubility, it crosses the blood–brain barrier rapidly leading to the onset of action within 1-3 minutes and is rapidly redistributed (Sabia, 2011). Brain to plasma ratio for ketamine is estimated to be 6.5:1, suggesting ketamine's preferential accumulation in the brain (Orser, 1997). Timing to maximum pain relief remains a controversial issue, since it depends on the mechanism of the pain. In the Mercadante et al series (Mercandate, 2010), maximum pain relief after a single intravenous dose occurred between 30 and 60 minutes after the infusion. Elimination due to metabolism has a half-life of 2 to 3 h. The plasma clearance is 15–20 ml/kg per minute in adults and higher for S (+)-ketamine than for the enantiomer. It has a large volume of distribution in the steady state (Vss: 3.1 L/kg), owing to its low plasma-protein binding of 27%. Because of the large Vss and relatively rapid clearance, it is clinically possible to administer ketamine as an infusion at 25 to 100 µg/min (Sabia, 2011). With scheduled administration, a steady state is achieved in 12-15 hours. The initial metabolite is norketamine and is produced by the N-demethylation of ketamine, which is mediated by the hepatic cytochrome P450 enzymes (Goldberg, 2010). This is shown to be enantioselective, with the N-demethylation of (S)-ketamine proceeding faster than that of (R)-ketamine (Kharasch, 1992). A dose reduction in patients with hepatic impairment is

advised due to the prolonged duration of action. In renal failure, dose increases may be considered. The urinary excretion of unmetabolized drug is approximately 4%. In forensic medicine, ketamine use can be detected in the urine for about 3 days. Concentration ranges for ketamine in urine have been reported as low as 10 ng/ml and up to 25 µg/ml.

Chemical Name	2O-chlorophenyl-2-methylamino-cyclohexanone
Chemical Structure	C 13 H 16 ClNO
Molecular Weight	274.4 M
Melting Point	258°C and 261°C
Solubility	Both lipid and water soluble
Isomers	S(+) and R(-) isomers S 3-4 times more potent than R as an anesthetic
BIOAVAILABILITY	
Intramuscular	93%
Nasal	25%-50%
Oral	17%
Protein Binding	20%–30%
ONSET OF EFFECTS	
Intravenous	seconds
Intramuscular	1-5 mins
Nasal	5-10 mins
Oral	15-20 mins
HALF LIFE	
Alpha	Alpha half-life (2–4 min)
Beta	Beta half-life 8–16 min (redistribution)
Terminal/elimination	2.5 to 3 hrs

Table 1. Pharmacological Properties

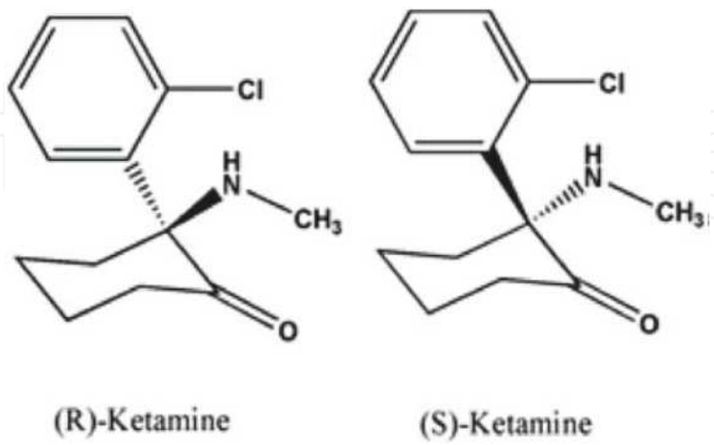


Fig. 2. Chemical Structure of Ketamine

The observation that oral administration is associated with higher serum concentrations of the main metabolite of ketamine, norketamine, compared to other routes of

administration has led to the idea that norketamine contributes to the analgesic effects of ketamine (Fischer, 2010). The oral bioavailability of ketamine after a single oral dose is about one fifth of the availability after an intravenous injection. When ketamine is administered as a racemic mixture, both S-norketamine and R-norketamine is formed. Analgesic effects of ketamine were observed with plasma levels of 100–200 ng/ml (sum of S- and R-isomer) following intramuscular and intravenous administration. Effective analgesia following oral dose occurs at much lower concentrations of ketamine (40 ng/ml) (Grant et al., 1981). Clinical studies have shown that with a prolonged infusion of ketamine the ratio of ketamine to norketamine serum levels remains constant at 3:14 (Ebert, 1997). It is also not sure why some patients do not respond to ketamine and in particular to oral ketamine. Rabben and Oye found a positive correlation between a long pain history and lack of analgesic effect and also between a short pain history and a long-term analgesic effect of low-dose ketamine. This finding was also observed in the study of Mathiesen et al, where patients suffering from pain for more than 5 years did not observe any analgesic effects. These results indicate that pain mechanisms are subject to alterations with time and that these alterations involve transition from NMDA to non-NMDA receptor-mediated transmission in central pain pathways.

4. Mechanisms of action of ketamine

4.1 Ketamine blocks the NMDA channel by 2 distinct mechanisms

1) it blocks the open channel and there by reduces channel mean open time, and 2) it decreases the frequency of channel opening by an allosteric mechanism (Orser, 1997). But the precise interactions of ketamine with NMDARs are still being elucidated (Orser, 1997; Kohrs, 1998). The main interaction is supposed to result from its binding to the phencyclidine receptor in the NMDA channel and thus inhibiting the glutamate activation of the channel in a non-competitive manner (Kohrs, 1998). However the complete spectrum of effects on NMDARs is not completely clear. There may be some actions mediated differently, which are selectively active at low doses. Drugs like memantine and amantadine have no appreciable anesthetic or analgesic properties but still inhibit NMDARs. This dual mechanism may be clinically relevant in treating patients with low dose and high dose ketamine, and my may in fact act through different pathways apart from molecular mechanisms.

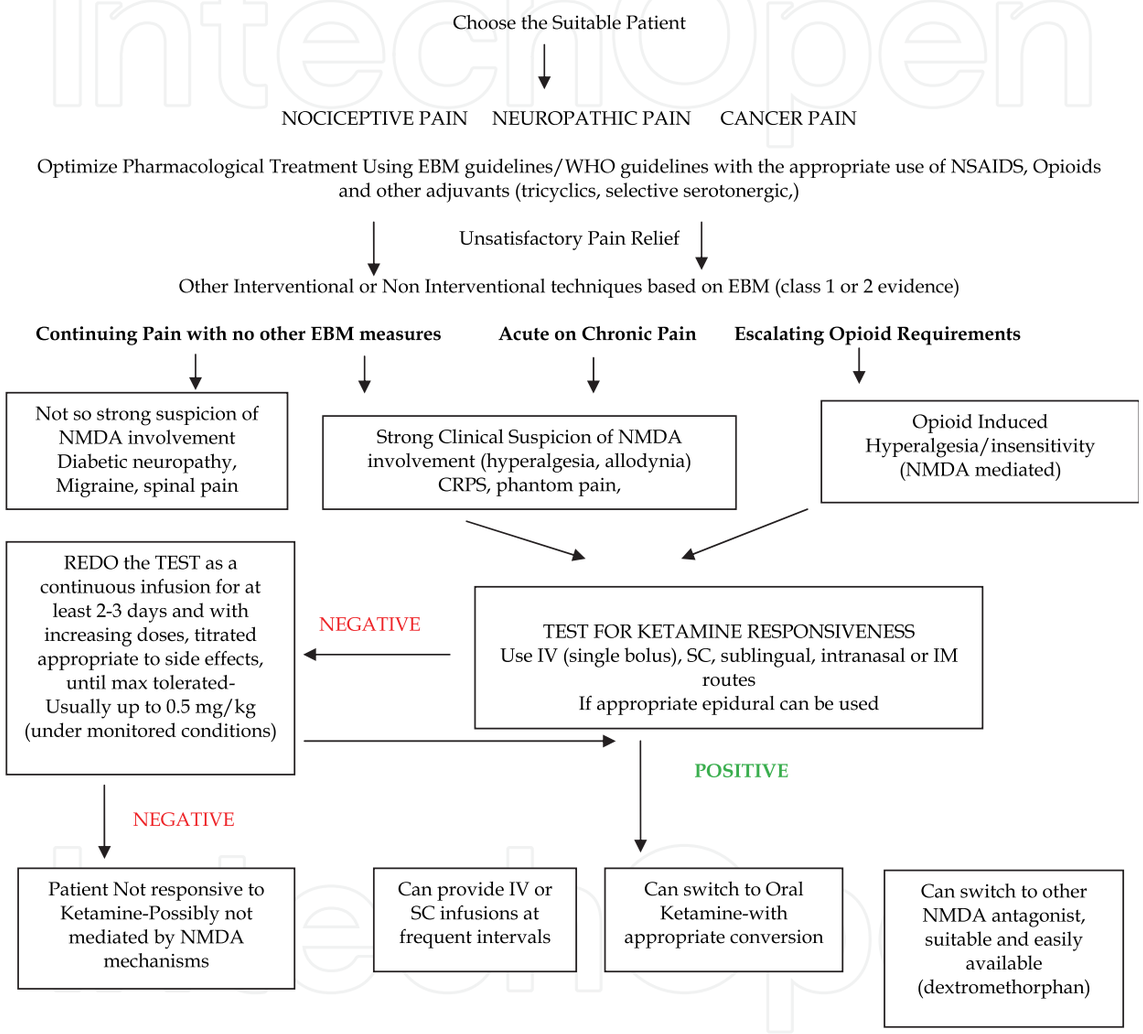
4.2 Other mechanisms of possible ketamine actions

1. Opioid: It is said to be an antagonist at mu and agonist at kappa receptors (Sinner & Graf, 2008; White, 1982).
2. Ketamine is known to produce local anesthetic effect similar to lidocaine and bupivacaine. Spinal administration of ketamine mixed with epinephrine produces motor and sensory block without respiratory depression or hypotension, even in humans, but are associated with central effects unlike in dogs. This has been used in war casualties.
3. Activation or increase in the activity of descending monoaminergic system (serotonergic).
4. Effects on muscarinic cholinergic receptors are not shown to be responsible for analgesia.

5. A practical algorithm for ketamine in chronic pain

For long term use

1. Monitor for Ketamine induced changes in cognition, memory and mood disturbances.
2. Monitor for Ketamine addiction, using the same guidelines as opioids.
3. Long term neuraxial use is not advised as it is supposed to be associated with side effects.



6. An analysis of RCT's of parenteral ketamine

The evidence for the use of Ketamine in chronic, neuropathic pain consists of RCT's, case reports, case series, retrospective studies and experimental studies. RCT's are considered as "level 2 evidence", as per the EBM standards. We performed a search of Pubmed and EMBASE to look for RCT's using ketamine for chronic pain. We also included studies on cancer pain management. Limits were put on English language and human controlled trials. Mesh terms used were as following: 'ketamine', 'administration', 'chronic pain', 'neuropathic pain', 'cancer pain', 'intravenous', 'subcutaneous', 'intramuscular'. Articles

describing a study based on animal research and research about acute postoperative pain and reviews were excluded by entering the term 'NOT' in the search strategy. Only abstracts were not included. We also cross referenced our search results with previous review articles (Hocking, 2003; Bell 2009). Finally a total of 33 articles were selected. Out of them 3 articles were excluded: Eide (1997): this is an N=1 trial, Hagelberg (2010): this trial was just looking at how antibiotic levels affect ketamine levels (the identical dose of ketamine was used in both arms of the trial), Neisters (2011): experimental study on human volunteers. Most included small numbers of patients with a variety of study objectives, designs and outcome measurements. None of the included studies had a high quality methodological design. Due to the above reasons and with the heterogeneity of data, it was not possible to perform a quantitative analysis.

In total we obtained 30 studies. Categorisation according to clinical diagnosis showed; 3 studies of CRPS, 2 were on fibromyalgia, 2 on ischemic pain, 2 on post herpetic neuralgia, 3 on peripheral neuropathic pain, 1 on post traumatic pain, 3 studies on various chronic neuropathic pain conditions, 2 on post nerve injury pain, 2 on phantom limb pain, 2 on whiplash, 1 on odontolgia and TMJ pain, 3 on spinal cord injury pain, 1 on post stroke pain, 1 on migraine treatment and prophylaxis, 1 on cancer pain, 1 was an experimental study. According to route of administration there were: 1 study on subcutaneous infusion, 2 studies on intranasal use, 1 study on intramuscular use, and a total of 26 studies on intravenous use.

Author/ Year	Design	Patient population and numbers	Design/ Methodology	Outcomes	Withdrawal/Side Effects
Carr (2004)	DB RCT PLC	N=22; Chronic pain; currently on 24hr opioid regimens	Ketamine intranasal spray (Ketamine HCL 10%) vs. placebo (NS) 1-5 sprays q90s x 5 for breakthrough pain (BTP)	Significantly lower BTP after IN Ketamine vs. placebo; pain relief up to 60 min. No patient in treatment arm required usual breakthrough pain meds vs. 7 who did in treatment arm	4 patients reported a change in taste, 2 experienced increase in blood pressure, 1 reported nasal passage irritation and rhinorrhea
Huge (2010)	DB RCT	N=16; Chronic neuropathic syndromes	Ketamine 0.2mg/kg intranasal vs. Ketamine 0.4mg/kg intranasal five sprays each nostril x 1	Significant decrease in resting pain in both groups up to 1 hr after application on 100 point pain scale; no change in quantitative sensory testing	75% of subjects reported vertigo, 70% reported sedation; 60% reported difficulty concentrating

Table 2. RCT's of Intranasal Route

6.1 Intranasal route

This route was used in 2 studies, breakthrough pain and various neuropathic pain conditions. This is also utilised in some outpatient clinics to help identify patient's responsiveness to ketamine without involving the logistics and preparation as necessary for IV ketamine infusion. Both studies were positive with respect to ketamine's analgesic actions. Huge studies the use of intranasal S ketamine randomised into 2 different doses (0.2 mg/kg and 0.4 mg/kg). Plasma concentrations of S Ketamine and S norketamine were also studied. The analgesic effects co-related with maximum plasma range of metabolites for both doses after which it decreased.

Intranasal ketamine can act similar to a parenteral route as it can bypass the hepatic metabolism. Apart from the known side effects, intranasal use can cause transient change in taste, rhinorrhea, irritation of nasal passage (Carr, 2004).

6.2 Intramuscular route

IM use is considered parenteral and for all reasons it is considered similar to IV ketamine administration, except that the onset of effect can be prolonged. The only study was done on TMJ pain patients suspected of myofascial pain. Ketamine injection was given as a single dose injection into the most painful part of masseter at a dose of 0.2 ml, in comparison to placebo. There were no differences in pain scores except a minor effect on jaw opening. Although the reason for injection at the local painful site is not provided, it may be assumed that a local or peripheral site of action was considered.

Author/ Year	Design	Patient population and numbers	Design/ Methodology	Outcomes	Withdrawal/ Side Effects
Castrillon (2008)	DB RCT	N=14; Myofascial TMJ syndrome	Ketamine injection (0.2 ml) into masseter vs NS injection x1	No difference in VAS pain questionnaire scores	None

Table 3. RCTs of Intramuscular Route

6.3 Subcutaneous route

The subcutaneous route is also considered parenteral. Although there have been many case reports and case series using sc route, there was only one RCT. Nicolodi et al used sc

Author/ Year	Design	Patient population and numbers	Design/ Methodology	Outcomes	Withdrawal/ Side Effects
Nicolodi (1995)	DB RCT PLC	N=17; Chronic migraine headaches	Ketamine (80 mcg/kg) subcut vs Placebo (NS) subcut daily x 3 weeks	Significant decrease in frequency and severity of migraine attacks	"Most" patients experienced mild side effects

Table 4. RCTs of Subcutaneous Route

ketamine as bolus and 3 times daily for acute migraine and its prophylaxis, compared to placebo infusion. Ketamine gave marked pain relief in both acute situation and as a prophylactic. However, subcutaneous administration of ketamine is associated with significant side effects. Apart from the central side effects such as hallucinations and delirium, peripheral side effects at the injection site are common. Ketamine is an irritant and requires daily changing of injection site (Hocking, 2003). Itching and painful indurations at the injection site were also observed by Eide et al (1995). Heparin ointment is supposed to help with this troublesome side effect (Klepstad, 1997)

6.4 Intravenous administration of Ketamine

Out of 26 studies of IV ketamine, 1 was experimental. Oga demonstrated that pain reduction with ketamine is correlated with ketamine induced changes in hallucinatory behaviour and excitement as measured by brief psychiatric rating scale (BPRS).

6.4.1 Whiplash disorder

Ketamine was found to be beneficial in both the studies. Both were done by Lemming et al. The exact nature of pathology in whiplash is still unknown. Interventional treatments such cervical facet denervation has been found to be very effective in many patients. The utility of ketamine in this group of patients needs further studies with well defined inclusion criteria.

6.4.2 Pain of vascular origin

Two studies (Mitchell, 2002; Perrson, 1998) examined the effect of ketamine on critical limb ischemia and arteriosclerosis obliterans respectively. Both had positive results. The numbers treated were small (total N=16). Ketamine at a dose of 0.45 mg/kg fared better than Morphine 10 mg in arteriosclerosis patients.

6.4.3 Fibromyalgia

This is perhaps the least understood of neuropathic pain conditions despite being quite prevalent. Although the etiology is unknown the pathology does involve myofascial and connective tissue layers, at least in terms of its involvement. Ketamine was used for fibromyalgia in 2 studies, both showing positive results.

6.4.4 Post amputation/phantom limb pain

This condition is quite resistant to treatment and up to 80% of patients, post amputation, develop phantom pain sometime during their life time. Central sensitization and wind-up phenomenon have been well demonstrated in these conditions. There is reorganisation of cortical representation as well, which is perhaps secondary to the above changes. Ketamine or other NMDA antagonists have a definite role, at least as understood through their pharmacological effects. There have been only 2 studies (Eichenberger, 2008; Nikolajsen, 1996) examining the role of ketamine IV infusions in this condition. Both found positive results with ketamine treatment. Unfortunately the duration of treatment effect has not been clearly followed. Perhaps this condition deserves more studies to establish the role of ketamine in its management.

6.4.5 Nerve injury pain and post herpetic neuralgia

These two are considered together as they both involve destruction of nerve elements, and cause deafferentation pain. Altogether there were 4 studies. Gottrup et al (2006) and Jorum et al (2003), both observed a decrease in spontaneous pain and not much effect on allodynia. However, Leung et al (2001) did not find any reduction in spontaneous pain but found decrease in stroking pain score. Eide et al (1994) found a decrease in over all pain score and found no difference in specific pain modalities.

Felsby (1996) used ketamine in peripheral neuropathic pain and found that to significantly benefit spontaneous pain and also touch evoked allodynia.

6.4.6 CRPS

3 studies examined the role of ketamine in CRPS. All 3 found positive results. Sigtermans et al (2009) and Dahan et al (2011), both had 60 patients and employed increasing doses of ketamine titrated to best effect. The former study showed statistically significant difference in pain scores between placebo and ketamine, which lasted up to 11 weeks. The latter study employed the same protocol; however the study parameters were different. They performed a pharmacokinetic-pharmacodynamic modeling to study the effect. It demonstrated that the treatment effect/analgesia outlasts the actual treatment period (determined by serum levels) by 50 days. Schwartzman et al (2009) performed an outpatient based ketamine treatment study. Although it planned to include 20 patients in each arm, it was stopped after a total of 19 patients, as the interim analysis showed little placebo effect. CRPS patients showed statistically significant decrease in pain scores over many parameters such as pain the most affected area, burning pain, pain when touched gently, and over all pain score. Follow up to 3 months showed that some treatment effects lasted up to 5-8 weeks (pain when touched). Further they state that the dose employed in that study, 25mg/h (100mg/4h) is perhaps less effective considering their newer treatment protocol using 50mg/h showing much better results. Further studies on larger group of well selected patients are needed to establish the role of ketamine in CRPS.

6.4.7 Central pain and spinal cord injury pain

These neuropathic pain conditions are very challenging to treat as they are not localised and involve most parts of the body. The nature of pathology causing pain in these conditions is not clearly known. NMDARs are supposed to play a role. Three studies examined the role of ketamine with spinal cord injury patients. Amr et al (2010) used ketamine with gabapentin and found it to be more effective than gabapentin alone in study of 40 patients. The treatment effect was lost after 3-4 weeks. Kvanstrom et al (2003) used ketamine in a study of 10 patients, with pain below the level of spinal cord injury. Ketamine reduced pain scores >50% in all 5 patients. It is not documented whether there was any longer duration effect. Eide et al (1995) examined 9 patients in a randomised protocol with cross over design. He compared ketamine with alfentanil and a placebo. It was found that both continuous and evoked pains were markedly reduced by the blockade of NMDA receptors by ketamine as well as by the activation of mu-opioid receptors by alfentanil.

Author/ Year	Design	Patient population and numbers	Design/ Methodology	Outcomes	Withdrawal/ Side Effects
Amr (2010)	DB RCT PLC	N=40; Neuropathic pain secondary to spinal cord injury	Ketamine (80 mg IV infusion in 500 ml NS over 5 hours) plus 300 mg gabapentin TID vs placebo (NS) and 300 mg gabapentin TID, daily X 1 week	Each day of infusion and weeks 1 and 2 post-infusion treatment arm had lower VAS scores that control arm; effect lost at post-infusion weeks 3 and 4	3 patients with short acting delusions after infusion, 2 patients with 15% increase in heart rate during infusion
Sitgermans (2009)	SB RCT PLC	N=60; CRPS-1	Ketamine (1.2 mcg/kg/min IV, increased as tolerated until good pain control up to maximum of 7.2 mcg/kg/min IV) vs Placebo (NS) for 100h	Statistically significant decrease in 10 point pain scale scores up to 12 weeks after initiation of study; no difference in functional improvement	63% of patients experienced nausea, 47% vomiting, 93% psychomimetic effects
Lemming (2007)	DB RCT PLC	N=20; >1 year of whiplash associated pain	Ketamine (IV infused over 20 min to a plasma concentration of 100 ng/ml) vs remifentanil (IV infused over 30 min to a plasma concentration of 1 ng/ml) vs combination vs placebo (NS) x 4 sessions	Both remifentanil and ketamine decreased habitual pain by VAS (no significant difference); ketamine had additional effect on electrical stimulation pain threshold	15 ketamine only patients experienced some level of sedation, 2 had strange dreams, 1 hallucinations, 1 nausea
Lemming (2005)	DB RCT PLC	N=33;Whiplash disorder	Ketamine (0.3 mg/kg IV infused over 30 min) vs Lidocaine (5mg/kg IV) vs morphine (0.3mg/kg IV) vs placebo (NS) x 1	No significant difference in response between all treatment arms; all treatment arms did illicit partial response	Not Documented

Author/ Year	Design	Patient population and numbers	Design/ Methodology	Outcomes	Withdrawal/ Side Effects
Persson (1998)	DB RCT	N=8; Lower extremity rest pain from arteriosclerosis obliterans	Ketamine (0.15, 0.3, 0.45 mg/kg IV over 2 hr) vs morphine (10 mg IV) x 4 sessions	Dose dependant improvement in resting pain; complete resolution of pain at highest doses	Dose dependent impairment in cognition and perception
Yamamoto (1997)	SB RCT PLC	N=39; Central post-stroke pain with thalamic or suprathalamic regions	Ketamine (5mg IV q5min x5) vs Morphine (3mg IV q5min x 6) vs Thiamylal (50mcg IV q5min x 5) vs Placebo (5 ml NS q5min x2)	47.8% of patients had significant drop in VAS spontaneous pain scores; no comment on significance as compared to other groups	2 patients had transient hallucinations and anxiety
Felsby (1996)	DB RCT PLC	N=10; Neuropathic pain disorders	Ketamine (0.2 mg/kg loading dose followed by 0.3 mg/kg/min infusion for one hour) vs Magnesium Chloride (0.16mmol/kg) vs placebo (NS)	Significant reduction in pain and of area of allodynia by VAS; no change to detection and pain thresholds to mechanical and thermal stimuli	7 patients reported anxiety or mood symptoms; 2 patients became sedated
Max (1995)	DB RCT PLC	N=8; Chronic post-traumatic pain and global allodynia	Ketamine (0.75 mg/kg/hr IV; doubled at 60 and 90 min if no effect, halved if side effects) vs Alfentanil (mean dose 11mg IV) vs placebo (NS) over 2 hours x 1	Ketamine superior to Alfentanil for peak effect of pain relief and relief of allodynia by VAS pain scores	3 patients sedated, 2 muteness, 2 dissociative reaction; 2 nausea
Backonja (1994)	DB RCT PLC	N=6; Neuropathic pain	Premedicated with benzodiazapine then ketamine (250 mcg/kg IV slow push) vs placebo (NS)	3/6 patients had at least 50% reduction in pain, 4/6 had similar reduction in allodynia and hyperalgesia	5 patients had side effects to ketamine (diplopia, nystagmus, psychomimetic effects, increased BP and HR)

Author/ Year	Design	Patient population and numbers	Design/ Methodology	Outcomes	Withdrawal/ Side Effects
Kvarnstron (2004)	10 PT DB RCT PLC	Spinal Cord Injury with Pain Below Injury Level	Ketamine (0.4 mg/kg IV) vs Lidocaine (2.5 mg/kg IV) vs Placebo (NS)	5 patients in ketamine group had >50% reduction in spontaneous VAS score 2 hours after administration	7 patients reported dizziness, changes in vision or somnolence, 5 reported paresthesias
Kvarnstrom (2003)	DB RCT PLC	N=12; Long lasting, post-traumatic neuropathic pain	Ketamine (0.4 mg/kg IV) vs Lidocaine (2.5 mg/kg) vs placebo (NS) infused over 40 minutes	Significant improvement in VAS scores with ketamine (mean decrease 55%) compared with placebo; no change in scores of thermal or mechanical stimulation	100% of subjects reported somnolescence, 75% light-headed, 83% paresthesias, 67% out of body sensation, 50% changes in vision
Baad-Hansen (2007)	Case-Control PRO DB PLC	N=20; 10 Patients with atypical odontalgia; 10 healthy age/sex matched controls	Ketamine (50 mcg/kg then 70mcg/kg IV) vs Fentanyl (1.43mcg/kg IV) vs Placebo (NS)	No change in VAS pain score of ongoing AO pain	5 patients reported dizziness, 4 "feeling drunk", 2 nausea
Eide (1994)	DB RCT PLC	N=8; Post-herpetic neuralgia	Ketamine (0.15mg/kg IV) vs morphine vs placebo (NS)	Overall "decrease in pain sensation" and decrease in wind-up pain with ketamine. No significant change in warm, cold, heat or tactile sensation. Both morphine and ketamine improve allodynia compared to placebo;	"Side effects" seen in all 8 ketamine patients

Author/ Year	Design	Patient population and numbers	Design/ Methodology	Outcomes	Withdrawal/ Side Effects
Eide (1995)	DB RCT PLC	N=9; Post spinal cord injury dysethesia	Ketamine (60 mcg/kg bolus then 6 mcg/kg/min) vs alfentanil vs placebo (NS)	Continuous and provoked pain were reduced with ketamine and alfentanil; no change in temperature sensation	"Bothersome dizziness" in one patient
Eichenberger et al (2008)	DB PLC RCT	N=20; Phantom limb pain in any extremity from surgical or traumatic amputation	Ketamine (0.4 mg/kg IV over 1 hour with calcitonin 200 IE x 4 total treatments every other day) vs Calcitonin vs placebo vs Ketamine (0.4 mg/kg IV over 1 hour) - later additions to study design	Statistically significant reduction in VAS scores only in ketamine group (not combination). 60% of treatment arm had at least a 50% reduction in symptoms	5 patients became unconscious, experienced visual hallucination, and hearing impairment during ketamine administration; in combination therapy, 4 patients became nauseous, had visual hallucinations; 9 became dizzy and 1 became unconscious
Nikolajsen (1996)	DB RCT PLC	N=11; Post-amputation stump pain	Ketamine (0.1 mg/kg IV bolus then 7 mcg/kg/min over 45 minutes) vs placebo (NS)	Improvement of McGill Pain Questionnaire and VAS pain Scores in treatment arm; decreased incidence of wind-up pain.	6 patients reported sensation of "insobriety"; 3 reported" discomfort"
Sorensen (1997)	DB RCT PLC	N=18; Fibromyalgia	Ketamine (0.3mg/kg IV) vs Morphine (0.3mg/kg IV) vs Lidocaine (5mg/kg IV) vs Placebo (NS) x 1 dose	All treatment arms showed significant reduction of resting pain; no comment on superiority/ inferiority of ketamine to other treatments	Not Documented

Author/ Year	Design	Patient population and numbers	Design/ Methodology	Outcomes	Withdrawal/ Side Effects
Graven-Nielsen (2000)	DB RCT PLC	N=29; Fibromyalgia	Ketamine (0.3 mg/kg) vs placebo (NS) over 30 minutes over 2 separate days [ketamine sensitivity detection]; ketamine vs placebo (NS) over 2 separate days with one week washout [ketamine effect]	Decrease in VAS score during and up to 60 minutes after infusion; decrease in referred pain and temporal pain	Not documented
Leung (2001)	DB RCT PLC	N=12; Post nerve damage pain	ketamine (IV infusion targeted to 50, 100 and 150 ng/ml) vs alfentanil (IV infusion targeted to 25, 50 and 75 ng/ml) vs placebo (diphenhydrinate)	No reduction in spontaneous VAS pain scores; dose dependant decrease in stroking pain score.	1/3 of ketamine subjects reported light-headedness, 3 subjects sedated
Mitchell (2002)	DB PLC RCT	N=35; Alloynia, hyperalgesia and hyperpathia secondary to critical limb ischemia	Ketamine (0.6 mg/m IV) with normal opioid doses vs placebo (NS) over 4 hours	69% of patients reported BPI improvement 5 days post administration	6 patients "felt more emotional than usual"
Gottrup (2006)	DB RCT PLC	N=19; Patients with nerve damage and allodynia	Ketamine (0.1 mg/kg IV bolus, then 0.007 mg/kg/min infusion over 7 minutes) vs lidocaine (5mg/kg IV) vs placebo (NS)	Reduction of spontaneous pain by VAS (mean 30% reduction), reduction of evoked pain to brush and pinprick by electronic VAS. No effect on allodynia.	5 patients reported tiredness, 4 dizziness, 4 paresthesia, 3 dry mouth, 1 patient dropped from study for aggressive behaviour and hallucinations

Author/ Year	Design	Patient population and numbers	Design/ Methodology	Outcomes	Withdrawal/ Side Effects
Schwartzman (2009)	DB RCT PLC	N=19; At least 6 mo of CRPS and failed three previous treatments	0.1 mg Clonidine and 2 mg of Midazolam then Ketamine (0.35 mg/kg infusion over 4 hours; 50% first day 75% second day) vs placebo (NS)	Statistically significant decrease in 'pain in most affected area', 'burning pain' 'overall pain; and 'pain when lightly touched' by pain questionnaire; ketamine group did not return to baseline level of pain	4 people in ketamine group reported nausea, headache, tiredness or dysphoria
Mercadante (2000)	DB RCT PLC	N=10; Cancer patients on morphine therapy and Karnofsky score > 50	Ketamine (0.25 mg/kg) vs ketamine (0.5mg/kg) vs placebo (NS) infused over 30 minutes x 1 each	Significant decrease in pain intensity at both ketamine doses 3 hours after administration on 10 point scale; more pronounced with 0.5mg/kg dose	4 patients experienced hallucinations; 2 patients experienced "out-of-body" sensation
Jorum (2003)	DB RCT PLC	N=12; Post traumatic or herpetic neuralgia	Ketamine (60 mcg/kg over 5 min then 6 mcg/kg/min for 20 min) vs alfentanil (7 mcg/kg bolus then 0.6 mcg/kg/min for 20 min) vs placebo (NS) x 1 session each	Decrease in VAS score to spontaneous pain and thermal hyperalgesia; no change on thermal cold threshold	5 patients experienced fatigue, 6 experienced dizziness, 3 experienced "feeling of unreality", 8 patients reported feeling intoxicated/ relaxed
Oga (2002)	SB RCT PLC	N=10; Chronic neuropathic pain	Placebo (5ml NS IV) x 2 then Ketamine (5 mg IV q5min) x 3	Average decrease on NRS pain scale from 10 to 3.75 with ketamine treatment compared with no significant decrease in saline treatment	Overall significant increase in BRPS scale of negative symptoms (blunted affect, emotional withdrawal and motor retardation)

Table 5. RCTs of IV Route

7. IV ketamine regimen

In experimental ischemic pain, it was observed that there were consistent increases of pain thresholds for plasma concentrations of racemic ketamine more than 160 ng/mL (0.36 μmol/L) (Clements, 1982). However, it has been difficult to establish clear dose-response relationship in clinical situations. The solution used for anesthesia is also utilised to prepare appropriate solutions for parenteral infusions. When given as an infusion, it can be diluted with NS (normal saline 0.9%) in a 1:1 strength (100 mg ketamine in 100 ml NS), and infused via a infusor for accuracy. The administration of ketamine must happen on a fully monitored place with appropriate resuscitation equipments.

As a general statement, parenteral administration, IV or SC, in the range 0.125–0.5 mg/kg/hr, appears to be optimal (level II) but there are occasional reports of larger or smaller doses (Hocking, 2003). The titration is usually dictated by patient's tolerability and clinical usefulness. Frequent (30 mins to 60 mins) assessments of pain and other measures of analgesia must be done. Once a reasonable upper level of infusion is established it may be given for 2-3 days. However there are no clear recommendations, but anecdotal reports suggest that a longer duration of treatment has more chance of effective analgesic actions which are prolonged and sustained. We have observed that the effects in some patients might last up to weeks to months.

If intermittent dosing is planned, it may be wise to consider night-time dosing as it can reduce side effects (level IV), perhaps because of the fact that patients tend to be more relaxed or perhaps because sleep intervenes (Hocking, 2003).

8. Conversion to oral ketamine (initiation and maintenance)

In opioid naïve patients, the recommended starting dosage in ketamine naïve patients is 0.5 mg/kg racemic ketamine or 0.25 mg/kg S-ketamine as a single oral dose. Doses can be increased in steps of 0.5 or 0.25 mg/kg according to the efficacy and adverse effects, respectively (Blonk, 2010).

According to Soto et al (2011), oral ketamine seems to be most effective when used at an initial dose of 0.3 to 0.7 mg/kg per d, titrated up to every 6 hours. This is based on several case reports most of which have used an initial parenteral test. For use of oral ketamine at the end of life, data published suggests a starting dose of 30 to 150 mg/d titrated up to 60 to 375 mg/d as the final dose.

For patients who have been on parenteral ketamine, the dose conversion is not simple. Blonk suggests that the daily dosage can be kept equal and, depending on clinical effect and/or adverse effects, is slowly increased (Blonk 2010). This is mostly in contrast with others who recommend lower conversion rates. Fitzgibbon and others started with a lower dose which was approximately one-third of the parenteral ketamine dose (Fitzgibbon, 2002). Most agree that a conversion factor of 15% is appropriate (Soto, 2011). Convert from intravenous to oral route using at least 15% of the total parenteral dose in up to 4 divided doses (70-kg patient, intravenous ketamine infusion 0.1mg/kg per h ¼ oral ketamine 20 mg every 12 hours). After the intravenous infusion, reduce opiate by 25% daily, once adequate analgesia has been reached. Titrate up by 0.3 mg/kg daily until adequate analgesia is achieved or side effects occur. The number of divided doses necessary for continuous

analgesic effect can range from once daily up to a frequency of 6 times daily (Blonk 2010). The duration of effect after a single dose can range from a few hours to 24 h or more.

9. Challenges and limitations of ketamine use in chronic pain

1. Unavailability: the use of Ketamine for chronic pain is not approved and is off label. There are no commercially available preparations. The injection solution has been used, both for parenteral and oral use. Because of its higher potency, the S (+) racemate of ketamine is approved for use in Europe where it is commercially available as a preservative-free formulation for the treatment of pain by oral, parenteral, and neuroaxial administration (Ben Ari, 2007).
2. Choosing the right patient, in terms of responsiveness.
3. Choosing the right dose, duration and route of administration: There are no fixed strategies. Even if a patient is responsive to parenteral ketamine he may not be as responsive in the longer run (Hocking, 2003). For oral route, the dose conversion is not straight forward and not based solely on decreased bioavailability.
4. There is no consistent dose–response relation. Even if one theoretically takes the serum levels of ketamine to maintain it at only a level required for therapeutic actions and not unwanted side effects, it is not possible to do so as the pharmacodynamics is still not entirely clear.
5. Managing side effects; specific side effects related to subcutaneous and intranasal route have been mentioned above. The most frequently observed adverse effects were effects on the central nervous system, such as sedation, somnolence, dizziness, sensory illusions, hallucinations, nightmares, dissociative feeling and blurred vision. Most consider hallucinations as most disturbing (Blonk, 2010). Patients also mentioned gastrointestinal adverse effects, such as nausea, vomiting, anorexia and abdominal pain. It is also known to cystitis and other urinary complications when used on a longer duration and in addicts.
6. Addiction: It is used as a street drug because of its psychotomimetic properties. It can be obtained as powder by heating the injection fluid, and used through snorting or inhaling (Blonk, 2010).
7. Monitoring for long term effects and change: Long term effects are unknown. There have been only a few case reports which have followed the patients for months to years on ketamine treatment. The knowledge that NMDA receptors are associated with several other functions, it is prudent to assume that long term side effects are possible, and should be kept in mind.

10. Long term use

In neuropathic pain patients on long term treatment, Enarson (1999) used oral ketamine up to 100-240 mg per day in 14% patients who continued to use it for at least an year. Many others have used it on a long term basis (Furuhashi-Yonaha, 2002). Lack of evidence regarding efficacy, and the poor safety profile, do not support routine use of oral ketamine in chronic pain management. There is only one case series (N = 32) which specifically studied the side-effects of ketamine in the long-term treatment (3 months) of neuropathic pain (Cvrcek P, 2008). Literature is not conclusive about the differences in safety profiles of ketamine as racemic mixture and S-ketamine (Kohrs, 1998).

11. Conclusions

Since there are no guidelines or good evidence regarding the introduction and use of ketamine in chronic pain conditions, the above based indications are mostly based on clinical reasoning, mostly with the view that NMDA receptors are involved in the generation or sustenance of the pain condition. Chronic pain conditions are quite heterogeneous in their pathophysiology; and there is still a huge knowledge gap in understanding several of them with regards to their clinical symptoms and variations. We also do not know how ketamine modulates pain pathways or its various actions leading to analgesic mechanisms. We still do not know whether oral route is better for analgesia. It has been suggested that oral ketamine administration causes fewer side effects (Hocking, 2003). Perhaps because of the smaller plasma levels an improved side effect profile of nor-ketamine is observed. With the above considerations, we are left with exploring its analgesic potential for the benefit of patients who have resistant chronic pain condition, despite not so good evidence. Many to most patients do not respond; in fact according to some estimates only up to 30% respond (Hocking, 2003). Considering placebo responses come quite close to it in numbers, it is not certain if it's a true response. Rabben and Oye suggested that there could be changes which may make the patient not susceptible to NMDA antagonists, as the clinical condition worsens. We might be able to improve the numbers of true responders if we get to know whether there are any variables, either disease specific or patient specific, telling us which patients may respond. In that direction there has to be further research and exploration. Until then it is not easy to formulate evidence based guidelines, despite having so many RCTs. From a present stand point use of ketamine is still directed by personal/clinician's preference, availability of resources, patient's acceptability, and above all a patient specific approach in terms of appropriate route, dose and duration.

Part B: Lidocaine

12. Pharmacological basis of Lidocaine use in neuropathic pain

Lidocaine is a local anesthestic compound belonging to the amide group. The chemical structure of lidocaine is 2,6-xylidine coupled to diethylglycine by an amide bond. Lidocaine was first synthesized in 1943 and was used for many years as a local anesthetic agent. It is metabolized chiefly by the liver, and the major pathway of degradation involves conversion to monoethylglycylxylidide, to 2,6-xylidine and finally to 4-hydroxy-2,6-xylidine. These and various other metabolites are excreted in the urine. In addition, a small percentage of unchanged lidocaine, up to 10 percent, is also excreted in the urine.The major metabolic end product is 4-hydroxy-2,6-xylidine since up to 70 percent of an administered dose of lidocaine appears as this compound in the urine. The chemical structure of lidocaine is given as below.

Lidocaine has been well studied and used as a local anesthetic agent. It was realised to have antiarrhythmic potential and has also been widely used for that purpose, as class IB agent. The first clinical use of lidocaine infusion in pain treatments was by 2 anesthesiologists (Bartlett and Hutaserani, 1961), for post-operative pain relief. Since then it has been used for various chronic pain syndromes, mostly of neuropathic nature, such as diabetic neuropathy, postherpetic neuralgia, and deafferentation pain.

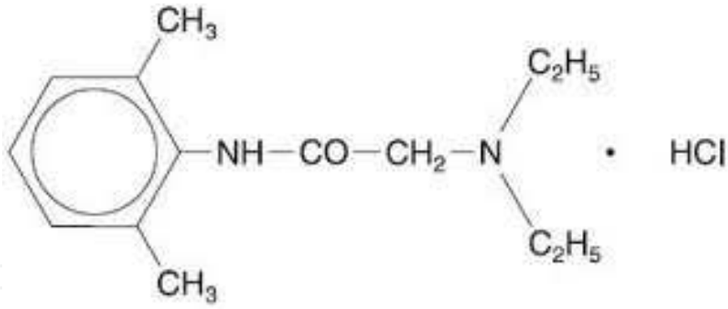


Fig. 3. Lidocaine chemical structure

How exactly systemic lidocaine works in neuropathic pain conditions and why it does work on only a selected number of patients is not yet completely known. However, the following description is based on the presently accepted concept (Mao & Chen, 2000).

1. Lidocaine acts on sodium channel receptors which functions as the basic unit of nerve action potential generation.
2. Neuropathic pain generates from ectopic, abnormal discharges of injured nerves in many neuropathic pain conditions (Nordin 1984).
3. Lidocaine is supposed to have a differential action; suppresses the ectopic discharges but does not interfere in the normal neural discharges.

Neuropathic pain is complex and heterogeneous. Apart from various diverse etiologies, it is also suggested that within diagnostic groups of neuropathic pain patients, there may be subgroups with distinct mechanisms and therefore possibly differing responses to drug treatments (Attal, 2004). Symptoms and signs of neuropathic pain may include spontaneous pain, hyperalgesia, allodynia, pain summation, and radiation of pain beyond the affected area (Dyke, 1984).There are many animal studies indicating that peripheral mechanisms of neuropathic pain may involve spontaneous ectopic discharges from the injured nerves. Experimentally, such injury may involve the form of complete deafferentation, loose nerve ligation, ligation of individual nerve root (Mao & Chen, 2000). When a peripheral nerve is injured the afferent input can be generated spontaneously without activation of peripheral receptors. Such input is referred to as spontaneous ectopic discharges (Devor, 1991). Electrophysiological studies have suggested that ectopic discharges can be initiated along the injured nerve, DRG, and peripheral neuromata (Wall and Gutnick, 1974; Mao & Chen, 2000). Such ectopic discharges may last for a few hours to many days after nerve injury. It is possible to distinguish the origin of ectopic discharges as "neuromata- high frequency, rhythmic, spontaneous discharges" and "DRG neurons- slow, irregular activities in the absence of central or peripheral input". Such aberrant, ectopic action potentials are supposed to be conducted along the nerve via the activation of sodium channels.

13. Sodium channel and neuropathic pain

The voltage-gated ion channels (VGICs) are a super family of glycoprotein molecules that form membrane spanning channels that 'gate' in response to changes in membrane potential. The biophysical properties include: channel opening or 'activation' which is dependent upon membrane potential, rapid 'inactivation' (which is governed not only by membrane potential but also time) and selective ion conductance. The major structural

component of the channel is a protein of approximately 260 kDa that has been named the alpha subunit. The alpha subunit comprises four repeated structural motifs (named I–IV) consisting of six alpha helical transmembrane spanning domains separated by intra and extracellular loops. These four repeated domains fold together to form a central pore and it is their structural components that determine selectivity and conductance of the ion (Scolz A, 2002). The central pore has been determined to be aqueous in nature as it has the capacity to conduct very large numbers of sodium ions through a single channel. By electrophysiology, biochemical purification and cloning, several different sodium channel a-subunits, named as "NaV1.1–1.9" have been identified. Studies have shown a link between several Nav channels and pain, namely 1.3, 1.7, 1.8 and 1.9. Nav 1.3 mediates the compound tetrodotoxin (TTX), a poison from the puffer fish, and has faster activation and inactivation kinetics. It is highly expressed in sensory nerve tracts and spinal cord white matter, dorsal roots and deep laminae of the dorsal and ventral horn. This channel is supposed to be involved in the development of spontaneous ectopic discharges and sustained firing associated with the injured nerves. Nav 1.3 expression is seen to be increased 20-30 fold in neuropathic pain models. Nav 1.7 and Nav 1.9 are observed to be associated with inflammatory or nociceptive pain (Wood et al, 2004). Functionally the sodium channels exist in three possible conformational states and it is the transition between these states that allows selective and temporally regulated ionic conductance. When a stimulus provides a depolarizing change in the cellular membrane potential, the ion channels undergo a physical conformational change and the so-called 'activation gate' is opened. Activation is very rapid, occurring within a fraction of a millisecond and is due to movement of gating charges within the membrane electric field. When the activation gate is opened, the channel pore selectively conducts sodium ions down an electrochemical gradient from the extracellular space to the cell interior. Within a few milliseconds, the sustained depolarization results in termination of the sodium conductance by a process known as inactivation. This occurs very

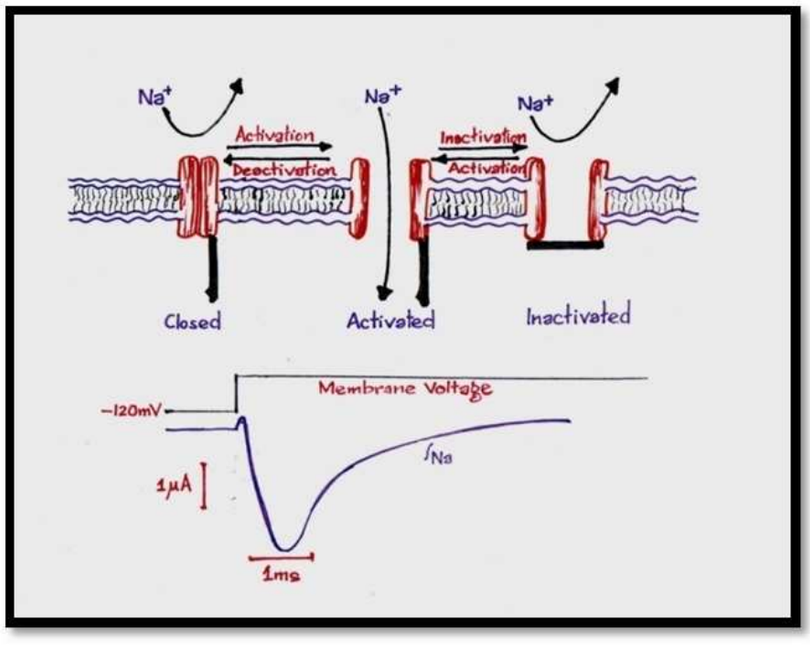


Fig. 4. Sodium channel kinetics as related to membrane potential

rapidly, producing attenuation of the sodium current and for this reason the process is often referred to as 'fast' inactivation. The second type of sodium channel inactivation, termed slow, occurs next. The ability of channels to recover from the fast inactivated state is dependent upon membrane potential and time, and is a mechanism that ensures adequate time for recovery before reopening of the channel.

Local anesthetics, including lidocaine are charged at a P_H below 6. The uncharged form is lipid soluble. It is now well understood and appreciated that LAs diffuse across the lipid membrane before getting to their active site. The receptor lies within the pore. The charged form of the compound acts on the receptor in a use dependent or phasic block. This means increasing impulses leads to accumulation of inhibition. The guarded hypothesis theory also means the binding site is within the pore and the pore has to be open for the LA molecule to bind. The impact of use dependent block would mean that as the firing frequency of the nerve fibre increases, lower concentrations of local anesthetics would be needed to block the action potentials (Scholz A, 2002).

14. Lidocaine in neuropathic pain

Lidocaine acts on these sodium channels to block the impulse transmission and selectively act on ectopic discharges (spontaneously produced without external stimuli). It is not clear, however, whether LAs acts by blocking impulse propagation or whether it prevents the very initiation of abnormal discharge. This should lead to the clinical inference that spontaneous pain symptoms must be more susceptible for lidocaine induced pain relief rather than evoked pain symptoms. In human studies on neuromata, two studies examined spontaneous discharges associated with peripheral nerve fibres following limb amputation. Spontaneous nerve activities recorded were not changed after local infiltration of neuromata with 1% lidocaine indicating a source of generators independent of neuromata. However, local lidocaine does block burst activities induced by tapping neuromata (Mao & Chen, 2000). However this is not the case in many other studies. On further analysis, it is also proposed that allodynia may represent a central phenomenon which is secondarily activated because of the sensitization of sodium channels on Ab fibres. In this regard, a model of neuropathic pain has been proposed in which ongoing nociceptive afferent input from a peripheral locus is thought to maintain the dynamically-altered central process underlying allodynia (Mao & Chen, 2000).

1. **Acting peripherally**, a number of studies have demonstrated that lidocaine suppresses ectopic activity arising out of injured neurons at clinically relevant doses. Another interesting observation is that systemic lidocaine has been shown to have dissociative effects on nerve conduction and ectopic discharges, i.e. suppression of ectopic discharges without blocking nerve conduction (Devor et al, 1992), indicating that sodium channels generating ectopic discharges are likely to be different from those mediating normal action potential conduction along a peripheral nerve.
2. **At the level of spinal cord**, lidocaine is also known to induce a selective depression of C fibre-evoked activity among spinal cord-wide dynamic range neurons and decrease the hyperexcitability of dorsal horn neurons in neuropathic pain models (Woolf, 1985).
3. **Supraspinal** mechanisms of lidocaine actions are demonstrated by its effectiveness in hemispheric lesions and central pain (Attal et al, 2000). Lidocaine can also induce changes in neuropathic pain behaviours (Mao & Chen, 2000). Neuropathic pain

behaviours responding to systemic lidocaine include hyperalgesia and allodynia. Procaine infusions on healthy volunteers have shown selective activation of anterior amygdalocentric limbic system. Lidocaine infusions can give rise to acute psychiatric reactions especially in patients having significant affective component (Leong & Solason, 2000).

15. Lidocaine use in clinical practice

Clinically the response to lidocaine varies in different chronic pain syndromes. In general peripheral neuropathic conditions are more susceptible (Galer et al, 1993; Tremont-Lukats et al, 2005; Attal et al, 2000). Even with the same condition the responsiveness may differ between two individuals with similar history and symptoms. Further even in a single patient only a subset of neuropathic pain symptoms (modality specific) may be responsive. Using quantitative sensory tests, Attal et al have shown that IV lidocaine induced selective and differential analgesic effects in patients with central neuropathic pain (Attal et al, 2000). Ketamine alleviated spontaneous pain and mechanical allodynia/hyperalgesia, but had no effect on thermal allodynia/hyperalgesia. Wallace et al studied the effects of IV lidocaine in CRPS patients and used diphenhydramine as a control. Intravenous lidocaine and diphenhydramine had no significant effect on the cool, warm, or cold pain thresholds. The effect on allodynia was seen only at the maximum plasma range. Lidocaine affected pain in response to cool stimuli more than mechanical pain in subjects with neuropathic pain (Wallace et al, 2000). This is in contrast to the study by Attal et al. Hence it is still not certain which modalities of neuropathic pain are particularly sensitive to lidocaine infusions.

Previously lidocaine was given as IV boluses; presently it is mostly given as an infusion. In many centres it is given using a computer controlled, targeted infusions. The commonly used range is 3-5mg/kg over 30-60 minutes. This may or may not involve an initial bolus. Most studies have shown to achieve a plasma concentration of 2-5 μg/ml (Mao & Chen, 2000). Ferrante et al studied the dose response and plasma concentration in 13 patients. Lidocaine was given at a rate of 8.35 mg/min (500 mg). Ten patients had complete pain relief as measured by VAS scores and scores from the short form of the McGill Pain Questionnaire and the Multidimensional Pain Inventory. After a certain plasma level of 0.62 μg/ml, there were steep changes of pain scores with small changes in lidocaine plasma concentration (Ferrante 1996). Carroll et al employed an appropriate dose to produce plasma levels of 5 μg/ml (Carroll 2007). Indeed up to 15 μg/ml was achieved in some initial studies without serious sequelae (Schinder, 1996; Carroll, 2007). Not much knowledge is available regarding the duration of pain relief after an IV bolus versus continuous infusion of lidocaine. The onset of lidocaine effect on pain relief ranges from 1 to 45 min after lidocaine administration (Mao & Chen, 2000; Carroll, 2007). There is still no consensus about the appropriate duration of observation after either lidocaine bolus or infusion. Apart from the anecdotal reports there are no studies documenting longer lasting pain relief (days-months).

16. Review of literature

The use of lidocaine in clinical practice has been well reviewed earlier by Tremont-Lukats et al (Tremont-Lukats et al, 2005). Their systematic search revealed 13 trials using lidocaine infusion. Most of these studies have fewer subjects and tend to suffer from the fallacy of

Study	Design	Patient Population	Treatment	Outcomes	Adverse/Side Effects
Gottrup (2006)	DB RCT PLC	N=19, Patients with nerve damage and allodynia	Ketamine (0.1 mg/kg IV bolus, then 0.007 mg/kg/min infusion over 7 minutes) vs lidocaine (5mg/kg IV over 30 min) vs placebo (NS)	Both ketamine and lidocaine significantly reduced evoked pain to pinprick stimuli; ketamine was superior to lidocaine in reducing spontaneous pain	7 tiredness, 4 nausea, 3 paresthesia, 3 blurred vision, 3 changed taste, 3 dysarthria, 2 headache, 2 dry mouth
Viola (2006)	DB RCT PLC	N=15, diabetic neuropathy, previous responders to lidocaine	Lidocaine (5mg/ml IV) vs Lidocaine (7.5mg/ml IV) vs placebo (NS), 5ml/kg over 4 hours x 1 each, four week washout	Both doses of lidocaine decreased MPQ resting pain scores compared to placebo; effect lasted up to 28 days post-infusion	1 patient reported light-headedness with 7.5 mg/ml infusion
Finnerup (2005)	DB RCT PLC	N=24, spinal cord injury with neuralgia at or below level of injury	Lidocaine (5mg/kg IV) vs placebo (NS) over 30 min x 1	Significant reduction of spontaneous pain in treatment group; no effect on evoked pain	11 somnolence, 7 dizziness, 7 dysarthria, 7 lightheaded, 3 blurred vision
Attal (2004)	DB RCT PLC	N=22, post-herpatic or post-traumatic neuralgia	Lidocaine (5mg/kg IV) vs placebo (NS) over 30 min x1	Significant reduction of spontaneous pain by VAS, as well as mechanical allodynia; no effect on thermal or hyperalgesia	16 patients experienced side effects including somnolence, lightheadedness, periorbital numbness
Medrik-Goldberg (1999)	DB RCT PLC	N=30, Sciatica	Lidocaine (5mg/kg IV) vs amantadine (2.5mg/kg IV) vs placebo (NS) over 2 hours x 1	Lidocaine significantly reduced spontaneous pain on VAS scale up to 30 min after infusion as compared with amantadine and placebo; also significant decrease in SLR evoked pain compared to other two arms	None reported

Study	Design	Patient Population	Treatment	Outcomes	Adverse/Side Effects
Scrivani (1999)	SB RCT PLC	N=30, Chronic neurogenic facial pain	Lidocaine (100mg IV) vs Phentolamine (30mg IV) vs placebo (NS) infused over 5-10 min x 1	Lidocaine infusion decreased spontaneous pain in 16 patient on 10 point VAS for up to 30 min	None reported
Baranowsky (1999)	DB RCT PLC	N=24, post-herpatic neuralgia	Lidocaine (0.5 mg/kg/h IV) vs Lidocaine (2.5mg/kg/h IV) vs placebo (NS) over 2 hours x 1	No significant difference in spontaneous pain on MCQ and VAS pain scales, allodynia and pressure provoked pain were both significantly improved with either dose of lidocaine	Not reported
Galer (1996)	DB RCT	N=9, Peripheral neuropathic pain	Lidocaine (2mg/kg IV) vs Lidocaine (5 mg/kg IV) over 45 min x 1	Both arms had significant decrease in VAS resting pain scores; higher dose lidocaine produced significantly greater pain relief than lower dose	1 patient dropped out due to severe dizziness and tinnitus
Wallace (1996)	DB RCT PLC	N=11, post-traumatic neuropathic pain	Lidocaine (targeted plasma concentrations of 0.5, 1, 1.5, 2 and 2.5 mcg/ml sustained over 10 min) vs placebo (NS) x 1 each	Significant decrease in spontaneous VAS pain scores starting at 1.5mcg/ml concentration; no change in evoked pain	6 patients reported lightheadedness, 1 patient reported nausea
Bruera (1992)	DB RCT PLC	N=?, Neuropathic cancer pain	Lidocaine (5mg/kg IV) vs Placebo (NS) over 30 min x 1	No change in VAS pain scores between groups	Unknown
Rowbotham (1991)	DB RCT PLC	N=19, Post-herpetic neuralgia	Lidocaine (?IV) vs Morphine (?IV) vs Placebo (NS)	Both morphine and lidocaine reduced pain intensity	Unknown

Study	Design	Patient Population	Treatment	Outcomes	Adverse/Side Effects
Wallace (2000)	DB RCT PLC	N=16, CRPS 1 and 2	Lidocaine (1,2,3mcg/ml plasma IV) vs placebo (diphenhydramine) x 1	Significant decrease in spontaneous VAS pain scores in 3mcg/ml; all concentrations caused significant decrease in response to stroking and cool stimuli in the affected area	Average side effect score (out of 100) for light headedness and sedation was more significant than placebo
Ellemann (1989)	DB RCT PLC	N=10, Cancer patients with cutaneous allodynia	Lidocaine (5mg/kg IV) vs placebo (NS) x 1	2 patients reported subjective pain relief in treatment arm, 3 in placebo arm	Unknown
Sharma (2009)	DB RCT PLC	N=50, cancer patients with opioid refractory pain	Lidocaine (2mg/kg bolus over 20 minutes followed by 2mg/kg infusion over 2 hr) vs placebo (NS)	Significant decrease in 10 point numeric pain scores in treatment group after 2 hours; significantly longer duration of analgesia than placebo	7 patients with periorbital numbness, 8 with tinnitus
Kastrup (1987)	DB RCT PLC	N=?, Diabetic neuropathy of >6 months	Lidocaine (5mg/kg IV) vs placebo (NS)	Significant beneficial effect of lidocaine arm on pain symptoms 1 and 8 days post infusion	Unknown
Tremonts-Lukats (2006)	DB RCT PLC	N=32, Peripheral neuropathic pain	Lidocaine (1,3,5 mg/kg IV) vs placebo (NS) over 6 hours x 1 each	Significant change in percentage pain intensity difference between 5mg/kg arm and placebo up to four hours post-infusion	10 light-headedness, 4 nausea, 6 periorbial numbness, 6 headache, 3 incoordination
Gormsen (2009)	DB RCT PLC	N=13, chronic neuropathic pain	Lidocaine (5mg/kg IV) vs NS1209 (AMPA receptor antagonist 322 mg total) vs placebo (NS) over 4 hours x1	No difference in any treatment arms of spontaneous current pain, both NS1209 and lidocaine exhibited significant effects on resting pain compared to placebo	All lidocaine patients experienced adverse events including headache, dizziness, somnolence, fatigue, cognitive impairment

Study	Design	Patient Population	Treatment	Outcomes	Adverse/Side Effects
Attal (2000)	DB RCT PLC	N=16, post stroke or spinal cord injury pain	Lidocaine (5mg/kg IV) vs placebo (NS) over 30 min x 1	Significant reduction in spontaneous pain on VAS in treatment arm; no significant difference in mechanical or thermal stimulation thresholds	7 patients with light-headedness, 5 somnolence, 3 nausea/ vomiting, 3 dysarthria, 2 malaise
Marchettni (1992)	RCT PLC	N=10, organic nerve injury causing neuropathic pain	Lidocaine (unknown IV) vs Placebo (NS)	Subjective report of mechanical hyperalgesia and spontaneous pain decreased significantly in treatment arm	Unknown
Wu (2002)	DB PLC RCT	N=32, phantom limb or stump pain	Lidocaine (1mg/kg bolus then 4mg/kg IV) vs Morphine (0.05mg/kg bolus then 0.2mg/kg IV) vs placebo (Diphenhydramine 10mg bolus then 40 mg IV) over 40 min x 1	Lidocaine significantly decreased stump pain by VAS pain score, Morphine decreased both stump and phantom limb pain.	No difference in sedation scores between treatment arms
Kvarnstrom (2003)	12 PT DB RCT PLC	Long lasting, post-traumatic neuropathic pain	Ketamine (0.4 mg/kg IV) vs Lidocaine (2.5 mg/kg) vs placebo (NS) infused over 40 minutes	No significant difference in VAS resting score between lidocaine and placebo; no significant difference in any evoked VAS scores	9 somnolence, 5 light-headedness, 4 "out of body sensation", 3 nausea, 2 pruritis, 2 paresthesia
Kvarnstron (2004)	10 PT DB RCT PLC	Spinal Cord Injury with Pain Below Injury Level	Ketamine (0.4 mg/kg IV) vs Lidocaine (2.5 mg/kg IV) vs Placebo (NS) over 40 min	No significant difference in response between lidocaine and placebo in VAS spontaneous pain scores and evoked allodynia	5 somnolence, 1 dizziness, 2 out of body sensation, 1 change in hearing, 2 paresthesias
Lemming (2005)	33 PT DB RCT PLC	Patients with whiplash disorder	Ketamine (0.3 mg/kg infused over 30 min) vs Lidocaine vs morphine vs placebo (NS)	No significant difference in response between all treatment arms; all treatment arms did illicit partial response	Not Documented

Table 6. RCTs of IV Lidocaine use

heterogeneity with respect to disease treated, dose employed and outcomes measured. Despite the deficiencies, they were able to synthesise the data and do a meta-analysis. For the lidocaine trials considered for analysis, the median Jadad score was 3. In the lidocaine trials included for meta-analysis 165 patients received lidocaine and 164 patients were treated with placebo. Lidocaine was superior to placebo (Weighted Mean Difference -10.02 mm; 95% CI: -16.51 to -3.54 mm, $P > 0.002$). The study concluded that systemic administration of sodium channel blocking drugs can relieve pain in selected patients with neuropathic pain and that this effect is superior to placebo. However, the mean effect was small (approximately 11 mm point on a 100 point scale). The commonly used dose range of lidocaine was 5mg/kg over 30-60 mins. The therapeutic benefit was seen more consistently with peripheral pain-trauma, diabetes and central pain. The duration of pain relief observed with lidocaine infusions are mostly short lived (up to 24 hrs). The same conclusion was drawn in the meta-analysis. Some animal experiments and few human trials have demonstrated prolonged effects far beyond the beyond the pharmacological half-time of lidocaine (Mao & Chen, 2000; Chaplan et al, 1995; Sinnott et al, 1999). The mechanism behind this is unknown.

Another important drawback of most studies was the outcome measures considered; allodynia which is an evoked pain measure rather than spontaneous pain was evaluated. This study has also been criticized as the conclusions may not be clinically relevant, however good methodology has been employed. Because of the quality of the studies the calculation of side effects was significantly affected resulting in inappropriate conclusions (Rathmell & Ballantyne, 2005). Our search identified 23 studies and was further cross referenced with the studies in the systematic review. The table gives a complete list of studies including methodology, results and complications. The place of IV lidocaine infusion in treating neuropathic pain patients is difficult to establish. In clinical practice it may be looked as an additional tool for diagnosis and therapeutic management, mostly to be used in resistant or challenging neuropathic pain conditions when other treatments fail. It could also be used to provide relief in “acute on chronic pain” conditions. Some use an algorithm in which an IV therapeutic drug is utilised only after testing the patient with 1-2 placebo treatments. But most employ a lidocaine test (see below), where in the patient is tested for responsiveness with increasing doses of lidocaine.

17. Intravenous lidocaine test

This is a test done to observe for pain relief achieved with IV lidocaine infusion. This is called a test only, because it is the first time that a particular patient having a specific neuropathic pain is being exposed to this treatment. Unlike a known analgesic such as opioid, lidocaine may not be effective or may cause significant dose related side effects even at minimal therapeutic range, which would limit its role in further management of pain condition. Since the effects are immediate and do not take time, one can quickly establish the clinical usefulness in a particular patient.

This is done in an appropriately monitored setting including heart rate, ECG, blood pressure and pulse oximetry. In fact, there are no strict or established protocols. These variations make the usefulness of this test individual specific and generalisations cannot be made. The dose range of systemic lidocaine in the test varies extensively among pain centers, from 100 mg/patient to 5 mg/kg of a patient's body weight (Mao & Chen 2000). The rate of

administration also varies from an IV push to a slow infusion over 30-60 min. Similarly the outcome measures of the lidocaine test also differ among pain centers: (1) what to measure to determine a positive test result, (2) how much change to be expected to indicate a positive result, and (3) when to measure after the lidocaine test to determine the test results. Some centres do blinding as reported earlier, however the blinding itself can be questioned as there are no active placebo controls. It is practically impossible for a patient not to notice CNS side-effects after systemic lidocaine administration. Wallace et al used diphenhydramine as a placebo in their study (Wallace et al, 2000). This is perhaps appropriate considering its side effect as a sedative and causing light headedness, similar to lidocaine.

18. Lidocaine test for the diagnosis of neuropathic pain syndromes

Perhaps the lidocaine test has more value as a diagnostic tool to identify true neuropathic pain patients rather than a prognosticator for further lidocaine treatment. Marchettini performed this test on ten patients with organic nerve injury causing chronic neuropathic pain. The effect of intravenous lidocaine versus saline was tested using psychophysical somatosensory variables. The variables assessed were the subjective magnitude of pain, area of mechanical hyperalgesia and presence and magnitude of thermal heat/cold hyperalgesia. Lidocaine was given in a dose of 1.5mg/kg over 60 secs and placebo-saline in the other group. The patients were then tested at 5, 15 and 35 mins intervals. It was found that spontaneous pain and mechanical hyperalgesia were consistently improved, transiently, by intravenous administration of lidocaine in all 10 patients; areas of hyperalgesia which extended beyond the territory of the nerve also improved transiently (Marchettini et al, 1991). Carroll et al performed a non randomised cohort study on 71 patients with neuropathic pain with an objective to identify a subgroup of patients who are more responsive to IV lidocaine treatment by analysing differing pain qualities of neuropathic pain such as stabbing and heavy. Baseline heavy pain quality, but not stabbing quality predicted subsequent relief of pain intensity in response to lidocaine (Carroll, 2010). The predictive value of the lidocaine test for a positive oral trial of lidocaine congeners remains to be determined (Mao & Chen, 2000).

19. Side effects and limitations

The side effects are usually mild, dose-dependent, and always resolve with a decrease in the infusion rate or discontinuation of the drug. Tremor is a probably the first sign of toxicity. Other neurologic side effects include insomnia or drowsiness, light-headedness, dysarthria and slurred speech, ataxia, depression, agitation, change in sensorium, a change in personality, nystagmus, hallucinations, memory impairment, and emotional lability. Susceptibility increases in older adults or in those with heart failure, settings in which CNS levels are increased due to a reduced volume of distribution, and in patients with significant liver impairment in whom the metabolism of lidocaine is reduced. Seizures occur at a higher plasma level, but can occur at a lower concentration if lidocaine is given to patients receiving oral tocainide or mexiletine, which are congeners of lidocaine. Cardiac side effects are usually infrequent. The primary cardiovascular side effects include sinus slowing, asystole, hypotension, and shock. These problems are most often associated with overdosing or with the overly rapid administration of lidocaine. The elderly and those with significant pre-existing heart disease are at greatest risk.

There are several limitations and caveats with the use of IV lidocaine in chronic pain.

1. As a sodium channel blocker it is expected that it relieves pain which is mostly spontaneous in origin, but most studies show that is effects more on evoked pain.
2. There is known consistent results even when used with a similar condition on a different patient.
3. There seems to be a subgroup of patients who truly respond to IV lidocaine therapy. The challenge is to identify them.
4. Even in patients in whom it works, the duration of analgesia is short lasting (mostly hours).
5. This also needs resources to administer, monitor treatment.
6. Most of the orally available sodium channel blockers do not have the same results when used on patients responsive to lidocaine.

20. Conclusion

Lidocaine therapy is a promising therapy for patients with neuropathic pain. Its routine use cannot be still advised considering the evidence and limitations. However for a resistant and challenging neuropathic pain patient this option should be tried, at least to test the responsiveness and may be utilised on acute on chronic pain situations. Potentially it may also serve to identify true neuropathic pain responders from placebo responders.

21. Acknowledgement

I am thankful to Mr Michael Herman for assisting me in data collection and literature review.

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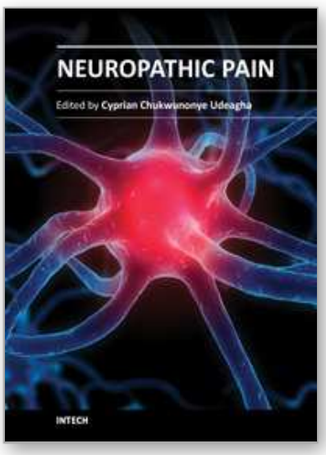

Neuropathic Pain

Edited by Dr. Cyprian Chukwunonye Udeagha

ISBN 978-953-51-0452-0
Hard cover, 140 pages
Publisher InTech
Published online 28, March, 2012
Published in print edition March, 2012

Neuropathic pain is known to be pain with nerve involvement. The intensity of which depends on the severity, pain threshold and the ability of suffers to cope. Neuropathic pain may need mono-therapy or combination of therapies to be resolved. Neuropathic pain may not resolve completely, therefore patient's compliance and understanding is essential in its management. Awareness and patient's education on targets may be of help during therapies for neuropathic pain. All chapters treated introduction, characteristics, diagnosis and randomized interventions to certain management of neuropathic pain. We acknowledge all those involve in the making of this book.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Harsha Shanthanna (2012). Intravenous Therapies in the Management of Neuropathic Pain: A Review on the Use of Ketamine and Lidocaine in Chronic Pain Management, Neuropathic Pain, Dr. Cyprian Chukwunonye Udeagha (Ed.), ISBN: 978-953-51-0452-0, InTech, Available from: http://www.intechopen.com/books/neuropathic-pain/intravenous-therapies-in-the-management-of-neuropathic-pain

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