PHASE 2 TRIAL OF CHEWING LIGNOCAINE SOAKED GAUZE: A NOVEL METHOD TO REDUCE GAG REFLEX.

BY

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Acknowledgement

First and foremost, I must say “Alhamdulillah”. As I remember those moments of feeling lost and not having a clue as to what or how to write and complete this thesis, I cannot help but acknowledge the divine hand I received in so many instances and ways.

I would like to express my utmost gratitude to my supervisors, Dr Wan Muhamad Mokhzani Wan Muhamad Mokhtar, Prof Madya Dr Mohd Faisal Jabar, Dr Mohd Ridzuan Abdul Samad, and Miss Nur Amalina Che Rahim for their kind attention, wisdom and guidance to ensure the success of this study.

I would like to thank my dearest wife, Azma Abu Bakar, my parents and my parents in law for their continuous support emotionally and physically to ensure this mission is accomplished. I hope one day in the future, my children will understand the sacrifices that have to be done for this journey.

ABSTRAK

Latar Belakang dan Objektif: Refleks gag telah dikenal pasti sebagai faktor yang mengurangkan toleransi pesakit terhadap prosedur yang melibatkan rangsangan kawasan pharyngeal, oleh itu kaedah yang lebih optimum untuk mengurangkan refleks gag perlu dikaji. Kajian ini bertujuan untuk mengkaji keberkesanan teknik mengunyah kain kasa yang direndam lignocaine untuk mengurangkan kadar refleks selain mengenal pasti dos optimum lignocaine.

Reka bentuk dan kaedah kajian: Ini adalah kajian fasa dua, tiga kumpulan, kawalan rawak beserta "double-blinded". Peserta dibahagikan kepada tiga kumpulan, kumpulan A mendapat kain kasa yang direndam dengan 160 mg lignocaine, kumpulan B menerima kain kasa direndam dengan 320 mg lignocaine dan kumpulan C menerima kain kasa direndam dengan air. Pembahagian peserta ditentukan oleh kaedah rawakan blok yang dijana oleh komputer. Maklumat asas, "vital signs", skor refleks gag dan lokasi refleks gag, direkodkan. Peserta dinilai oleh dua individu yang ditetapkan pada akhir 3 minit dengan skor refleks gag. "vital signs" dipantau dan kesan buruk direkodkan. Keputusan dianalisis dengan menggunakan ANOVA dan ujian post hoc sehala.

Hasilnya: 30 peserta telah direkrut dan dibahagikan kepada tiga kumpulan dengan rasio 1: 1: 1 mengikut blok rawak. Maklumat asas, "vital signs" dan skor refleks gag oleh kumpulan telah dibandingkan dan homogen kecuali usia. Pengurangan refleks Gag dilihat paling tinggi dalam kumpulan B (M = 2.3, SD = 0.67, p = 0.000, t = 10.776, 95% CI = 1.817, 2.813) , p = 0.343, t = 1.000, 95% CI = -0.126, 0.326). Terdapat perbezaan yang signifikan secara statistik dalam skor kemerosotan gag refleks antara kumpulan (p = 0.00, F = 27.271). Tiada perbezaan yang dilihat dalam tekanan sistolik, tekanan diastolik, kadar nadi, dan ketepuan oksigen antara pretest dan posttest untuk semua kumpulan. Perbezaan yang signifikan dalam skor refleks gag dilihat antara kumpulan A dan kumpulan C (p = 0.000, 95% CI = -2.90, 1.30) dan antara kumpulan B dan kumpulan C (p = 0.000, 95% CI = -2.70, -1.10) . Tidak terdapat perbezaan yang signifikan antara kumpulan A dan kumpulan B (p = 1.00, 95% CI = -1.00, 0.60).

Kesimpulan: Mengunyah kasa lignocaine yang direndam adalah satu kaedah yang boleh dilakukan untuk mengurangkan refleks gag dan kekuatan 320 mg lignocaine tidak mempunyai kesan lebih daripada kekuatan 160 mg lignocaine dalam pengurangan refleks gag.

ABSTRACT

Background and objective : The gag reflex has been identified as a factor that reduces patient tolerance towards the procedure that involves stimulation of pharyngeal area, hence a better method to reduce the gag reflex is investigated. This study aimed to look at the feasibility of chewing lignocaine soaked gauze to reduce gag reflex besides identifying the optimum dosage of lignocaine.

Study design and method : This is phase two, 3 arms, double-blinded, randomized control trial. Participants were divided into three groups, group A received gauze soaked with 160 mg lignocaine, group B received gauze soaked with 320 mg lignocaine and group C received gauze soaked with water. Allocation of participants was determined by computer-generated block randomization. Baseline information, vital signs, gag reflex score and gag reflex location, were recorded. Participants were assessed by two designated individuals at the end of 3 minutes, and gag reflex score is given. Vital signs were monitored and adverse effect recorded. Results were analysed using one-way ANOVA and post hoc test.

Result : 30 participants were recruited and divided into three groups with 1:1:1 ratio according to block randomization. Baseline information, vital signs and gag reflex score between groups were compared and were homogenous except age. Gag reflex reduction was seen highest in group B (M = 2.3, SD = 0.67, p = 0.000, t = 10.776, 95% CI = 1.817, 2.813) and no statistically significant changes in the control group (M = 0.1, SD 0.316, p = 0.343, t= 1.000, 95% CI = -0.126, 0.326). There was statistically significant difference in gag reflex severity score between the groups (p = 0.00, F = 27.271). No difference were seen in systolic pressure, diastolic pressure, pulse rate, and oxygen saturation between pretest and posttest for all group. Significant difference in gag reflex score were seen between group A and group C (p = 0.000, 95% CI = -2.90, 1.30) and between group B and group C (p = 0.000, 95% CI = -2.70, -1.10). There was no significant difference between group A and group B (p = 1.00, 95% CI = -1.00, 0.60).

Conclusion : Chewing lignocaine soaked gauze is a feasible method to reduce gag reflex and 320 mg lignocaine is not superior to 160 mg of lignocaine in gag reflex reduction.

1.1 INTRODUCTION

Oesophagogastroduodenoscopy (OGDS) is an essential diagnostic and therapeutic procedure in clinical gastroenterology.(Clarke *et al.*, 2001; Van Kouwen *et al.*, 2003) OGDS is a procedure where a flexible fibre optic wire is introduced either through the mouth or nasal cavity, passes through pharynx, oesophagus, stomach and until the second part of the duodenum. It provides both visual and tissue diagnosis, together with a therapeutic option for the patient. Low risk of complications are attributable to it, such as bleeding, perforation, infection and medication reaction.(Ross and Newton, 2004; Seinelä *et al.*, 2003; Van Kouwen *et al.*, 2003) This procedure has evolved in a parallel fashion with the advancements in medical technology and clinical research. As a result, improvements are seen in its performance, safety, cost efficacy and tolerability. Many studies were conducted to identify factors that may reduce patient anxiety and increase the tolerability of the procedure. Advanced age and the presence of cardiopulmonary diseases can at times be relative contraindications to the procedure, especially with the use of high doses of intravenous sedatives and analgesics.(Campo *et al.*, 1999; E. Mulcahy, 2001; Van Kouwen *et al.*, 2003) Although unsedated OGDS is a feasible option and is practised in some parts of the world, the majority of patients require the use of sedative medications.(Bell, 2002; Campo *et al.*, 1999; E. Mulcahy, 2001; Mulcahy *et al.*, 2001) A high level of anxiety before the procedure remains one of the major factors affecting the choice of sedation during such procedures.(Campo *et al.*, 1999; Dean *et al.*, 1996; Melchart *et al.*, 2002; Stermer *et al.*, 1998; Trevisani *et al.*, 2002)

Intravenous benzodiazepines and opiates have been used to provide anxiolytic, amnestic and analgesic effect since early 1980 and exclusively used in OGDS procedure.(Keeffe and O'Connor, 1990; Tu *et al.*, 2006; Waring *et al.*, 2003) These agents have potential side effect especially if used among elderly and high-risk cardiopulmonary patient.(Brussaard and Vandewoude, 1988; Chillemi *et al.*, 1996; Külling *et al.*, 2003; Ristikankare *et al.*, 2000; Tang *et al.*, 2001; Van Dam and Brugge, 1999) It can lead to respiratory depression, hypoxia,

hypotension, and paradoxical agitation. This will add on to avoidable morbidity to these populations.

Moreover, a significant portion of the cost and complications of such procedures is often attributed to conscious intravenous sedation.(Dean *et al.*, 1996) Indirectly, those who underwent such procedure will have the additional risk of unexpected hospitalization at times, loss of ability to carry out usual activities and work-related absenteeism. Therefore, researches are directed in finding the best form of anaesthesia and sedation in OGDS procedure while not compromising patient's satisfaction, safety, and endoscopist comfort. A few studies have explored the possibility of using a different form of a topical anaesthetic such as lignocaine with mixed results.(Clarke *et al.*, 2002; Davis *et al.*, 1999; Dhir *et al.*, 1997; Ljubičić *et al.*, 2003; Mulcahy *et al.*, 1996; Stolz *et al.*, 2005)Different modalities of topical anaesthesia are currently available such as lignocaine gel, spray or inhaler with or without side effects. The spray form of topical lignocaine has been used widely with or without intravenous sedatives and analgesia in OGDS.(Leitch *et al.*, 1993; Pereira *et al.*, 1994; Soma *et al.*, 2001)

Chewing lignocaine soaked gauze prior to OGDS is a novel method to provide pharyngeal anaesthesia which subsequently reduced to some extend ameliorates sensory stimulus of the glossopharyngeal nerve, which is responsible for the gag reflex. In our study, we plan to determine the feasibility of this method as opposed to conventional lignocaine spray method in providing a better OGDS experience to the patient without compromising the success of the endoscopic procedure.

1.1 LITERATURE REVIEW

Oesophagogastroduodenoscopy (OGDS) is an essential and a standard procedure to assess various gastrointestinal symptoms including reflux, dysphagia, odynphagia, haemorrhage and epigastric pain. Over the years, this procedure has gained acceptance among patients owing to its advancement in preprocedural and periprocedural preparation and technique. When it was first introduced, this procedure was done using a rigid fiberoptic scope, and it required general anaesthesia or conscious sedation to ensure patient tolerance and endoscopist comfort to complete the procedure. With the invention of flexible, smaller diameter and direct camera vision of this instrument, its tolerability has increased. Nowadays, this procedure is possible to be done with topical pharyngeal anaesthesia alone without sedation. In Europe, a third of their total OGDS was done without sedation, and a few studies have shown good tolerability of patient and adequate endoscopist completion of the procedure. However, there is still a stigma that lingers around patient and endoscopist regarding the need for sedation in order to achieve maximum patient comfort and technical adequacy for the endoscopist. Discomfort during OGDS procedure is partly attributed by gag reflex, which is stimulated by the introduction of the instrument into the oral cavity. Conscious sedation, by definition, is the administration of carbamazepine group drug to cause sedation effect, but arousal is possible with voice or light tactile stimulus. It also causes drowsiness, reduces anxiety and amnesia, and it is not without adverse effect, especially to the elderly and high-risk population. It has been reported to cause a cardiopulmonary compromise in high-risk population apart from requiring a more extended hospital stay, increases cost and to require a caretaker to accompany patient post procedure. This study is aimed to evaluate the effect of chewing lignocaine soaked gauze in reducing gag reflex among unsedated patient undergoing OGDS procedure.

Gag reflex has been identified as a factor of discomfort during OGDS procedure, not only to the patient but to the endoscopist. The gag reflex is a complex body mechanism to protect pharynx and larynx from aspirating harmful or foreign particles. It consists of the afferent and efferent arch. The gag reflex is elicited by touch sensation at either base of tongue,

uvula, palate, posterior pharyngeal wall, palatopharyngeal or palatoglossal fold.(Bassi *et al.*, 2004) Upon stimulation, the afferent arch received an electrical impulse from glossopharyngeal nerve fibre and relayed it to nucleus solitaris in the midbrain.(Miller, 2002) The efferent arch is supplied by nucleus ambiguous through the vagus nerve and caused elevation of soft palate and constriction of bilateral pharyngeal constrictor muscles.(Miller, 2002) The nuclei are at close proximity to the vomiting and salivating centre, and this explains the experience of retching and excessive salivation when gag reflex is stimulated.(Bassi *et al.*, 2004) Both superficial and deep sensory receptors are involved in gag reflex, thus making pharyngeal plexus block superior to topical lignocaine spray in suppressing the gag reflex.(Valley *et al.*, 1992) Pharyngeal plexus block is achieved by injecting lignocaine to pharyngeal plexus, which situated adjacent to the carotid artery and jugular vein hence increasing the risk of vascular injury besides having low patient tolerance. It is postulated that if lignocaine to be applied to the trigger areas in the pharynx, then gag reflex will be markedly attenuated or even ablated during the procedure hence increasing patient tolerance.

This hypothesis has made topical lignocaine application one of the best yet simple option to achieve pharyngeal anaesthesia. However, the value of topical pharyngeal anaesthesia in OGDS is still controversial.(Pereira *et al.*, 1994; Soma *et al.*, 2001) Two randomized studies concluded that topical lidocaine spray does not facilitate OGDS and that the use of meperidine and midazolam intravenously were the basis for a successful endoscopy.(Davis *et al.*, 1999; Dhir *et al.*, 1997) However, in a randomized, double-blind placebo-controlled study by Campo et al.,the use of topical anaesthesia with benzocaine in unsedated patients undergoing OGDS facilitated both intubation and examination and made the procedures better tolerated and more comfortable to perform.(Campo *et al.*, 1995) In a similar study by Leitch et al.,-the use of topical lignocaine produced better acceptability and tolerability for the procedure performed.(Leitch *et al.*, 1993) In another randomized, double-blind placebo-controlled study by Soma et al., topical pharyngeal anaesthesia (5 mL of 2% lignocaine gel) significantly reduced the risk of discomfort in gastroscopy by 44% in all patients and by 80% in patients younger than 40 years old and

those undergoing gastroscopy for the first time.(Soma *et al.*, 2001) However, in the same study, a high trait-anxiety score correlated with a high chance of discomfort to intubation during gastroscopy. Some studies examined the effect of the lignocaine dose applied to the pharynx during the procedure. Mulcahy et al. concluded that 100 mg of topical lignocaine correlated with less discomfort during intubation and diagnostic examination versus the use of 30 mg of topical lidocaine.(Mulcahy *et al.*, 1996)

Moore et al. explored the effect of chewing lignocaine soaked gauze on intubation condition during awake video laryngoscopy. He randomized 24 patients to either receive 20ml of 2% lignocaine soaked gauze or saline as an adjunct to lignocaine spray prior to video laryngoscope. In this study, he failed to show any statistically significant difference in the intervention. He identified several factors that might contribute to the reduction of efficacy such as the viscosity of the solution, concentration, and dosage of the solution and the effect of lignocaine spray given in both arms which might mask the effect of lignocaine spray.

Lignocaine is a medication used to numb tissue in a specific area and to treat ventricular tachycardia. It was first synthesized by a Swedish chemist, Nils Lofgren in 1943. It was commercialized in 1948 and has been listed in the lists of essential medicine by WHO. It is available worldwide, and its generic form is available at an affordable price.

Lignocaine alters signal conduction in the neuron by blocking the fast voltage-gated sodium channel in the cell membrane and prevents the propagation of the electrical signal. Sufficient blockage will prevent the postsynaptic neuron from depolarizing and preventing transmission of an action potential. This creates an anaesthetic effect by not only preventing pain signal propagation but eliminates it before it begins. The precise and targeted application allows for a high degree of selectivity in the blockage of the sensory neuron. The same principles apply to its action in preventing heart arrhythmias.

Lignocaine is mostly metabolized in the liver, mainly by CYP3A4 to the pharmacologically active metabolites, monoethylglycinexylidide (MEGX) and then

subsequently to the inactive glycine xylide. MEGX has a longer half-life than lignocaine but also has less potent sodium channel blocker. The volume distribution is 1.1-2.1 litre/kg, 60-80% circulates bound to the protein alpha1 acid glycoprotein. Oral bioavailability is 35%, and topical bioavailability is 3%. Its half-life elimination is biphasic and takes around 90-120 minutes in the average patient, longer in a patient with hepatic impairment (343 minutes) or congestive heart failure. It is excreted in the urine as 90% metabolites and 10% unchanged.

In our study, we are conducting a phase 2 trial to prove the feasibility of this hypothesis. We are using Xylocaine 4% (Appendix 2) with lignocaine concentration of 40mg/ml in the intervention group. 2 ml of this solution will be used, amount to 8 mg of lignocaine each, to a total of 160 mg. This dosage is below the recommended toxic level, which is 5mg/kg. Two pieces of 5cm x 5cm gauzes will be soaked in this solution for 30 seconds and placed behind both patient's molar. The patient will be asked to chew the gauze for 3 minutes without swallowing the excess fluid. 3 minutes is the minimum period for local absorption of lignocaine. At the end of 3 minutes, the patient will be asked to spit off the excess fluid together with the gauzes. While in the control group, the patient will receive two pieces of 5cm x 5cm gauzes soaked with saline solution and chew for 3 minutes, spitting the gauze and excess fluid at the end of the designated period. We will also have another group who received two pieces of gauzes, soaked with 4 ml of xylocaine 4%, amount up to 16 mg each and chewed for 3 minutes, spitting the gauzes together with the excess fluid at the end of the period. We plan to assess the best dosage of lignocaine to achieve the optimum analgesia hence better gag reflex reduction.

1.2 RATIONALE OF STUDY

Among the main concern with OGDS procedure is patient comfort and endoscopist capability to achieve a technically adequate view to providing the best diagnostic and therapeutic option. These factors are interrelated and strongly achievable with the patient's comfort. The gag reflex is one of the main concern regarding this procedure. Due to stimulation of pharynx, which subsequently activates the gag reflex, oesophageal intubation will be impaired. Nevertheless, the effort to maintain gastric wall distention by air insufflation is also affected by retching, which initiated by gag reflex. Previously, conscious sedation technique was used successfully to reduce gag reflex and increased patient compliant to the procedure, however, with the increased frequency of OGDS being done and inadequate training with anaesthetic sedation, not to mention increasing cost burden, this will put the patient at higher risk and contribute to unnecessary morbidity. Hence, a new modality such as topical anaesthesia has been invented to nullify the pharyngeal sensation. Oral lignocaine spray has gained popularity in OGDS procedure. However, its efficacy in reducing gag reflex is controversial, as demonstrated by Luke T Evan et al. in his study. Six out of eight RCT favoured pharyngeal anaesthesia instead of placebo however, only three demonstrated statistical significance. The various method has been explored to administer topical lignocaine to reduce pharyngeal sensation as listed in the table below.

Investigator	**Modality**	**N**	**Assessment tool**	**Endoscopist's perspective**		**Patient's perspective**	
				Intervention	Control	Intervention	Control
Assaad M Soweid et al	Posterior lingual lidocaine	80	Gag reflex assessment by endoscopist and ease of the procedure.	1 (1,5)	4 (1,5)	2 (1,4)	4 (2,5)

			Patient assessment base on scale 1 to 5				
Chakid Ayoub et al	Lidocaine lollipop	50	Gag reflex assessment by endoscopist base on 1 to 5 scale. Patient assessment	2.8 (±1.3)	4 (±0.8)	2.5 (±1.3)	3.2(±1.3)

This study is aimed to look into the effectiveness of using lignocaine soaked gauze to achieve pharyngeal desensitization thus reducing gag reflex during the procedure. It will lead to a better overall experience during OGDS procedure, both to patient and endoscopist without increasing risk and financial burden.

2.1 Document submitted for ethical approval

STUDY PROTOCOL

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Protocol number and date : USM/JEPeM/18030183

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Department of Surgery, HUSM

Study site :

Hospital University Sains Malaysia (HUSM)

Introduction

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Problem Statement and Study rationale

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This hypothesis has made topical lignocaine application one of the best yet simple option to achieve pharyngeal anaesthesia. However, the value of topical pharyngeal anaesthesia in OGDS is still controversial.(Pereira *et al.*, 1994; Soma *et al.*, 2001) Two randomized studies concluded that topical lidocaine spray does not facilitate OGDS and that the use of meperidine and midazolam intravenously were the basis for a successful endoscopy.(Davis *et al.*, 1999; Dhir *et al.*, 1997) However, in a randomized, double-blind placebo-controlled study by Campo et al.,the use of topical anaesthesia with benzocaine in unsedated patients undergoing OGDS facilitated both intubation and examination and made the procedures better tolerated and more comfortable to perform.(Campo *et al.*, 1995) In a similar study by Leitch et al.,-the use of topical lignocaine produced better acceptability and tolerability for the procedure performed.(Leitch *et al.*, 1993) In another randomized, double-blind placebo-controlled study by Soma et al., topical pharyngeal anaesthesia (5 mL of 2% lignocaine gel) significantly reduced the risk of discomfort in gastroscopy by 44% in all patients and by 80% in patients younger than 40 years old and

those undergoing gastroscopy for the first time.(Soma *et al.*, 2001) However, in the same study, a high trait-anxiety score correlated with a high chance of discomfort to intubation during gastroscopy. Some studies examined the effect of the lignocaine dose applied to the pharynx during the procedure. Mulcahy et al. concluded that 100 mg of topical lignocaine correlated with less discomfort during intubation and diagnostic examination versus the use of 30 mg of topical lidocaine.(Mulcahy *et al.*, 1996)

Moore et al. explored the effect of chewing lignocaine soaked gauze on intubation condition during awake video laryngoscopy. He randomized 24 patients to either receive 20ml of 2% lignocaine soaked gauze or saline as an adjunct to lignocaine spray prior to video laryngoscope. In this study, he failed to show any statistically significant difference in the intervention. He identified several factors that might contribute to the reduction of efficacy such as the viscosity of the solution, concentration, and dosage of the solution and the effect of lignocaine spray given in both arms which might mask the effect of lignocaine spray.

Lignocaine is a medication used to numb tissue in a specific area and to treat ventricular tachycardia. It was first synthesized by a Swedish chemist, Nils Lofgren in 1943. It was commercialized in 1948 and has been listed in the lists of essential medicine by WHO. It is available worldwide, and its generic form is available at an affordable price.

Lignocaine alters signal conduction in the neuron by blocking the fast voltage-gated sodium channel in the cell membrane and prevents the propagation of the electrical signal. Sufficient blockage will prevent the postsynaptic neuron from depolarizing and preventing transmission of an action potential. This creates an anaesthetic effect by not only preventing pain signal propagation but eliminates it before it begins. The precise and targeted application allows for a high degree of selectivity in the blockage of the sensory neuron. The same principles apply to its action in preventing heart arrhythmias.

Lignocaine is mostly metabolized in the liver, mainly by CYP3A4 to the pharmacologically active metabolites, monoethylglycinexylidide (MEGX) and then

subsequently to the inactive glycine xylide. MEGX has a longer half-life than lignocaine but also has less potent sodium channel blocker. The volume distribution is 1.1-2.1 litre/kg, 60-80% circulates bound to the protein alpha1 acid glycoprotein. Oral bioavailability is 35%, and topical bioavailability is 3%. Its half-life elimination is biphasic and takes around 90-120 minutes in the average patient, longer in a patient with hepatic impairment (343 minutes) or congestive heart failure. It is excreted in the urine as 90% metabolites and 10% unchanged.

In our study, we are conducting a phase 2 trial to prove the feasibility of this hypothesis. We are using Xylocaine 4% (Appendix 2) with lignocaine concentration of 40mg/ml in the intervention group. 2 ml of this solution will be used, amount to 8 mg of lignocaine each, to a total of 160 mg. This dosage is below the recommended toxic level, which is 5mg/kg. Two pieces of 5cm x 5cm gauzes will be soaked in this solution for 30 seconds and placed behind both patient's molar. The patient will be asked to chew the gauze for 3 minutes without swallowing the excess fluid. 3 minutes is the minimum period for local absorption of lignocaine. At the end of 3 minutes, the patient will be asked to spit off the excess fluid together with the gauzes. While in the control group, the patient will receive two pieces of 5cm x 5cm gauzes soaked with saline solution and chew for 3 minutes, spitting the gauze and excess fluid at the end of the designated period. We will also have another group who received two pieces of gauzes, soaked with 4 ml of xylocaine 4%, amount up to 16 mg each and chewed for 3 minutes, spitting the gauzes together with the excess fluid at the end of the period. We plan to assess the best dosage of lignocaine to achieve the optimum analgesia hence better gag reflex reduction.

Product Information

NAME OF DRUG

Xylocaine 4% Topical Solution contains lignocaine hydrochloride as the active ingredient.

The CAS number for lignocaine is 137-58-6.

Molecular Formula: $C_{14}H_{22}N_{2O}$

Molecular Weight: 234.3

The chemical name for lignocaine is 2-diethylamino-2',6'-dimethylacetanilide.

DESCRIPTION

Xylocaine 4% Topical Solution is a colourless, aqueous, topical anaesthetic solution for use on mucous membranes.

Each mL of solution contains lignocaine hydrochloride 42.8 mg (equivalent to lignocaine hydrochloride anhydrous 40 mg), methyl hydroxybenzoate, sodium hydroxide or hydrochloric acid (for pH adjustment) and water for injections.

PHARMACOLOGY

Pharmacodynamics

Lignocaine, the active ingredient of Xylocaine Topical Solution, stabilises the neuronal membrane and prevents the initiation and conduction of nerve impulses, thereby effecting local anaesthetic action.

Pharmacokinetics

Xylocaine Topical Solution acts intact on mucous membranes to provide prompt local anaesthetic action. Anaesthesia usually occurs within 1-5 minutes, and the XYLOCAINE 4% TOPICAL SOLUTION Product Information PAIN.000-129-050.3.0 2(8) effect lasts for approximately 15-30 minutes. It is ineffective when applied to intact skin.

Lignocaine may be absorbed following topical administration to mucous membranes, its rate of absorption and amount of dose absorbed depending upon concentration and total dose administered, the specific site of application and duration of exposure.

In general, the rate of absorption occurs most rapidly after intratracheal administration. Lignocaine is well absorbed from the gastrointestinal tract, but little intact drug appears in the circulation because of biotransformation in the liver. Lignocaine is metabolised rapidly by the liver, and metabolites and unchanged drug are excreted by the kidney.

Excessive blood levels may cause changes in cardiac output, total peripheral resistance and mean arterial pressure. These changes may be attributable to a direct depressant effect of the anaesthetic agent on various components of the cardiovascular system.

Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage and conjugation. The pharmacological/toxicological actions of the metabolites are similar to but not less potent than, those of lignocaine. Approximately 90% of lignocaine is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline.

The plasma binding of lignocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 μg of free base/mL, 60 to 80% of lignocaine is protein bound. Binding is also dependent on the plasma concentrations of the alpha-1-acid glycoprotein.

Lignocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Studies of lignocaine metabolism following iv bolus injection have shown that the elimination half-life is usually 1.5 to 2 hours. The half-life may be prolonged 2-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lignocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lignocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 μg free base/mL. In the rhesus monkey, arterial blood levels of 18 to 21 μg/mL have been shown to be the threshold for convulsive activity.

INDICATIONS

Anaesthesia of mucous membranes of the oropharyngeal, tracheal and bronchial areas, e.g. in bronchoscopy, bronchography, laryngoscopy, oesophagoscopy, and endotracheal intubation.

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CONTRAINDICATIONS

Known history of hypersensitivity to lignocaine or other local anaesthetics of the amide or ester type or to other components of the solution.

Hypersensitivity to methyl and/or propyl hydroxybenzoate (paraben) or to their metabolite para-aminobenzoic acid (PABA).

Xylocaine 4% Topical Solution is intended for topical use only and must not be used for injection.

PRECAUTIONS

Patients should not exceed the recommended dose or use Xylocaine 4% Topical Solution for prolonged periods except on the advice of their physician. The lowest dose that results in effective anaesthesia should be used to avoid high plasma levels and serious adverse effects. Tolerance to elevated blood levels varies with the status of the patient.

Dosage reduction

Debilitated, elderly and/or acutely ill patients and children should be given reduced doses commensurate with their age and physical status.

Excessive absorption

Absorption from wound surfaces and mucous membranes is relatively high, especially in the bronchial tree. This should be taken into consideration when the solution is used in children for the treatment of large areas. Because of the possibility of significant systemic absorption, Xylocaine Topical Solution should be used with caution in patients with traumatised mucosa and/or sepsis in the region of the proposed application.

If the dose or site of administration is likely to result in high blood levels, lignocaine, in common with other local anaesthetics, should be used with caution in patients with epilepsy, impaired cardiac conduction, bradycardia, impaired hepatic function, in severe shock, patients in poor general health, patients with severe renal dysfunction and the elderly.

Eating and drinking

The use of topical anaesthetic agents in the oral cavity may interfere with swallowing and thus enhance the danger of aspiration of food or drink. For this reason, food or drink should not be ingested within 60 minutes of using local anaesthetics in the mouth or throat area. Numbness of the tongue or buccal mucosa may increase the danger of biting or heat trauma. Food, chewing gum or hot drinks should not be taken while the mouth or throat area is anaesthetised.

Contact with the eyes

Xylocaine Topical Solution is not intended for ophthalmological use. If Xylocaine Topical Solution inadvertently comes into contact with the eyes, rinse immediately with copious amounts of water for at least 15 minutes and seek medical advice. XYLOCAINE 4% TOPICAL SOLUTION Product Information PAIN.000-129-050.3.0 4(8)

Paralysed patients

In paralysed patients under general anaesthesia, higher blood concentrations may occur than in spontaneously breathing patients. Unparalysed patients are more likely to swallow a large proportion of the dos, which then undergoes first-pass hepatic metabolism following absorption from the gut.

Malignant hyperthermia

Many drugs used during the conduct of anaesthesia are considered potential triggering agents for familial malignant hyperthermia. It has been shown that the use of amide local anaesthetics in malignant hypothermia patients is generally safe, but cases of malignant hyperthermia have occasionally been documented after use.

Gargling

The use of Xylocaine Topical Solution as a gargle is not indicated. The use of concentrated Xylocaine Topical Solution 4% for gargling increases the risk of systemic toxicity due to overdosing and rapid uptake over the mucosa and/or ingestion.

Porphyric patients

Xylocaine 4% Topical Solution is probably porphyrinogenic and should only be used on patients with acute porphyria where there are strong or urgent indications. Appropriate precautions should be taken for all porphyric patients.

Carcinogenic and Mutagenic Potential

Genotoxicity tests with lignocaine are inconclusive. In genotoxicity studies, a metabolite of lignocaine, 2,6-xylidine, showed evidence of activity in some tests but not in other tests. This metabolite has been shown to have carcinogenic potential (nasal and subcutaneous tumours) in preclinical toxicological studies evaluating chronic exposure.

Use in Pregnancy - Category A

Lignocaine crosses the placental barrier and may be taken up by foetal tissues. When used for surface anaesthesia, lignocaine blood levels after normal doses are low so the little drug is available for placental transfer.

There are, however, no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats at doses of 500 mg/kg/day and have revealed no evidence of harm to the foetus caused by lignocaine.

It is reasonable to assume that a large number of pregnant women and women of childbearing age have used lignocaine. No specific disturbances to the reproduction process have so far been reported.

Labour and delivery

Lignocaine is not contraindicated in labour and delivery. XYLOCAINE 4% TOPICAL SOLUTION Product Information PAIN.000-129-050.3.0 5(8)

Use in lactation

Lignocaine enters breast milk, but in such small quantities that there is generally no risk of affecting the child at therapeutic dose levels.