LID Study: Plasma lidocaine levels following airway topicalisation for paediatric microlaryngobronchoscopy (MLB)

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Abstract

Background A dose of 5mg/kg lidocaine is considered appropriate for paediatric airway topicalisation. Existing literature suggests younger children are susceptible to toxic lidocaine plasma levels and achieve this at a faster rate. Aims The primary outcome of this study was to ascertain peak plasma lidocaine levels after topicalisation for airway endoscopy. Secondary endpoints included: time to peak lidocaine plasma levels, signs of lidocaine toxicity (restricted to ECG changes or seizures when under anaesthesia) and clinical adverse events of laryngospasm, coughing or desaturation during the procedure. Methods Data was collected prospectively over 18 months at Royal Manchester Children's Hospital. Children aged 0-8 years undergoing elective diagnostic or therapeutic airway endoscopy were included within the study. Standardised 2% lidocaine was used for airway topicalisation. Dose varied depending upon practitioner usual practice. Venous blood sampling occurred at 5, 10, 15 and 20 minutes post administration and plasma lidocaine levels (ng/ml) analysed. Results A significant relationship exists between higher peak plasma levels and ages <18 months (p=0.00973). Strong linear correlation exists between weight and age for our cohort (r=0.88). Higher peak plasma lidocaine levels occur with total dose volumes between 2 and 3mls of 2% lidocaine local anaesthetic (p=0.03) compared with <2ml total dose volumes. Data suggests a potential relationship of lower weights achieving higher peak plasma levels (p=0.0516). Reduced IQR variation of peak plasma lidocaine levels exists when lidocaine dosing is <5mg/kg. Conclusions Age and total dose volume of topicalised lidocaine have a significant relationship with plasma lidocaine levels. A dose of 5mg/kg topicalised lidocaine for paediatric airway endoscopy is safe and provides good operating conditions. Lower patient weights trend toward higher peak lidocaine plasma concentrations and require further investigation.

Abstract (277 words)

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Methods

Data was collected prospectively over 18 months at Royal Manchester Children's Hospital. Children aged 0-8 years undergoing elective diagnostic or therapeutic airway endoscopy were included within the study.

Standardised 2% lidocaine was used for airway topicalisation. Dose varied depending upon practitioner usual practice. Venous blood sampling occurred at 5, 10, 15 and 20 minutes post administration and plasma lidocaine levels (ng/ml) analysed.

Results

A significant relationship exists between higher peak plasma levels and ages <18 months (p=0.00973). Strong linear correlation exists between weight and age for our cohort (r=0.88). Higher peak plasma lidocaine levels occur with total dose volumes between 2 and 3mls of 2% lidocaine local anaesthetic (p=0.03) compared with <2ml total dose volumes. Data suggests a potential relationship of lower weights achieving higher peak plasma levels (p=0.0516). Reduced IQR variation of peak plasma lidocaine levels exists when lidocaine dosing is <5mg/kg.

Conclusions

Age and total dose volume of topicalised lidocaine have a significant relationship with plasma lidocaine levels. A dose of 5mg/kg topicalised lidocaine for paediatric airway endoscopy is safe and provides good operating conditions. Lower patient weights trend toward higher peak lidocaine plasma concentrations and require further investigation.

Five Key Points

- Strong linear correlation exists between weight and age for our cohort (r=0.88)
- A significant relationship exists between higher peak plasma levels and ages [?]18 months (p=0.00973)
- Data suggests a potential relationship of lower weights achieving higher peak plasma levels (p=0.0516)
- Higher peak plasma lidocaine levels occur with total dose volumes between 2 and 3mls of 2% lidocaine local anaesthetic (p=0.03) compared with <2ml total dose volumes
- Reduced IQR variation of peak plasma lidocaine levels exists when lidocaine dosing is <5mg/kg.

Key words

Airway endoscopy, drug levels, Lidocaine, paediatric airway, paediatric anaesthesia, topical anaesthesia, toxicity

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What is already known about the topic

A dose of 5mg/kg lidocaine is considered appropriate for paediatric airway topicalisation. Existing literature suggests younger children are susceptible to toxic lidocaine plasma levels and achieve this at a faster rate.

What new information this study adds

Age and total dose volume of topicalised lidocaine have a significant relationship with plasma lidocaine levels. A dose of 5mg/kg topicalised lidocaine for paediatric airway endoscopy is safe and provides good operating conditions. Lower patient weights trend toward higher peak lidocaine plasma concentrations and require further investigation.

Introduction

Airway endoscopy is a diagnostic and therapeutic procedure involving instrumentation of the airway. Anaesthesia is typically performed using a spontaneous ventilation technique with topical lidocaine applied under direct vision to the supra- and sub-glottis. Local anaesthetic is applied to the airway to provide a good operative field, minimise the risk of complications such as laryngospasm and apnoeas, but also to minimise the peak blood concentration of anaesthetic agent and facilitate a spontaneous ventilation technique[1].

Despite not being licensed for airway topicalisation, lidocaine has been used for over three decades in paediatric airway examination under general anaesthesia[2, 3]. Its use is established practice in many specialist

institutions including [removed for blind peer review]. The administered dose of topical lidocaine varies between practitioners from 3-5mg/Kg. The maximum topical dosage of 5mg/Kg is extrapolated from the manufacturers guidance regarding intravenous administration. Since intravenous administration is presumed to have 100% bioavailability, the topical route of administration potentially will result in reduced plasma lidocaine concentrations due to swallowing, surgical suction and application of vasoconstrictors such as adrenaline[8]. This then poses a clinical quandary as to the safe dose of topically administered lidocaine, and whether a larger dose will result in increased clinical effectiveness and complications such as toxicity.

Currently there is little data from well-controlled paediatric studies regarding peak lidocaine plasma concentrations in airway endoscopy[1,2,3,5,6]. Further dosing studies are required to ensure peak plasma levels do not exceed 5000ng/ml, as this concentration may potentially be harmful[5]. In this study we measured sequential plasma lidocaine levels in order to ascertain the peak plasma concentration of lidocaine following airway topicalisation. This would allow us to ensure the safety of our current dosing regimen, and guide us to any future changes.

Methodology

Study location

Written approval was sought and obtained from the [removed for blind peer review] in November 2015 and [removed for blind peer review] in March 2016. Data was prospectively collected over an 18-month period from January 2017 to June 2018 at [removed for blind peer review].

Study Design

This was a prospective Type A, single arm dosing study aimed at informing future interventions. There was no modification to standard clinical care. This trial adhered to the principles outlined in the [removed for blind peer review]. It is also compliant with [removed for blind peer review] requirements.

Participants

Participants were recruited on a voluntary basis. Children aged 0-8 years undergoing an elective diagnostic or therapeutic airway endoscopy were eligible.

Individuals were excluded if there had been any pre-operative exposure to lidocaine, taking medication that interfered with lidocaine metabolism or clearance (for example phenytoin, beta blockers or cimetidine) or informed consent was not obtained from a parent or guardian. Patients were also excluded from the study if there was a contra-indication or inability to insert a second intravenous (IV) cannula for blood sampling.

Eligible patients were identified by a nominated investigator on the hospital management system greater than 24 hours prior to the procedure. Individuals with parental responsibility were contacted via telephone and a trial information sheet sent either via post or email. On the day of surgery, those that had received trial information were approached and inclusion within the study discussed. Written, informed consent was obtained from persons with parental responsibility.

Any subject could withdraw from the study at any point.

Intra-operative procedure

Individual investigators were trained in standardised sampling techniques by the project leads [removed for blind peer review].

Standard pre-operative care was delivered, with induction and maintenance of anaesthesia achieved either by inhalational or intravenous techniques.

Lidocaine was applied under direct visualization to the airway using a mucosal atomization device (MAD) at a dose of 3-5mg/kg with standardised 2% solution across all study participants. Once the lidocaine was delivered to the patient, a stopwatch was commenced and the investigator inserted an IV cannula for blood sampling (using aseptic technique as per trust policy). No more than 3 sites were attempted and if the

investigator was unable to cannulate, the subject was excluded from trial. The supplementary cannula was reserved only for blood aspiration, and therefore no drugs were administered via this route.

Venous blood was taken at 5, 10, 15 and 20 minutes post lidocaine administration. Sampling procedure required aspiration of 0.5ml blood from the cannula to exclude dead space, which was then discarded. The 1ml sample was then withdrawn, stored in a plain bottle and the cannula flushed with 1ml normal saline.

A 2-minute window was allowed for the taking of blood samples. If this elapsed, the sample was omitted. For example, if the 10-minute sample was not taken by twelve-minutes, it was omitted, and the next sample taken at fifteen-minutes. If a participant had an incomplete set of samples due to untimely sampling or cannula failure, they remained within the study and their results were analysed for plasma lidocaine levels. They were then transferred to [removed for blind peer review] for preparation, freezing and storage, and then later transferred to [removed for blind peer review] for analysis. Analysis was conducted using a validated LC-MS/MS method. The validation was performed over the lidocaine concentration range 0.5 to 250 ng/mL.

The supplementary cannula was removed at end of case prior to emergence, unless clinical need suggested otherwise.

The case report form was completed with patient details such as weight and DOB and procedure details: administered lidocaine dose and volume, anaesthetic technique and supplementary drugs administered, intraoperative IV fluid administration, surgical technique including any endotracheal suction and topical application of adrenaline. We also recorded any clinical adverse events to include laryngospasm, coughing, desaturation and evidence of local anaesthetic toxicity.

Study outcomes

The primary outcome of the study was to ascertain peak plasma lidocaine levels after topicalisation for airway endoscopy. Secondary endpoints included: time to peak lidocaine plasma levels, signs of lidocaine toxicity (restricted to ECG changes or seizures when under anaesthesia) and clinical adverse events of laryngospasm, coughing or desaturation during the procedure.

Statistical analysis

Normally distributed variables were summarised by mean (standard deviation, SD) and non-normally distributed variables by median (interquartile, IQR) [range]. Categorical variables were summarised by count (percentage). In comparison tests, ANOVA or equivalent non-parametric tests were used for continuous variables. In assessing the relationship between peak plasma and age, weight or volume univariable regression models were used. As a result, multivariable models were not followed due to the small sample size. Due to the exploratory nature of the study, a nominal p-value of <0.05 indicates areas for further investigation.

Sample size

The sample size was derived from recruitment frequency at a specialist institution and a quantity that allowed a clear relationship between the primary outcome and defined variables to be explored. Fifty patients undergoing airway endoscopy were recruited within the study and a total of 198 samples were sent for analysis. A total of 198 human serum samples were received frozen on dry ice and in good condition from the [removed for blind peer review] on 26 Oct 2018 for preparation and analysis at [removed for blind peer review]. Sample analysis was performed between 17 Feb 2019 and 22 Feb 2019.

Results

Study demographics and baseline

Table 1 summarises the study demographics, baseline and descriptive data.

We found strong linear correlation between weight and age (r=0.88) as demonstrated in Figure 1. This adds strength to our study results in an era of paediatric obesity and the potential confounding effects of weight

and age on drug handling.

Primary outcome – Peak plasma lidocaine levels after airway topicalisation

Linear regression models were used to assess the relationship between peak lidocaine plasma concentration and variables of age, weight, volume and dose. The correlation coefficient (r) and p-values are derived from Spearman's correlation test.

Age

Data presented in Figure 2 demonstrate a significant quadratic relationship between peak plasma level and age (p=0.00973). Ages <18months have higher peak plasma lidocaine levels after airway topicalisation. This relationship peaks at 18 months and then regresses. This is confirmed in the linear regression of peak plasma against age. Both age and age^2 (p=0.0672) are statistically significantly related to peak plasma lidocaine levels.

Median peak plasma lidocaine levels are comparable across the age groups of <1 year, 1-3 years and >3years. However the <1 year age group demonstrates the widest distribution range of peak plasma lidocaine levels. In the age groups of 1-3 years and >3 years there are outliers of peak plasma lidocaine concentrations exceeding the recommended toxic levels of 5000ng/ml. There were no incidences of related clinical adverse effects.

Weight

Data presented in Figure 3 suggest potential quadratic correlation between weight and peak plasma lidocaine levels (p=0.0516). At weights between 10kg and 12kg, there is a trend toward higher peak plasma lidocaine concentrations. The covariates have not reached significance level but this could be due to the small sample size. It suggests an area for further investigation regarding patients' with smaller weights reaching higher peak plasma levels.

As demonstrated in Figure 1, weight and age are strongly correlated within our cohort. Weights between 10kg and 12kg correspond to an age of 18 months. This adds further support to our results of higher peak plasma lidocaine concentrations in <18months old patients following airway topicalisation.

Total dose volume of local anaesthetic

Data in Figure 4 suggest a significant quadratic relationship between volume of lidocaine utilised and its peak plasma levels (p=0.0352).

Airway topicalisation using a total dose volume between 2 and 3mls of 2% lidocaine led to higher peak plasma levels when compared to <2ml total dose volume. This suggests that using low volume, high concentration local anaesthetic solution for airway topicalisation may have a superior safety profile.

Dose

Dosing regimes did vary between practitioners dependent upon usual practice. Dosing regimes in the study comprised of 5.0 (4.93,5.0)[3.0,5.0] mg/kg, median (IQR)[range]. P-values from Mann-Whitney U test demonstrate no significant difference between the distribution of peak lidocaine plasma levels between doses at 5mg/kg and <5mg/kg (p=0.18). However, a narrow IQR within toxic limits has been suggested with doses <5mg/kg. This could imply a safer dosing profile, with no clinical adverse effects demonstrated for both the patient and surgical conditions.

Secondary outcomes

Time to peak lidocaine plasma levels

Non-parametric Kruskal Wallis test does not suggest a statistically significant relationship between patients' age, weight or volume of lidocaine used with time to peak lidocaine plasma level (p=0.54, p=0.62, p=0.68 respectively).

Signs of lidocaine toxicity and occurrence of clinical adverse events

All patients' median and IQR plasma lidocaine levels (ng/ml) do not exceed toxic levels at each measured time point of 5, 10, 15 and 20 minutes. However outlying plasma lidocaine levels exceeding 5000ng/ml do exist at every time point. Nevertheless there were no incidences of clinical adverse events or symptoms of local anaesthetic toxicity. This suggests toxic levels may differ between intravenous and mucosal administration of local anaesthetic agents. Our median time to peak plasma lidocaine concentration was 10 minutes as demonstrated in Table 1.

Four patients in the study exceeded lidocaine plasma levels of 5000ng/ml. Summary of demographics, baseline and descriptive data for these patients are in Table 2. There was no relationship between exceeding toxic lidocaine levels and age, weight or surgical procedure. However, a sample size of 4 in one group does not provide enough power to detect a difference.

Surgical procedure type and interventions

Plasma lidocaine levels did not statistically differ between diagnostic and therapeutic surgical groups at any measured time point. All p-values were calculated as >0.05 utilising Mann-Whitney U-tests.

Peak lidocaine plasma levels were also analysed by surgical procedure group, diagnostic or therapeutic, and the use of adrenaline, endotracheal (ET) suction, both or neither. Due to the very small numbers in some subgroups, comparison tests are not robust. However, the plot suggests that there is no difference in the distribution of peak lidocaine plasma between these groups.

This suggests surgical suction and application of vasoconstrictors have no effect on peak plasma lidocaine levels.

Discussion/Analysis

Our study has demonstrated that 5mg/kg dosing of lidocaine for airway topicalisation in paediatric airway endoscopy is safe. We had no incidences of clinical adverse events, symptoms of local anaesthetic toxicity and maintained good surgical conditions for the required procedure. This qualitative data supports the safety profile of this pilot study.

Our study primary outcome achieved significant results. We successfully demonstrated a quadratic correlation between higher peak lidocaine plasma levels and ages <18 months (p=0.00973) as shown in Figure 2. Previous studies have demonstrated similar findings with younger patients achieving higher peak lidocaine plasma levels. In 1978 Eyres et al found higher peak lignocaine plasma levels following topical application to mucous membranes in children under 3 years old, with those under 1 year occurring earliest at 2 minutes[5]. The median time to peak lidocaine plasma level in our study was found to be 10 minutes as demonstrated in Table 1. This is significantly longer than the 2 minutes demonstrated in 1978[5]. Whilst we did not record the average length of the surgical procedures, our lidocaine plasma levels would most likely peak during the surgical procedure or following completion of the endoscopy in the recovery room. In 1983 Eyres et al repeated their 1978 study and again showed a variation in the time to peak level in different age groups[2,5]. In children less than 1 year of age the time to peak lignocaine plasma level was 5.8 minutes, increasing to 6.5 minutes between 1-3 years, and over 10 minutes in the 5 plus group. We did not demonstrate a significant relationship between age and time to peak lidocaine plasma level as our secondary outcome measure.

Whilst our covariates for patients' with smaller weights achieving higher peak lidocaine plasma levels did not reach significance level (p=0.0516), it suggests an area for further review whilst supporting the safety profile of this pilot study. Figure 3 illustrates a trend for higher peak plasma lidocaine levels in patients weighing between 10 and 12kg. This correlates well with ages up to 18 months as shown in Figure 1. Extremes of weight are a known risk factor for local anaesthetic toxicity. Many previous studies[2,5] have focused on age of patients rather than weight. Sitbon[1] et al altered the dose administered dependent on weight as well as age. The dosing used was much smaller (0.9 and 2.6 mg/kg) with corresponding lower maximum peak levels

of 1.05 mcg/ml. They concluded that younger children less than 6 months old did not present with peak levels earlier, although they did not analyse the relationship of weight versus lidocaine levels in more detail.

Our study cohort did not have extreme outliers regarding weight for age as indicated by Figure 1. As an urban tertiary paediatric hospital, our results can therefore reliably be extrapolated to a wider paediatric population ensuring the external validity of the study.

In 2016 Roberts and Gildersleve aimed to review practice amongst paediatric anaesthetists regarding their use of topical lignocaine[4]. As demonstrated in our study, variation in the dose of lidocaine was recognised with a range of 1-10 mg/kg (median dose 4 mg/kg). Amongst the respondents the most commonly documented dose was 3mg/kg as per the British National Formulary for Children[10]. In our study anaesthetic participants did not alter their usual practice. The median dose at [removed for blind peer review] was 5mg/kg. Despite this no significant adverse effects were recorded. Roberts and Gildersleve did note some respondents using significantly higher doses in line with adult bronchoscopy practice. Previous rationale for this was that some of the lidocaine would be suctioned by the surgeons or swallowed. We found no change in plasma lidocaine levels with the use of surgical suction, topical vasoconstrictors or by surgical procedure group.

An interesting and significant result from this study is shown in Figure 4. We demonstrated higher peak plasma lidocaine levels when utilising total dose volumes between 2 and 3mls of 2% lidocaine local anaesthetic (p=0.0352) when compared with volumes less than 2mls. The relationship between volume and time to peak lidocaine plasma levels however was not significant (p=0.68). This would suggest higher concentrations of local anaesthetic solution at lower total dose volumes could achieve a better safety profile. However whether this would affect surgical conditions or lead to clinical adverse effects would be an area for investigation in a larger future study.

A non-significant, but noteworthy result from this pilot study was the reduced IQR variation of peak plasma lidocaine levels when lidocaine dosing was <5mg/kg. With dosing <5mg/kg we again demonstrated no occurrences of clinical adverse events, signs of local anaesthetic (LA) toxicity or compromise of surgical conditions.

Most importantly, despite four patients exceeding recommended toxic levels of >5000ng/ml, no symptoms of LA toxicity or clinical adverse effects occurred. It is therefore possible differing toxic levels exist for mucosal application versus intravenous application of LA agents. Studies have previously failed to show clinical signs of toxicity in anaesthetised adults with serum lidocaine levels over 5000ng/ml[2,7]. One theory is some protection is offered by general anaesthesia[8]. Further research is needed to extrapolate this to the paediatric population. Pharmacological research has shown extremes of age including neonates and infants are at greatest risk of LA toxicity[9]. This age group have reduced plasma concentration of the proteins that bind the anaesthetic agents (alpha1- acid glycoprotein). The unbound portion undergoes metabolism and determines toxicity.

A limitation of our study was not standardising the dose and volume of lidocaine used. As this was a pilot study with an aim to avoid changes in usual practice variations were expected. The small sample size is acknowledged but felt to be adequate to allow relationships between outcomes and variables to be analysed. Further studies with larger samples sizes are planned.

Conclusion

This pilot study adds to the current body of evidence regarding dosing of lidocaine in paediatric airway topicalisation. Our results support the safety profile of this study and the use of its protocol in future studies. Additionally it has identified areas for further investigation to include volume of local anaesthetic utilised for airway topicalisation.

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Tables

Table 1- Demographics and Baseline of all study participants

	N=50
Age (months), median (IQR)[range]	23.50 (12.25, 37.75) [2.00,81.00]
< 1 year years > 3 years	12 (24%) 22 (44%) 16 (32%)
Weight (kg), mean (SD)[range]	12.43 (5.11) [3.2,23]
Surgical Procedure, n (%) Diagnostic Therapeutic	27 (54%) 23 (46%)
Dose (mg), mean (SD)	58.5 (23.94)
Dose (mg/kg), median (IQR)[range]	5.0 (4.93,5.0) [3.0,5.0]
Volume (ml), mean (SD)[range]	2.94 (1.16) [0.8,5.6]
Plasma at 5 minutes (ng/ml), mean (SD)[range]	2575.8 (1185.47) [88.7,5630.0]
Plasma at 10 minutes (ng/ml), mean (SD)[range]	2960.0 (1154.45) [191.0,5440 .0]
Plasma at 15 minutes (ng/ml), mean (SD)[range]	2851.0 (1078.01) [245.0,5530.0]
Plasma at 20 minutes (ng/ml), mean (SD)[range]	2614.0 (986.85) [252.0,5290.0]
Peak Plasma (ng/ml), mean (SD)[range]	3275 (1164.43) [252,5630]
Time to Peak Plasma (min), median (IQR)[range]	10 (10,15) [5,20]
Plasma above toxicity level of 5000ng/ml, Count (%)	4 (8%)
Adverse Effect, Count (%)	0
Fluid bolus, Count (%)	7 (14%)
Signs of LA toxicity, Count (%)	0

	N=50
Second cannula removed, Count (%)	45 (90%)

Table 2 – Patients exceeding 5000ng/ml peak lidocaine plasma levels demographics and baseline data

ID	Dose (mg/kg)	Peak Plasma Level (ng/ml)	Age (months)	Weight (kg)	Volume (ml)	Total Dose (mg)	Surgical Procedure(s)	Time to Peak Plasma Level (mins)
1	5	5250	38	13.3	3.2	64	Diagnostic ET suction*	15
2	5	5530	16	9.2	2.2	48	Diagnostic 1:10000 adrenaline	15
3	5	5250	20	10.8	2.7	54	Diagnostic None	10
4	5	5630	53	22.5	5.6	112.5	Diagnostic ET suction	5

**ET=Endotracheal*

Figure Legends

Figure 1- Weight versus Age

Figure 2- Peak Plasma against Age

Figure 3- Peak Plasma against Weight

Figure 4- Peak Plasma against Volume