

Effect of Lidocaine on Olfactory Perception in Humans

Abstract

Objective: The effect of local anesthesia to the nasal mucosa on olfactory acuity is the subject of some debate. This study was aimed to investigate the effect of local anesthesia on olfactory perception. **Materials and Methods:** Six healthy participants, five males and one female, were chosen from the academic population of Cardiff University. Olfactory perception was monitored at intervals following administration of 4% lidocaine to the nasal mucosa in the volunteers. Lidocaine was administered using a nasal spray as used in routine otolaryngological investigations. The olfactory stimulus (amyl acetate) was delivered directly to the nostril using an olfactometer. Olfactory perception was determined by the use of a 13 trial, forced choice scoring task. **Results:** Lidocaine caused a small, transient reduction in olfactory perception. The maximum reduction in olfactory perception (35%) was achieved by 60 mg lidocaine 15 min following administration, but perception could be increased to almost normal levels by increasing the odor stimulus dose. Detection of the lowest stimulus strength returned to normal levels after 30 min. **Conclusions:** Intranasal application of lidocaine, caused a reduction in olfactory perception, however, did not abolish the olfactory function 15 min following administration. Physiological/psychometric olfactory testing would not be precluded under these circumstances, and the effects of anesthesia could be overcome by increasing the stimulus strength.

Keywords: Lidocaine, local anesthesia, olfaction, olfactory acuity, smell

Introduction

Local anesthesia is widely used in otolaryngology both for examination purposes and for surgical procedures. Among the prerequisites for electro-olfactogram (EOG) recording, is the accurate placement of the electrode in the olfactory epithelium.^[1] Although great care may be taken during electrode insertion for EOG recording, it remains an uncomfortable procedure for the participants. The use of local anesthetic could alleviate this problem. However, its use may render the participant temporarily anosmic, making it impossible to measure olfactory perception. Okhado,^[2] in his clinical studies on the EOGs both in normal and anosmic participants, noticed no influence of lidocaine on EOG. Kimura^[3] observed that cocaine abolished the frog's olfactory bulb response to odorants but that the EOG remained almost unchanged. Furukawa *et al.*^[4] in their experiments on human subjects found that vasoconstriction and lidocaine did not interfere with the recording of the EOG. It follows from the findings of Ottoson,^[1] Kimura,^[3]

and Okhado^[2] that nasal anesthesia may preclude an assessment of olfactory perception, and although recording of the EOG may still be possible, the correlation of olfactory perception with EOG would be compromised. Welge-Lüssen *et al.*^[5] reported that routine anesthesia was not found to affect the chemosensory event-related potentials in humans.

To investigate the effect of lidocaine on olfactory perception, a protocol was devised which measured olfactory acuity in normal human participants following varying doses of lidocaine under standard delivery conditions.

Materials and Methods

Six participants, five males and one female, were chosen from the academic population of Cardiff University. All were healthy, between 20 and 40 years old, and gave their informed consent. Ethical approval for the study was granted by the Local Ethics Committee (Bro Taff Health Authority, Cathays Park, Cardiff, UK).

Lidocaine (4%) was delivered to the nostril by a nebulizer spray bottle. Each spray of the lidocaine dispenser contained 10 mg of

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the active ingredient lidocaine. The spray also contained ethanol, menthol natural, polyethylene glycol 400, essence of banana, saccharin, and purified water (Astra Pharmaceuticals Ltd, UK).

Amyl acetate (Sigma Chemical Co., Poole, England), a substance with a sweet odor of pear drops was used as the odor stimulant. This is presented as fixed concentration of odor vapor to smell, and duration can be varied to change the stimulus intensity. For practical purposes, each dose of stimulus is designated as odor pulses. The strength of each pulse is noted as duration of stimulus measured in milliseconds.

Before the start of experiment, the olfactory detection threshold for amyl acetate was determined for each participant individually. This was done by presenting an ascending series of stimulus pulses (35 ms, 70 ms, and 140 ms) delivered by the olfactometer, starting with the lowest stimulus (35 ms pulse width). Each participant was given 13 pulses of test sequences, and some of these sequences were control humidified air, randomly interspersed with odor stimulus. The test stimulus strength was set at the level at which the participants scored 50% correct detections. This was called Level 1 (35 ms). Level 2 was twice the detection threshold (70 ms pulse width), and Level 3 was four times this strength (140 ms pulse width).

Odor delivery

The olfactometer (described in detail in Wang *et al.*^[6,7]) consisted of a filtered air supply delivery system of narrow tubes, a computer-controlled odor switching device, solenoid valves (Cole Palmer, Bishops Cleeve, UK), and a water bath. A constant airflow was delivered to the nostril through a Teflon nasal cannula inserted through a self-expanding bung (an Aero Ear Protector, Stockport, UK) approximately 1.5 cm into the nostril. The participants were instructed to breathe through their mouths. Olfactory stimulation was achieved using computer-controlled valves to direct part of the airflow into the amyl acetate reservoir without altering the pressure or flow rate by a valve switching system. The concentration of amyl acetate in the odor reservoir, calculated from the vapor pressure at 20°C, was approximately 5200 ppm. The switching mechanism was designed in such a way that during stimulation, odorant pulses of preestablished concentrations (diluted 1:3 with humidified air) reached the olfactory region without altering the flow rate, and during the interstimulus intervals (ISIs), only non-odorous control air reached the nose. This ISI (30 s) is calculated from previous authors and denotes approximately the recovery time for olfactory receptors.^[8]

Both the amyl acetate and air (no odor control) stimuli were presented at regular ISIs of 30 seconds, with stimulus duration of 200 ms at a flow rate of 4 L/min to one nostril. During the experiment, this would be the anesthetized

nostril. The high flow rate minimized the contralateral flow of odorant molecules. The temperature of the air flowing into the nostril was regulated to 28.5°C by passing it through a coil immersed in a water bath. The relative humidity was maintained at 80% by passing the continuous air stream through a small glass reservoir containing water. This arrangement created a discrete pulse of the odorant in the air stream, which was delivered to the nose using the olfactometer without altering mechanical or thermal conditions at the mucosa, thus reducing the chances of trigeminal activation.

Test protocol

Blocks of trials were then administered with the concentration of the olfactory stimulus at this initial level (Level 1), twice this level (Level 2), or four times this level (Level 3). The protocol was then repeated following exposure to varying doses and exposure times (10, 15, and 30 min) of lidocaine administration. The anesthetic and odor were always delivered to the same nostril.

Olfactory perception was determined by the use of a 13 trial, forced choice scoring task. A flashing LED indicated when each trial would begin; the participant would then score as to whether pulse of odor or of control air (an odor “blank”) had been delivered to the nose, by marking on a sheet. Participants were instructed to mark if they were smelling the odor or not on the sheet each time the LED flashed. Odor blanks were randomly interspersed with odor trials. A percentage correct score was calculated at the end of each block of 13 trials.

Statistical analysis

The effect of the anesthetic on olfactory function was determined by analysis of the variance (ANOVA) of the responses at the different time intervals following administration of the lidocaine and by the general linear model (GLM) for repeated measures with time and stimulus intensity as within participants’ factors, dose as between participants’ factor. *Post hoc* analysis using the Bonferroni test was carried out to determine the doses of lidocaine that produced significant differences in detection rates from control (no anesthetic).

Results

The detection scores (%) for different stimulus strengths of amyl acetate over time are shown in Figure 1 for no anesthetic (black line and symbols) and for 30, 60, and 120 mg of lidocaine at two different time intervals. In the absence of anesthetic (lidocaine), there was no significant difference in detection between the different stimulus intensities – the stimuli were all suprathreshold, and thus, the detection rate was between 80% and 90%. However, statistical analysis using the GLM for repeated measures (time and stimulus intensity as within participants’ factors, dose as between participant’s factor)

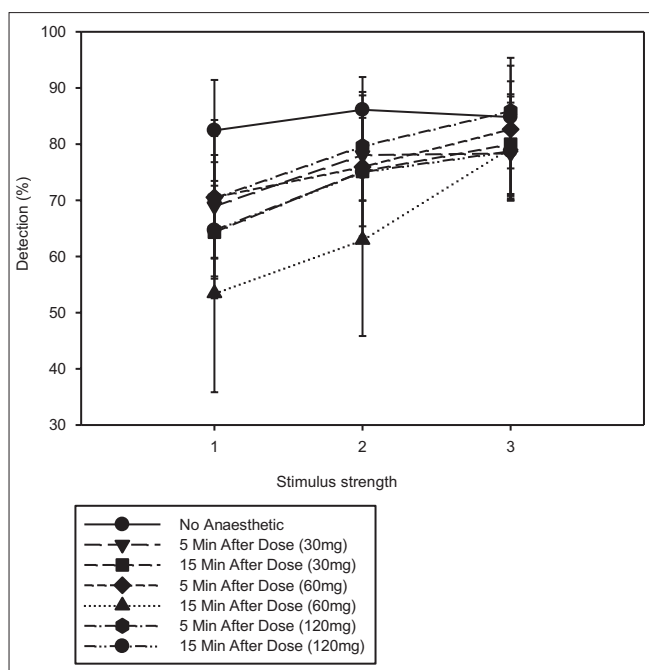


Figure 1: The effect of increasing doses of lidocaine on olfactory perception. The odor stimulus was amyl acetate delivered at three different strengths. Data represent the mean detection (%) ± standard error (bars) from 6 participants for, no anesthetic (black circles and lines), and 30 mg, 60 mg and 120 mg lidocaine at 5 and 15 min following administration

of the detection rate following administration of anesthetic demonstrated that stimulus intensity ($F = 9.007$, $df = 2$, $P < 0.001$) and time ($F = 6.087$, $df = 1$, $P = 0.025$) were significant factors. The application of anesthetic, therefore, resulted in a significant reduction in detection, particularly for the lowest stimulus intensity (pairwise comparison for the three stimulus intensities was significant for Level 1 vs. Level 2, $P = 0.002$ and Level 1 vs. Level 3, $P = 0.001$), and *post hoc* analysis (Bonferroni) showed that the 60 mg dose of lidocaine was the closest to reaching significance from the control (60 mg lidocaine vs. no anesthetic; $P = 0.076$), causing a 35% reduction of detection from 82.4% ± 9.0% to 53.5% ± 17.6% ($n = 6$). However, increasing the stimulus strength four-fold restored detection levels to close to normal, 79.4% ± 9.1% compared to the control (no anesthetic) detection levels of 84.8% ± 9.2%.

When the perceptual scores for the 60 mg dose were examined over an extended time course, the perception decreased 15 min following administration the lidocaine, to rise again after 30 min, indicating that anesthetic action is transient and most pronounced during this period [Figure 2]. The graph shows a similar reduction in scores for all three stimulus strengths. However, while there was a consistent reduction in the scores for all three test conditions, these values failed to reach statistical significance when tested with GLM. Pooling the data for each of the stimulus strengths at each of the three time intervals (10, 15, and 30 min) produced a drop in detection from 86% ± 4% at 10 min to 58% ± 9% (average reduction of 28%) at 15 min

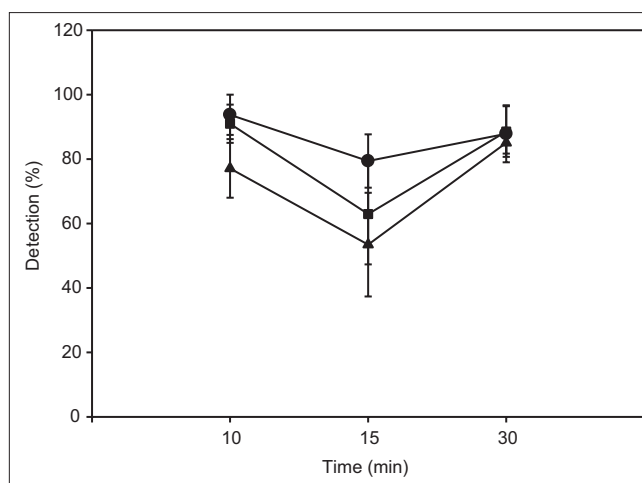


Figure 2: The effect of 60 mg lidocaine on the perception of varying doses of amyl acetate. The different symbols represent different strengths of the amyl acetate stimulus; Level 1 (triangles), Level 2 (squares), and Level 3 (circles). Level 2 is ×2 and Level 3 is ×4 Level 1 (see Methods). Perceptual scores decreased 15 min following administration of 60 mg lidocaine but recovered by 30 min

which recovered to 88 ± 4 at 30 min ($n = 15$). Comparing the means for each time interval demonstrated a significant difference ($F = 7.847$, $df = 2$, $P < 0.001$, one-way ANOVA). Multiple comparisons (ANOVA) showed that the detection scores at 15 min were significantly different from 10 min and 30 min ($P = 0.005$ and $P = 0.003$, respectively). The recovery of olfactory function after 30 min was demonstrated by the fact that the score was not different to that at 10 min ($P = 0.975$).

The mean perceptual scores (pooling the data for 3 stimulus strengths) recorded 15 min after administration of 120 mg, fell less markedly to 67% ± 6% (average reduction of 19%), a significant reduction in perception, compared to the control ($F = 14.967$, $df = 1$, $P < 0.001$).

Detection of the lowest stimulus pulse of amyl acetate is reduced after 15 min by all doses of lidocaine, but the maximal effect is achieved with 60 mg, and olfactory function is not further affected by the application of 120 mg of lidocaine. In fact, the detection scores with 120 mg lidocaine appeared higher than those for 60 mg; at 15 min, the detection scores were 53.5% ± 17.6% and 64.7% ± 12.1% for the 60 mg and 120 mg doses at 15 min, respectively [Figure 1], although this was not significant ($P > 0.05$).

Full recovery in olfactory function occurred by 30 min following the lidocaine application irrespective of the dosage in all our six participants. For the 60 mg dose, the detection scores at 30 min were 85.1% ± 3.4%, 88.6% ± 7.9%, and 87.9% ± 8.9% for the three increasing strengths of amyl acetate stimulus pulses, which compares to control values of 82.4% ± 9.0%, 86.1% ± 5.8%, and 84.8 ± 9.2%, respectively.

Discussion

Local anesthetics prevent or relieve pain by interrupting nerve conduction. They prevent the generation and the conduction of the nerve impulse and their primary site of action being the cell membrane. Lidocaine, introduced in 1948, is the most widely used local anesthetic.^[9] It is used routinely in otorhinolaryngology both for examination purposes and for minor procedures. As a general rule, small nerve fibers are more susceptible to local anesthetics than large fibers. The axons of the olfactory nerve are among the smallest (0.1-0.3 μ in diameter) in the vertebrate nervous system and are unmyelinated.^[10] The sensory nerve supply of the nose consists mainly of the ophthalmic and the maxillary division of trigeminal nerve. The former gives rise to the nasociliary nerve, and branches from the maxillary nerve include the nasopalatine nerve, which enters the nasal cavity through the sphenopalatine foramen.

Olfactory receptor potentials are more resistant to the action of local anesthetic than impulse activity.^[11] In early experiments on rabbits, Ottoson^[12] found that cocaine did not block the olfactory response. This suggested that the potential recorded did not represent summated nerve activity.

Okhado^[2] used local anesthesia (lidocaine) in EOG recordings and was successful in recording slow negative potentials in 68% of his participants with normal olfactory function. He reports that although his participants were in anosmia with local anesthesia of the olfactory cleft, EOG did not disappear. He concluded that EOG was not influenced by the application of lidocaine before the experiment. Furukawa *et al.*^[4] conducted that similar experiments from the same center (Kanazawa University, Kanazawa, Japan) observed vasoconstriction and lidocaine application did not interfere with the recording of EOG.

We sprayed the drug primarily into respiratory region of the nasal mucosa as would be performed in the routine otolaryngological investigation. Lidocaine spray can have a fruity or banana smell; however, our participants were unable to identify any specific smell associated with the application of spray. The principal aim of this preferential application was to observe whether this would make the introduction of an intranasal electrode for EOG recording more comfortable, without compromising the olfactory ability. Psychometric responses derived from six participants in our study show that while reducing the perception by 28% and 19% with 60 mg and 120 mg of lidocaine, respectively, 15 min after administration, it did not abolish the olfactory function. While we found that the effect of lidocaine on perception was greatest 15 min following administration, almost 100% olfactory function returned by 30 min.

Stimulation of the trigeminal nerve can, under certain circumstances, affect olfactory perception.^[8] Welge-Lüssen

et al.^[5] studied the effect of local anesthesia on olfaction and chemosensory event-related potentials in 20 volunteers using 4% lidocaine and 1% tetracaine. It was noted that even though anesthesia influenced self-assessment, measurable olfactory function remained unchanged. The possibility that anesthesia of the trigeminal nerve was wholly or partly responsible for the reduction in olfactory perception in our study is unlikely. We carried out our experiments using concentrations of amyl acetate below the threshold for activation of the trigeminal nerve and at levels where its effect is predominantly olfactory.^[8] Jung *et al.*^[13] noted that the topical use of intranasal phenylephrine and lidocaine did not affect olfactory ability in a randomized controlled trial.

A significant finding of this study, which is of great practical importance, is that the application of lidocaine (spraying into the nostril) is very unpleasant. All the participants felt that administration of 120 mg dose was intolerable. To achieve this high level of lidocaine, 12 pumps of the spray bottle are needed, delivering 1.2 ml (the recommended maximum is 20 spray applications). Part of the lidocaine goes directly into the nasopharynx by the action of the spray, by-passing the olfactory mucosa, and another fraction is rapidly transported to the pharynx by the normal ciliary action of the mucosa. The 120 mg dose is not well tolerated, and the sheer volume of anesthetic means that much passes into the nasopharynx unabsorbed without affecting the olfactory mucosa. These factors may have been responsible for the smaller inhibitory effect of the 120 mg dose of lidocaine on the olfactory ability compared with the 60 mg dose.

Conclusions

Intranasal application of lidocaine, caused a reduction in olfactory perception, however, did not abolish the olfactory function 15 min following administration. Physiological/psychometric olfactory testing would not be precluded under these circumstances, and the effects of anesthesia could be overcome by increasing the odor stimulus strength. While we found that the effect of lidocaine on olfactory perception was greatest 15 min following administration, almost 100% olfactory function returned by 30 min.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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