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SHORT COMMUNICATION

Serum Concentration of Lignocaine After Pertubation: An Observational Study

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Abstract
Objective The objective of this study was to report the serum concentration of lignocaine after pertubation in patients with endometriosis.
Design Prospective observational study.
Setting The study was carried out at a gynaecological outpatient unit in Stockholm, Sweden.
Population Eligible patients had endometriosis with a dysmenorrhoic pain score of >50 mm on a visual analogue scale, and patent fallopian tubes.
Methods Patients with endometriosis ($n = 25$) were included in the study. The patients received pre-ovulatory pertubations with lignocaine hydrochloride 10 mg ($n = 16$) or ringer acetate (placebo, $n = 9$). The procedure comprised passing the study solution through the uterus and the fallopian tubes via an intra-cervical balloon catheter. Serum samples were collected at 0, 5, 15 and 30 min after pertubation.
Main Outcome Measures The serum samples were analysed for the concentration of lignocaine with an LCMS-SIM method.
Results Low levels of lignocaine were detected in the serum samples following pertubation of 10 mg lignocaine hydrochloride. The highest observed concentration was seen after 30 min (mean 0.050 μg/ml), with an individual maximum of 0.124 μg/ml. Maximum concentration (C_{max}) and time to C_{max} (T_{max}) could not be calculated, since the highest values were observed in the 30-min samples, which was the last sample obtained. Lignocaine was not detected after pertubation with placebo.
Conclusions The serum levels of lignocaine following pertubation of 10 mg lignocaine hydrochloride are detectable but low. Lignocaine pertubated through the fallopian tubes reaches the peritoneal cavity and diffuses through the peritoneum into the blood circulation. Pertubation with lignocaine is safe and has no lignocaine-related adverse events.

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1 Introduction

Lignocaine in high concentrations has the ability to block sodium channels and is used for local and regional anaesthesia and for antiarrhythmic treatment. Lignocaine is also thought to stabilize the cell membrane and have effects on inflammatory cells in lower concentrations [1, 2].

The definition of endometriosis is the presence of viable endometrial tissue outside the uterine cavity, most commonly located on the peritoneal surfaces in the lower abdominal cavity. A local sterile inflammation occurs in the peritoneal cavity in women with endometriosis [3] and might be an explanation for the main symptoms of endometriosis, which are dysmenorrhoea and/or infertility [4,

5]. Increased density of sensory nerve fibres in the endometriotic lesions and in the eutopic endometrium have also been found [6].

Pertubation comprises passing solution through the uterine cavity and the fallopian tubes into the peritoneal cavity via a cuffed intra-cervical balloon catheter. Earlier studies have shown that pertubations with lignocaine hydrochloride can improve fertility and reduce dysmenorrhoea in patients with endometriosis [7–9]; the highest dosage of lignocaine in these studies has been 10 mg. In total, more than 400 pertubations with lignocaine have been carried out without any lignocaine-related adverse events. Local anaesthetics in low concentrations have anti-inflammatory properties, and the clinical effect seen on pain and fertility might be due to decreased inflammation in the peritoneal cavity [2].

The adverse effects of lignocaine have been well investigated and manifest most commonly on the central nervous system (CNS) and cardiovascular systems [10, 11]. Plasma concentrations of lignocaine above 5 μg/ml can cause adverse effects (i.e. nausea, dysphoria, drowsiness, cardiovascular instability), but concentrations of lignocaine above 10 μg/ml are needed to produce serious toxicity. Serum levels above 10 μg/ml can cause disorientation, respiratory depression, seizures and even coma, but serum levels exceeding 20 μg/ml are needed to cause cardiovascular collapse [10].

Serum levels of local anaesthetics after non-vascular administration correspond with the vascularity of the tissue [12]. The surface area of the peritoneum is about equal to that of the skin, i.e. >2 m^2. Small molecules diffuse rapidly and the diffusion rates decrease with the molecular weight to become extremely slow for molecules with a molecular weight of 100,000 Da [13–15]. Lignocaine hydrochloride has a molecular weight of 271 Da.

A review of systemic levels of local anaesthetics after intra-peritoneal application was conducted in 2010; nine trials in which lignocaine was used were found [11]. The dosage used varied from 100 to 1,000 mg, and serum levels were detected as early as 5 min after application, with a time to maximum concentration (T_{max}) ranging from 5 to 40 min for plain lignocaine. The addition of adrenaline prolonged the T_{max}. Mean concentration maximum (C_{max}) ranged from 1.01 to 4.32 μg/ml, and the highest observed value was detected after intraperitoneal administration of 80 ml lignocaine 0.5 % (400 mg) [16]. No report of serum or clinical toxicity was found in any of the reviewed studies [11].

We have previously reported a randomized controlled trial that was carried out to evaluate the effect of pertubation with lignocaine 10 mg on dysmenorrhoea and quality of life in patients with endometriosis. The study demonstrated a significant reduction of pain after three pertubations with lignocaine compared with placebo [17] and the health-related quality of life improved significantly on the dimension social support (unpublished data). The reduced pain level lasted up to 9 months after the third treatment [17].

It is unclear how fast and in what amount the small dosage of lignocaine diffuses through the peritoneum and reaches the blood after pertubation. In the above clinical study, serum samples were therefore collected before and after the treatment for later analysis of lignocaine in serum.

This observational study reports the serum concentration of lignocaine after pertubation of 10 mg lignocaine hydrochloride.

The hypothesis is that the pertubated dosage of 10 mg lignocaine hydrochloride reaches the central circulation and gives rise to low systemic levels of lignocaine.

2 Methods

2.1 Study Design, Participants and Procedures

A randomized, double-blind and controlled study was conducted to study the effect of pertubation with lignocaine (1 mg/ml, 10 ml) on dysmenorrhoea and quality of life. A total of 42 patients were included in the study, 24 of whom were randomized to active treatment and 18 to placebo. The methods of this trial have previously been described in detail [17].

The patients were recruited through advertisements and from the gynaecological outpatient unit at the three participating clinics in Stockholm, Sweden. The first patient was included in March 2007 and the last in November 2008.

The main inclusion criteria were presence of peritoneal or ovarian endometriosis verified by laparoscopy and dysmenorrhoea, with a pain score of >50 mm on the visual analogue scale (VAS). The exclusion criteria included reduced patency in the fallopian tubes and the intention to achieve pregnancy during the forthcoming year. Detailed eligibility criteria for the study have been previously published [17].

Written informed consent was obtained before any study-related procedures, and the CONSORT (Consolidated Standards of Reporting Trials) guidelines were followed. The procedure was approved by the Medical Products Agency in Sweden, 8 November 2006 (151:2006/56028) and after amendment, 12 December 2007 (151:2007/76934), as well as by the Regional Ethical Review Board in Stockholm, 10 January 2007 (2006/1416-32) and after amendment, 14 December 2007 (2007/1398-32).

Before inclusion, the patients were scrutinized and tested concerning all criteria. Three treatments were given

pre-ovulatory on cycle day 6–12 in three sequential menstrual cycles, since the effect on dysmenorrhoea increased after repeated treatments [7]. A thin plastic catheter (PBN-Medicals, Stenløse, Denmark) was inserted and cuffed in the cervical canal or in the caudal part of the uterine cavity; 10 ml of ringer-lignocaine 1 mg/ml (active treatment) or ringer acetate (placebo) was infused through the uterine cavity and pertubated into the peritoneal cavity. The solution was infused under vaginal ultrasound supervision over approximately 5 min and an increased amount of fluid could be seen in the Pouch of Douglas after the treatment. Patients did not receive lignocaine by any other route during the study. Blood pressure and pulse were recorded before and 5 min after pertubation.

Serum samples were collected on a single occasion and, for practical reasons, at only one of the study centres. All patients who accepted the serum sampling at this centre were included in this additional study ($n = 25$). A peripheral venous catheter was inserted in vena brachialis before the treatment, and a 10 ml blood sample was collected at 0, 5, 15 and 30 min after pertubation, i.e. a total of 40 ml. The samples were centrifuged, the serum was stored at −70 °C (for 6–24 months) and later analysed in one batch for the concentration of lignocaine. The samples were collected from April 2007 until November 2008, and the analyses were conducted in April 2009. Since the study was blinded, tests were conducted both on patients who received lignocaine ($n = 16$) and on those who received placebo ($n = 9$).

The concentration of lignocaine in serum was determined with an LCMS-SIM method (OncoTargeting AB. Rapsgatan 7, 754 50 UPPSALA). The smallest observed peak with this method was 6 nM (1.4 ng/ml), the detection limit was 18 nM (4.2 ng/ml) and the limit of quantification was 60 nM (14.1 ng/ml).

2.2 Statistical Methods

The data were analysed using descriptive statistics in Microsoft® Excel 2007.

3 Results

In total, 124 pertubations were carried out; 70 with lignocaine and 54 with placebo.

A total of 97 serum samples were collected from 25 patients, of whom 16 had been treated with lignocaine hydrochloride 10 mg and nine with placebo (ringer acetate). Due to problems with the peripheral venous catheter, samples could not be taken from one patient in the lignocaine group after 0 and 30 min, and a 30-min sample is also missing from the placebo group.

Baseline data for patients included in the serum screening can be seen in Table 1. All patients were healthy and without cardiovascular or hepatic disease that might affect the pharmacokinetics of lignocaine. Most patients used analgesics when needed and some patients also used

Table 1 Demographics and medication

Parameter	Lignocaine, $n = 16$		Placebo, $n = 9$	
	Mean (SD)	Min–max	Mean (SD)	Min–max
Age, years	34.1 (5.8)	25–44	32.7 (5.6)	26–40
Weight, kg	66.9 (11.2)	50–90	69.8 (15.3)	50–98
Height, cm	164.3 (4.5)	155–172	168.3 (9.9)	156–181
Systolic blood pressure	121 (96)	105–140	118.4 (17.9)	100–148
Diastolic blood pressure	76.8 (8.5)	63–90	76.0 (8.8)	67–92
Heart rate	72.1 (9.4)	58–91	67.3 (5.9)	60–76
Number of smokers	2		0	
Medication	Number of patients		Number of patients	
Non-steroidal anti-inflammatory drugs	16		5	
Codeine	4		4	
Paracetamol	9		2	
Acetylsalicylic acid	3		1	
Dextropropoxifen	2		0	
Selective serotonin reuptake inhibitors	2		2	
Oral contraceptives	3		2	
Levothyroxine	1		2	

oral contraceptives, selective serotonin reuptake inhibitors (SSRIs) or levothyroxine (Table 1).

Overall low levels of lignocaine were detected in the serum samples following pertubation with lignocaine hydrochloride 10 mg. The highest observed concentration was 531 nM, which corresponds to 0.124 μg/ml or 124 ng/ml, and was seen after 30 min (Table 2; Fig. 1).

Of 16 patients, 14 had the highest level in the last sample, i.e. after 30 min. One had the highest level after 5 min and one after 15 min. T_{max} and C_{max} could not be calculated, since the highest values were observed in the 30-min samples.

Lignocaine was not found in any of the serum samples after pertubation with placebo (nine patients).

In total, 166 gynaecological examinations were carried out during the study, 42 of which were screening visits and 124 were treatment visits. There were no adverse events related to the treatment with lignocaine. Blood pressure and heart frequency recorded before pertubation were normal and did not change in either the lignocaine or the placebo group following treatment. Mild discomfort was experienced during the pertubation process at 11 of 124 treatments.

4 Discussion

This study shows that pertubation with lignocaine is safe. The serum levels of lignocaine following pertubation of 10 mg lignocaine hydrochloride are detectable but low.

Our highest level was 0.124 μg/ml, which is about 80 times below the toxic levels of 10 μg/ml. The serum concentrations detected are consistent with other studies and correspond to the low dose pertubated [11].

Study data support the theory that lignocaine pertubated through the fallopian tubes reaches the peritoneal cavity and diffuses through the peritoneum into the blood circulation. The levels rose during the follow-up time, and the highest values were observed after 30 min.

The major part of the pertubated fluid is thought to reach the peritoneal cavity. Some lignocaine might also be absorbed by the endometrium or by the lining of the fallopian tubes during the pertubation process of approximately 5 min.

Table 2 Serum concentration of lignocaine

Time point (min)	Concentration of lignocaine in ng/ml			
	Mean (SD)	Interquartile range	Median	Min–Max
0	0 (0)	0–0		0–0
5	16.1 (23.4)	1.1–20.5	7.3	0–90.2
15	38.0 (25.1)	18.3–57.9	30.8	7.3–80.4
30	49.7 (24.8)	36.6–59.3	43.3	18.7–124

Lignocaine is a potent drug and a high dosage of lignocaine in the central circulation would be a potential risk. During the pertubation treatment, the solution is infused into the uterine cavity under ultrasound supervision and could possibly be accidently placed directly into a blood vessel. However, if the solution had accidently been infused into a vessel, the serum concentration would have risen much faster. The highest level in one patient was reached after 5 min, but the level was very low (0.090 μg/ml).

Subjective toxic effect of lignocaine on the CNS appears at concentrations above 3–5 μg/ml, but objective adverse manifestations, including muscular irritability, convulsions and coma, appear at concentrations above 6–10 μg/ml [10]. Plasma concentrations of lignocaine above 10 μg/ml tend to produce more serious adverse effects on the CNS and can also affect the cardiovascular system with symptoms such as bradycardia, atrioventricular blockade and cardiac arrest. Both hypotensive and hypertensive reactions can occur. The dose required to induce cardiac arrest is several times that which produces respiratory arrest [12].

The optimal dosage and therapy intervals for the clinical effect seen on fertility and pain are unknown. The pertubation dosage of 10 mg was chosen as a safety precaution due to a minimal risk of depositing the substance directly into the circulation. Lignocaine 10 mg injected intravenously is known to be safe, and the dosage would be far below the initial dosage for treatment of ventricular arrhythmia. For treatment of ventricular arrhythmia with lignocaine, an initial dose of 50–100 mg is given intravenously (0.5–1.0 mg/kg bodyweight) as compared with the pertubated dose of 10 mg/70 kg, approximately 0.14 mg/kg bodyweight. Data from previous studies performed in the 1960s suggest that large amounts of lignocaine may be infused intravenously before toxicity is produced, and the largest dosage given intravenously in these studies was 200 mg [18].

The study has limitations due to the short follow-up time; pharmacokinetics with C_{max} and T_{max} could therefore not be calculated. The sampling was not performed for

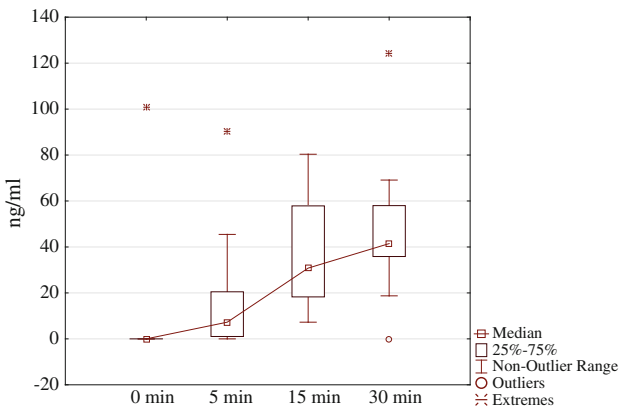

Fig. 1 Serum concentration of lignocaine

longer than 30 min after pertubation due to considerations for the patients, who would have had to stay longer for an additional blood sample. Earlier pharmacokinetic studies after intraperitoneal administration had indicated a T_{max} ranging from 5 to 40 min, and six of seven studies with plain lignocaine indicated a T_{max} ranging between 5 and 30 min [11]. The absorption of lignocaine was expected to be faster, and the slower absorption registered might be because no abdominal operation was carried out, which was the case in all of the reviewed studies. The T_{max} for lignocaine ranges between 15 and 30 min after injection for dental anaesthesia and after a subcutaneous injection [10, 12]. According to earlier studies, the T_{max} in our study is probably around 30 min and is unlikely to be above 40 min. Accordingly, it is not possible for the C_{max} to reach above 0.20 μg/ml after pertubation of 10 mg lignocaine.

The present study data, together with previous pharmacokinetic studies of lignocaine, confirm our hypothesis that pertubation with 10 mg lignocaine produces very low, and therefore safe, levels of lignocaine in serum. Overall, the pertubation treatments were well tolerated and there were no treatment-related adverse events.

Pre-ovulatory pertubation with lignocaine does not affect ovulation and even increases the chance of achieving pregnancy [9]. Pertubation with lignocaine can relieve pain in patients with endometriosis and might also have an effect on quality of life. The procedure is easy for any gynaecologist to learn and perform. Further studies are in progress to assess the mechanism of the clinical effect on dysmenorrhoea as well as the optimal dosage and therapy intervals.

This study supports the hypothesis that pertubation with 10 mg of lignocaine is safe and indicates that it might be possible to try a higher dose to further improve the clinical effect on pain.

5 Conclusions

Lignocaine pertubated through the fallopian tubes reaches the peritoneal cavity and diffuses through the peritoneum into the blood circulation. The serum levels of lignocaine following pertubation of 10 mg lignocaine hydrochloride are detectable but low. Pertubation with lignocaine is safe and produces no lignocaine-related adverse events.

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