Forensic Science International 244 (2014) 259–262

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Use of lidocaine in endotracheal intubation. Blood and urine concentrations in patients and deceased after unsuccessful resuscitation

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ARTICLE INFO

Article history:
Received 4 August 2014
Received in revised form 8 September 2014
Accepted 14 September 2014
Available online

Keywords:
Forensic toxicology
Lidocaine
Local anesthetics
Postmortem toxicological analysis
Cardiac surgery
Resuscitation

ABSTRACT

In toxicological analysis of postmortem samples the local anesthetic lidocaine is often identified. In most cases, lidocaine levels result from its use as aid in endotracheal intubation. The range of the drug's concentration in blood and urine was studied under controlled conditions from a cohort of cardiac surgery patients ($n = 35$).

Plasma concentrations 1 h after exposure to lidocaine in the range of the recommended 81 mg coating the endotracheal tube were less than 0.2 mg/l, its metabolite monoethylglycinxylidide (MEGX) less than 0.05 mg/l (median ratio 0.18, range 0.03–1.23). Also the concentrations of lidocaine and MEGX in urine samples were low (less than 1.2 and 0.1 mg/l, respectively) with MEGX/lidocaine ratios of 0.11 (median, range up to 1.2). These data were compared with results obtained by analyzing postmortem blood and urine samples of 18 deceased with a documented cardiopulmonary resuscitation attempt prior to death. Blood concentrations were in the same range (lidocaine median 0.07, range 0.02–1.07 mg/l; MEGX median 0.01, range <0.001–0.044 mg/l); besides low lidocaine concentrations in urine. MEGX was detected only in 2 out of 9 urine samples.

The results of the present study confirm that lidocaine is absorbed in the trachea from the endotracheal tube coated with lidocaine containing gel. Postmortem quantitative results can be explained on the basis of the data obtained in the controlled study.

1. Introduction

Lidocaine was the first local anesthetic drug of the amino amide-type [1]. It is widely used in infiltration anesthesia or for topical application as spray and gel on skin or mucous membranes, also as class 1B antiarrhythmic drug for the treatment of ventricular arrhythmia [2]. Its previous application as a first line emergency drug is no longer recommended [3,4].

In forensic toxicology, lidocaine is frequently detected in postmortem blood and urine samples. In most cases, circumstances suggest that lidocaine was used in the course of resuscitation attempts such as when applied on the endotracheal tube. This may cause the absorption into blood [5,6] and tissues [7–10] where it may be metabolized to monoethylglycinxylidide (MEGX) [11]. Moreover, lidocaine is an adulterant of illicit drug preparations (e.g. cocaine) [12] and it may be used by taking high doses [13–15].

It has been postulated that after resuscitation postmortem lidocaine concentrations are only present in a low or subtherapeutic range [5,6]. In the present study the concentration of lidocaine and of its metabolite MEGX in blood and urine after the application of lidocaine gel to an endotracheal tube was determined. Coating the endotracheal tube with lidocaine is routinely performed to facilitate intubation by improving sliding properties and for analgesia. The analytical data are compared to those measured in postmortem samples of deceased, where resuscitation attempts had been made antemortem.

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http://dx.doi.org/10.1016/j.forsciint.2014.09.008
0379-0738/

2. Materials and methods

2.1. Chemicals

Pure reference substances of lidocaine, monoethylglycinxylidide (MEGX) and lidocaine-D_{10} were purchased from Toronto Research Chemicals (Toronto, Canada). All other chemicals (analytical grade) and solvents (HPLC grade) were purchased from Merck (Darmstadt, Germany).

2.2. Lidocaine application, blood and urine sampling from surgery patients

The study protocol was approved by the local ethics committee of the university hospital Frankfurt and written informed consent has been obtained from each patient. Exclusion criteria were an age <18 years and liver or kidney diseases which may cause delayed excretion. In the study 35 patients with a median age of 68 (41–83) years and a median body mass index of 28 (19–40) were included. The preoperative care of the patients undergoing cardiac surgery followed routine procedures including insertion of a venous catheter for blood sampling. For intubation the endotracheal tube was manually coated with a lidocaine containing gel (Xylocaine® Gel 2%, AstraZenca GmbH, Wedel). In four cases the Xylocaine drug was weighed before and after application to allow an estimation of the gel amount applied. Venous blood (10 ml EDTA tubes) and urine samples were collected 1 and 6 h and urine samples 12 and 24 h after intubation. Blood samples were centrifuged for 10 min at 3500 × *g* and the separated plasma and the urine samples were stored at −18 °C until analysis. In the urine samples the creatinine level was analyzed (Microgenics DRI Creatinine-Detect Test on a Hitachi 902 analyzer, Thermo Fisher Scientific, Passau).

2.3. Study on postmortem samples

Postmortem samples were obtained from 18 corpses autopsied at the Institute of Legal Medicine in Frankfurt/Main, Germany, during 2008–2010 with documented unsuccessful cardio-pulmonary resuscitation prior to death (median age 35 years, range 0.6–89; body mass index median 23, range 15–33). Detailed information such as how long cardio-pulmonary resuscitation was performed or whether the heart eventually resumed beating was not available. All autopsies were performed by two forensic physicians according to Section 87 subs. 2 of the German Code of Criminal Procedure in accordance with the rules of the European Council in Legal Medicine about performance of the Medico-Legal Autopsy [16] and DIN ISO EN 17025 (the Institute is accredited). Blood collected from the thoracic vena cava inferior (cardiac whole blood) and from the vena femoralis if available. Blood of the vena femoralis was immediately centrifuged to yield postmortem serum which was obtained in 9 of the 18 samples. Cardiac whole blood, postmortem serum and urine were stored at −18 °C until analysis.

2.4. Sample preparation

For analysis, blood/plasma (1 ml) or urine (0.2 ml) were mixed with an equal volume of phosphate buffer (1 M, pH 9.5). Extraction was performed with a fivefold volume of 1-chlorobutane/diethyl ether (1:1, v/v) containing 50 μl of internal standard (1 ng/μl lidocaine-D_{10} in acetonitrile). The mixture was vortexed for 1 min and centrifuged for 10 min at 3500 × *g*. The supernatant was evaporated to dryness at 25 °C with a stream of compressed air. Residues were redissolved in 100 μl of 0.1% formic acid/acetonitrile (80:20, v/v).

2.5. Analysis of blood and urine extracts

The analysis of lidocaine and of its metabolite MEGX was performed using an Agilent (Waldbronn, Germany) 1100 series liquid chromatograph interfaced to an Agilent 1100 series orthogonal acceleration-TOF system operated in positive electrospray ionization mode (ESI). ESI source parameters were set according to the recommendations of the supplier for a flow rate of 0.4 ml/min (nebulizer 45 psig, capillary voltage 3000 V, drying gas flow 10 l/min at 350 °C). The fragmentor voltage was set to 125 V according to preliminary optimization studies. Data acquisition was performed in a mass range from *m*/*z* 101 to 1100 Da with simultaneous internal mass calibration in each recorded spectrum (system reference mixture supplied by the Agilent dual-sprayer interface) providing mass accuracies in the range of ±5 ppm. Chromatographic separation was achieved on a 100 mm × 2.0 mm Polaris C18-Ether column with 3 μm particle size (Varian, Darmstadt, Germany) at 50 °C using a mobile phase gradient consisting of 0.1% formic acid (solvent A) and acetonitrile (solvent B). Following an isocratic phase of 0.5 min with 5% (B) the organic solvent was increased to 75% (B) within 5.5 min followed by 2 min at 100% and reequilibration for 5 min. Calibration standards were prepared in drug-free serum and urine by spiking with lidocaine (0.1, 0.5, 1, 2.5, 5 mg/l) and MEGX (0.05, 0.25, 0.5, 1.25, 2.5 mg/l) and were processed as described above. The injection volume of all extracts was 2 μl. Identification of analytes, internal standard and integration were performed using the Agilent's Mass Hunter quantitative software (version B.05.01). The method was validated according to current guidelines [17]. For the determination of lidocaine and MEGX in serum the limits of quantification (LOQ) were 0.001 mg/l and the limits of detection (LOD) were 0.00032 mg/l. For the determination of lidocaine and MEGX in urine the LOQ was 0.002 mg/l resp. 0.005 mg/l and LOD was 0.001 mg/l resp. 0.002 mg/l. The linear range was from 0.002 up to 2 mg/l, for lidocaine in serum up to 8 mg/l. Extraction recovery was >80%, ion suppression was not observed. Bias and precision were tested at 3 levels (serum) and 2 levels (urine) in the range of 0.01–8 mg/l. Bias was 10% at most, intra-day and inter-day precisions were at most 11%.

2.6. Statistics

Statistical evaluation of the data was performed using the non-parametric Mann–Whitney-*U* Test of the IBM SPSS Statistics version 20 (IBM, Ehningen, Germany). Results with $p < 0.05$ were considered significant.

3. Results and discussion

The aim of the present study was to establish criteria for the evaluation of lidocaine and MEGX concentrations in postmortem samples. In forensic toxicology, the detection of lidocaine in postmortem samples may be an evidence that reanimation was attempted prior to death. As lidocaine is no longer used as a first line antiarrhythmic drug during reanimation and is replaced by amiodarone [3,4], it may still be used as an aid during endotracheal intubation. The absorption of lidocaine from the endotracheal tube during resuscitation has already been described [5,6,11] and postmortem concentrations have been reported. It is assumed that lidocaine may be absorbed during unsuccessful resuscitation, but only low levels in blood and no or only very low concentrations of the metabolite MEGX may occur. Such concentrations should be distinct from pharmacologically effective concentrations e.g. after use of lidocaine as an antiarrhythmic drug [18] or after lidocaine abuse [13]. In the present study the insertion of a lidocaine coated endotracheal tube during initiation of general anesthesia was regarded to be equivalent to the procedure during a resuscitation