Pharmacokinetics and clinical efficacy of lidocaine in cattle after intranasal administration during rhinotracheobronchoscopy

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Extensive clinical research in human medicine demonstrates that lidocaine is an effective topical anesthetic for bronchoscopy (Efthimiou *et al.*, 1982; Kirkpatrick, 1989; Sanderson, 2000; Fahy, 2003; Charalampidou *et al.*, 2006). Today, endoscopy of the upper respiratory tract represents an essential method also in bovine medicine for aiding in both, diagnosis and prognosis (Allen *et al.*, 1991; Anderson *et al.*, 1994; Franz & Baumgartner, 2007). Even though adverse reactions seem to be rare when lidocaine is used as a topic anesthetic in humans, it was of interest to investigate the intranasal (IN) use of lidocaine in cattle as no data are available in this species. Therefore this study was designed to i) obtain initial pharmacokinetic data after IN lidocaine application, ii) examine the cardiovascular response to lidocaine and iii) study the benefit for the examiner in regards to the compliance of cattle during rhinotracheo-bronchoscopy.

The Institutional Ethics Committee at the University of Veterinary Medicine, Vienna, Austria, approved all procedures performed in this study. Government approval was also obtained (BMBWK-68.205/0061-BrGT/2006).

Eight none lactating, healthy cows of different breed were studied at two occasions.

At one occasion lidocaine HCl (Xylanaest purum 2%, Gebro Pharma, Fieberbrunn, Austria) was administered IN (1.5 mg/kg BW) (lidocaine group), at the second occasion an equivalent volume of normal saline (0.9% NaCl, B.Braun Melsungen AG, Melsungen, Germany) was given IN to the animals. There was at least one week between each study period.

Invasive arterial blood pressure and heart rate were recorded continuously. Drug solutions were sprayed into the ventral nasal meatus and pharynx. Eight minutes after IN application, rhinotracheobronchoscopy was performed using a flexible endo-scope (diameter: 12 mm; length: 250 cm; Karl Storz, Tuttlingen, Germany). The specified duration of this procedure was 7 min.

Experiments were audio/videotaped for subsequent analysis of behavioral changes at three different time points/segments: 1) rhinoscopy of ventral nasal meatus, 2) insertion of the endoscope into the trachea (number of attempts required), 3) tracheal bifurcation. Scoring was 0 for no change, 1 for mild (flinching of the head), 2 for medium (movement of the limb, head tossing) and 3 for severe changes in behavior (kicking, trying to jump).

Blood samples were collected from the jugular vein before and 1, 2, 3, 4, 6, 8, 15, 30 and 60 min after IN lidocaine application, centrifuged immediately after clotting and serum was stored at −20 °C until analysis. Sera were analyzed for lidocaine concentrations by a fluorescence polarization immunoassay technique using a TDx/TDxFLx kit (TDx/TDxFLx Lidocaine assay; Abbott Laboratories, Abbott Park, IL, USA). The sensitivity of this assay permits measurements of serum concentrations as low as 0.1 μg/mL.

The concentration–time curves of lidocaine in serum were adjusted to the data sets via nonlinear iterative least-square regression analysis. Curve modelling was performed using the two-compartment open pharmacokinetic model with the program WinNonlin (version 1.5, Scientific Consulting, Mountain View, CA, USA). The following parameters were calculated: area under the concentration curve from 0 to 60 min ($AUC_{0-60\ min}$) using the linear trapezoidal rule, maximum observed serum drug concentration (C_{max}), time after lidocaine administration at which C_{max} was observed (T_{max}), absorption half-life ($t_{1/2a}$), distribution half-life ($t_{1/2\alpha}$) and elimination half-life ($t_{1/2\beta}$).

Statistical analysis was performed with SPSS 14.0 (SPSS Ltd., Chicago, IL, USA). To compare observed frequencies chi-square-tests with Yates-correction were performed. Main effects and the

interaction of groups and time points were calculated with an ANOVA for repeated measures, using the two groups as a grouping factor and time points as within factor. Significance level was set at 0.05.

Rhinotracheobronchoscopy was possible in all cows at both occasions. None of the cows of the lidocaine group showed severe changes in behavior. One animal showed reactions rated as medium and two cows showed no changes. In the control group the reactions of three animals were rated as severe. Two animals showed reactions rated as medium and three cattle showed mild changes. None of the control animals was rated as showing no behavioral changes. Overall there were significantly less defence reactions observed in cattle treated with lidocaine ($x^2 = 4.27$; $P = 0.039$). Insertion of the endoscope into the trachea was easy to perform in cattle treated with lidocaine IN. In three cattle insertion was successful at the first attempt. In four animals up to five attempts and in one animal up to 10 attempts were needed. In the control group frequent swallowing often prevented easy insertion of the endoscope through the larynx. In none of these animals insertion was possible on the first, second or third attempt. Up to five attempts were needed in three animals, up to 10 attempts in two cows, up to 15 attempts in two cattle, and in one animal it took more than 15 attempts. The difference in the number of attempts of insertion between the two groups was statistically significant ($x^2 = 7.11$; $P = 0.029$). When the endoscope was moved to the tracheal bifurcation no behavioral changes were observed in all but three animals: one cow of the lidocaine and two cows of the control group showed mild reactions.

Animals did not show cardiovascular reactions leading to significant changes in heart rate (HR) or mean arterial blood pressure (MABP) in the first 8 min after IN lidocaine administration. During rhinotracheobronchoscopy animals of both groups showed an increase in HR rising from mean baseline values of 81.88 ± 17.65 beats/min (lidocaine group) and 80.88 ± 21.64 beats/min (control group) to a maximum of 93.38 ± 13.68 beats/min and 91.5 ± 16.2 beats/min, respectively. The increase in HR during the procedure was not significantly different between the groups. In conformance with these findings, MABP slightly increased during rhinotracheobronchoscopy in both groups. No statistically significant
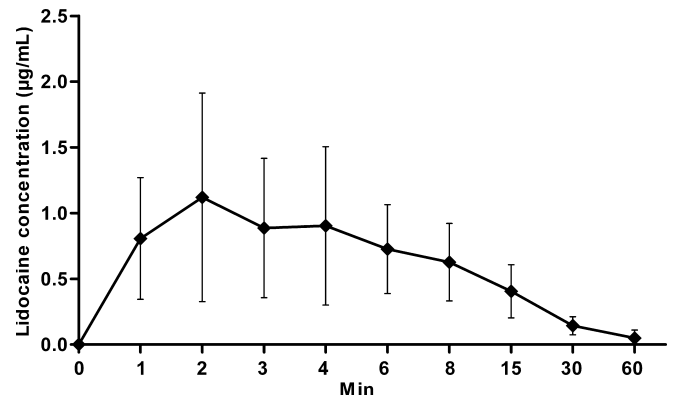

Fig. 1. Venous lidocaine serum concentration (mean ± SD) over 60 min following IN application of 1.5 mg/kg BW.

difference was observed between the groups. Mean baseline values for animals in the lidocaine and the control group were 143.38 ± 15.99 mm Hg and 142.75 ± 19.08 mm Hg rising to a maximum of 161.87 ± 11.13 mm Hg and 161.38 ± 23.24 mm Hg, respectively.

Absence of lidocaine toxicity in terms of cardiovascular reactions correlated with low blood concentrations in all animals measured for up to 60 min after IN application (Fig. 1). Two animals of the lidocaine group were excluded from further pharmacokinetic analysis due to problems during blood sampling. In the six cows appraised, intranasal lidocaine absorption was fast ($t_{1/2a}$: 2.07 ± 1.34 min) leading to mean maximum concentrations of 1.21 ± 0.73 μg/mL about 2 min after administration. Short mean $t_{1/2\alpha}$ and $t_{1/2\beta}$ of 1.05 ± 0.62 and 14.4 ± 9.02 min, respectively, was observed corresponding to a mean $AUC_{0–60 \text{ min}}$ of 16.88 ± 7.01 μg·min/mL (Table 1). Sixty minutes after IN application, lidocaine serum concentration was below 150 ng/mL.

Unlike in the United States of America and other countries (e.g. Canada, Switzerland), where lidocaine containing medicinal products labelled for the use in cattle are on the market, off-label use is necessary when using lidocaine for treatment of cattle in an EU Member State.

Overall we conclude from the results presented that lidocaine is a safe and effective topical anesthetic for endoscopic

Table 1. Pharmacokinetics of intranasally administered lidocaine

Animal	Dosis (mg/kg)	BW (kg)	$AUC_{0–60 \text{ min}}$ (μg·min/mL)	C_{max} (μg/mL)	T_{max} (min)	$t_{1/2a}$ (min)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)
# 1	1.50	705	13.31	0.65	3.27	2.85	1.34	17.11
# 2	1.50	681	29.77	2.61	2.23	1.22	1.16	7.45
# 3	1.50	775	11.92	0.78	1.63	0.49	0.28	13.18
# 4	1.50	868	20.31	0.84	2.21	3.71	0.57	31.24
# 5	1.50	218	13.25	1.35	2.05	0.94	0.93	7.99
# 6	1.50	456	12.74	1.04	2.08	3.18	2.03	9.41
Mean ± SD	1.50 ± 0	617 ± 239	16.88 ± 7.01	1.21 ± 0.73	2.24 ± 0.55	2.07 ± 1.34	1.05 ± 0.62	14.4 ± 9.02

$AUC_{0–60 \text{ min}}$, area under the concentration curve from 0 to 60 min; C_{max}, maximum observed serum drug concentration; T_{max}, time after lidocaine administration at which C_{max} was observed; $t_{1/2a}$, absorption half-life; $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life.

procedures of the upper respiratory tract in cattle when given IN at a dosage of 1.5 mg/kg.

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