Title: A NEW MODEL FOR EVALUATING LIDOCAINE INDUCED SEIZURE ACTIVITY

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Introduction: Lidocaine induced seizure activity (LISA) in the clinical setting has been well documented. However, our understanding of the pharmacologic mechanism and the dependency of LISA upon dose and plasma concentration during the perioperative period is obscured by many variables that can alter the disposition of this drug. In order to better study the influence of general anesthetics and to evaluate comparative anticonvulsant actions of other drugs, a new model was developed to test LISA.

Method: Ten mongrel dogs, weighing 17 to 27 kg. were anesthetized with 5 mg/kg. of IV Ketamine and intubation facilitated with pancuronium. Ventilation was controlled with a Siemens 900C ventilator to maintain an end-tidal CO_2 between 6 and 7%. Anesthesia was maintained with 75% N_2O:O_2 and pancuronium. The right common carotid artery (CCA) and internal jugular vein (IJV), femoral artery and femoral vein were cannulated. Arterial and venous pressures, EKG, end-tidal CO_2 and esophageal temperature were monitored continuously, as were serial blood gases, pH and urine output. D_5RL was infused intravenously at 5-7 ml/kg/hr. Care was taken to keep the dogs normal physiologically. EEG was monitored via three symmetrically placed pairs of metal cup electrodes over the frontal, parietal and occipital regions of the scalp. All recordings were made on a model 7 Grass polygraph. Lidocaine was infused into the CCA as bolus injection or as continuous infusion using a Harvard pump. Five dogs received lidocaine at 123.4 mg/min until electrographic seizure activity (SA) was observed. Upon cessation of each seizure, the initial lidocaine dose was readministered until five periods of SA were induced. Blood samples from IJV drawn at the initiation and cessation of SA were analyzed for lidocaine plasma concentration using the EMIT assay system.[1] The relationship between JV lidocaine concentration and SA was determined from concurrent EEG activity and lidocaine concentrations in the group administered bolus lidocaine. The lidocaine infusion rates required to produce plasma lidocaine concentrations above the seizure threshold were based on the mean calculated clearance. Subsequently, lidocaine was infused continuously at an average rate of 1.6 mg/kg/min in 5 dogs. Infusion settings were selected to maintain the lowest lidocaine concentration which produced sustained SA. Statistical analysis were performed using analysis of variance and Newman-Keuls range tests.

Results: With intermittent bolus injections, the dose of lidocaine required to initiate SA was 26.15 ± 2.1 mg/kg (mean ± SE) and ranged from 13.0 to 39.0 mg/kg. The duration of LISA increased with each repeated lidocaine dose from 3.3 ± 1.6 min to 33.9 ± 6.3 min ($P<0.01$) from the first to the fifth dose respectively (Fig 1). The average increase in LISA duration shortened when each successive dose of lidocaine was compared. The plasma lidocaine concentration at the end of SA decreased with each successive dose from 142 ± 51.1 to 45.7 ± 9.0 µg/ml ($P<0.05$) from the first to the fifth dose respectively (Fig 2). In contrast, the total duration of LISA in the continuous infusion method was an average of 122.8 min. After discontinuation of lidocaine infusion SA lasted an average of 27.5 minutes. There was no significant change in BP and heart rate.

Discussion & Conclusion: A new model of LISA was developed using two techniques, repeat bolus and continuous infusion, producing intermittent and continuous SA respectively. Administration into the CCA in dogs produced LISA before cardiovascular depression occurred. Although the dose required to initiate SA is similar to that reported with IV administration, LISA is of considerably longer duration using our seizure model. This permits qualitative and quantitative assessment of SA. In order to assess the effectiveness of anticonvulsants in LISA, quantitative data is necessary with multiple administrations. This obviates errors incurred by a single dose administration. The bolus method thus permits quantitative assessment of an anticonvulsant without producing other systemic effects which would obscure the results. Intermittent SA is also quantitatively related to dose number (Fig 1) and allows evaluation of the dose dependent effects. The continuous infusion method allows evaluation of prolonged SA with lidocaine concentration just above the seizure threshold. Both methods should be valuable in elucidating the possible role of anesthetic agents, other frequently used drugs, and metabolic, electrolyte, and acid base disturbances that may influence the CNS toxicity of lidocaine and other commonly used local anesthetics.

References:

1. Pape BE, Whiting R, Parker KM, Mitra R: Enzyme immuno assay and gas-liquid chromatography compared for determination of lidocaine in serum. Clin Chem 24:2020-2022, 1978.