THE COMPARATIVE ANTIARRHYTHMIC EFFECTS OF MEPIVACAINE AND LIGNOCAINE

BY

R. B. BOETTNER, R. W. DUNBAR, J. V. HALEY AND D. H. MORROW

SUMMARY

A comparison of the antiarrhythmic effects of 2 mg/kg of mepivacaine and lignocaine, as measured by elevations in the end-diastolic ventricular stimulation threshold (EDVST), was made in open-chest dogs. Both mepivacaine and lignocaine increased the EDVST significantly. The peak elevation of EDVST occurred within 2 minutes after injection and averaged 0.013 mA (13 μA) with mepivacaine and 0.022 mA (22 μA) with lignocaine. The greater early response to lignocaine as compared with mepivacaine was significant. After 4 minutes the rate of decreasing effect was approximately 0.001 mA/min for both mepivacaine and lignocaine. The studies provide new evidence demonstrating the antiarrhythmic properties of mepivacaine and support the continued evaluation of related compounds in the search for better antiarrhythmic agents.

Ventricular arrhythmias occurring during the administration of anaesthesia are of continued concern. Of particular importance are those alterations in cardiac rhythm resulting in severe haemodynamic deterioration and/or progressing to ventricular tachycardia or fibrillation.

A wide variety of agents including beta blockers, such as propranolol, alpha blockers and beta stimulators, such as phentolamine, as well as such diverse agents as bretylium, phenytoin, quinidine, procaine amide and numerous local anaesthetics have been shown to have antiarrhythmic properties. Even the general anaesthetics cyclopropane and halothane, whose pharmacological effects on the cardiovascular system are poles apart generally, exhibit antiarrhythmic properties under certain conditions.

No drug is ideally suited for the therapeutic management of every ventricular arrhythmia. Intravenous lignocaine, 1–2 mg/kg, is the most commonly employed pharmacological agent for treating dysrhythmias of ventricular origin. The popularity of this drug is based on the early work of Southworth and associates (1950), and the later findings of Harrison, Sprouse and Morrow (1963), who demonstrated reliable antiarrhythmic effects without decrements in ventricular contractile force and systemic arterial pressure. However, the half-life of lignocaine administered as a single bolus is only 20 minutes (Ettinger et al., 1967) and the blood level (2–5 μg/ml) necessary to prevent arrhythmias when it is given as a constant infusion is close to the toxic level of 5–9 μg/ml (Gianelly et al., 1967). Because of this we have undertaken studies to determine if other local anaesthetics might be superior to lignocaine as antiarrhythmic agents.

Mepivacaine, a local anaesthetic resembling lignocaine chemically and possessing similar pharmacological properties, is equipotent on a milligram per milligram basis and has somewhat greater duration of sensory analgesia than lignocaine (Ulfendahl, 1957). In addition, Foldes and associates (1965), on the basis of intravenous infusion studies, found mepivacaine to be less toxic than lignocaine. A comparison of the antiarrhythmic effects of mepivacaine and lignocaine, as measured by their ability to protect the heart from electrically induced premature ventricular contractions, is the subject of this report.

METHODS

The studies were performed in fourteen unpremedicated, open-chest dogs anaesthetized with an intravenous injection of pentobarbitone 30 mg/kg. Endotracheal intubation was performed and

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ventilation was controlled with an air-oxygen mixture delivered from a volume-limited ventilator. Systemic arterial pressure was transduced from a polyethylene catheter in the femoral artery. A femoral vein was cannulated for injection of the test drugs. The stimulating electrode was sewn into the right ventricle. Lead II of the electrocardiogram and the systemic arterial pressure were continuously recorded. Heparinized arterial blood samples were drawn at 10-minute intervals during each experiment for the polarographic determination of Po₃, Pco₂, and pH. The minute volume of ventilation was adjusted as required to maintain pH at approximately 7.4 units. Rectal temperature was maintained between 37 and 39°C with the aid of radiant heat.

Measurements of the antiarrhythmic effects of lignocaine and mepivacaine were performed utilizing a modification of the method of Galindo and Sprouse (1962) for determining the end-diastolic ventricular stimulation threshold (EDVST). Briefly, this technique involves determination of the milliamperes of current, applied directly to the ventricle through epicardial electrodes, required to produce ventricular extra systolic beats when delivered at various intervals.

![Diagram](image)

**Fig. 1**

Electronic circuit for determining EDVST.

A standard vacuum tube electrocardiograph was modified to take a 20 V positive R wave pulse from a pen driver tube cathode and feed it to the single-shot synchronizer.

Activation of the stimulus button on the synchronizer caused a single trigger pulse, synchronized with the first following R wave, to be sent to the model S4GR Grass Stimulator. The circuit was then “locked out” until the next determination was made.

The pulse from the synchronizer triggered the Grass Stimulator to generate a stimulus of 7.1 V, lasting 2 m.sec and delayed so that it occurred during late diastole. The stimulus then went through the stimulus isolator to the constant current generator where it was modified and delivered to the right ventricle via the epicardial electrodes.

The constant current pulse generator,* a solid state, battery-operated unit, furnished feedback regulated current pulses from 1 μA to 30 mA at varying voltages up to 120 V, depending on the load impedance. The current delivered was known to within ±1 per cent of the true current. The variation at any one setting on repeated measure was less than 0.1 per cent.

The oscilloscope sweep was triggered by every second R wave independent of the stimulation circuit. The e.c.g. and stimulus artefact were monitored on the oscilloscope, allowing for a continuous visual check of the timing of the stimulus and of the presence of premature beats if any were elicited.

* Designed by Irvine P. Stapp jr., Consultant Engineer, and built by Research Engineering, University of Kentucky Medical Center.
in the cardiac cycle. Figure 1 shows in diagrammatic form the electronic circuit used in this study. The stimulation threshold was determined by starting with a stimulus above the anticipated threshold and applying stimuli of decreasing intensity until the ventricle no longer responded. The least stimulus which elicited a premature ventricular contraction was taken as the threshold stimulus. Stimulation during the T wave was avoided because of the hazard of ventricular fibrillation. A few stimuli applied at the start of the P wave produced typical fusion beats. Preliminary studies with the drugs indicated that they elevated the stimulation threshold (an antiarrhythmic effect) but did not change the shape of the strength-interval curve (fig. 2). Because of the repeated measures employed in the present studies, only changes in the plateau phase of late diastole, approximately 60 per cent of the preceding R-R' interval, were determined. No attempt was made to determine the effect on the absolute or relative refractory periods.

In order to study both mepivacaine and lignocaine a latin square experimental design was used (Weiner, 1962; Cochran and Cox, 1957). This permitted evaluation of 2 mg/kg of each drug in each animal. Baseline EDVST determinations were obtained during a 30-40 min control period during which time heart rate, blood pressure, anaesthetic state and ventilation were allowed to stabilize. One of the local anaesthetics was then rapidly injected. The EDVST was determined 1, 2, 3, 4, 5, 6, 10, 15, 20, 25 and 30 minutes after the injection. After the drug effect had dissipated and the measurements returned to control levels the other drug was rapidly injected and the measurements repeated. Seven dogs received mepivacaine first and seven lignocaine first. The data were analyzed for statistical significance by a latin square design with repeated measures.

RESULTS

Both mepivacaine and lignocaine elevated the EDVST significantly (P<0.01). Mepivacaine raised the stimulation threshold 0.016 mA at 1 minute, 0.013 mA at 2 minutes, 0.012 mA at 3 minutes and 0.011 mA at 4 minutes, while lignocaine raised the threshold 0.017 mA at 1 minute, 0.022 mA at 2 minutes, 0.021 mA at 3 minutes and 0.012 mA at 4 minutes. Beyond 4 minutes the rate of decreasing effect was approximately 0.001 mA/minute for both drugs (fig. 3). Although a point-by-point comparison of differences was not made, the slightly greater early
End-diastolic ventricular stimulation threshold (milliamperes).

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T₀ = Control values; T₁, T₂ etc., values at 1, 2 etc. minutes after injection of drug.
I = Sequence of lignocaine followed by mepivacaine.
II = Sequence of mepivacaine followed by lignocaine.
X₀ = Mean of combined lignocaine data.
Xₘ = Mean of combined mepivacaine data.
Xₛ₀ = Mean of measurements following injection of first drug.
Xₛ₁ = Mean of measurements following injection of second drug.

(First 4 minutes) response to lignocaine was significant (P<0.05). The slightly higher baseline for lignocaine may be related to persistence of mepivacaine effect when mepivacaine was injected before lignocaine—the lignocaine control for this sequence (0.1049 mA) was considerably higher than the other controls.

The experimental data are shown in table I.

COMMENT

These studies provide new evidence demonstrating the antiarrhythmic properties of mepivacaine. Although the magnitude and duration of its effect on the end-diastolic ventricular stimulation threshold was less than the response to lignocaine, the results obtained warrant the continued evaluation of related local anaesthetic compounds for their potential usefulness in the clinical management of cardiac arrhythmias which may occur during anaesthesia or outside the operating theatre.

The elevation of the EDVST produced by lignocaine confirms the earlier studies of Galindo and Sprouse (1962), and reaffirms the value of the EDVST as a reliable method for quantitating the antiarrhythmic properties of various agents.

Of additional potential importance in this regard is an appraisal of the effect of mepivacaine and related drugs on digitalis-induced arrhythmias and those resulting from acute coronary artery occlusion. Each of these latter considerations is currently under investigation in this laboratory.

REFERENCES

COMPARATIVE EFFECTS OF MEPIVACAINE AND LIGNOCAINE


LES EFFETS ANTI-ARRHYTHMIQUES COMPARATIFS DE MEPIVACAINE ET LIGNOCAINE

SOMMAIRE
Une comparaison des effets anti-arrhythmiques de 2 mg/kg mepivacaine et lignocaine, mesurés par l'élevation du seuil de stimulation ventriculaire diastolique terminal (EDVST) a été faite chez des chiens à thorax ouvert. Mepivacaine et lignocaine ont tous les deux significativement élevé le EDVST. L'élevation maximale se manifeste deux minutes après l'injection et atteint en moyenne 0,013 mA (13 µA) avec mepivacaine et 0,022 mA (22 µA) avec lignocaine. La réaction précocé plus marqué à la lignocaine, comparativement à mepivacaine, fut significative. Le taux d'effet réduisant fut circa 0,001 mA/min. après 4 minutes, pour mepivacaine et lignocaine. Ces études apportent une nouvelle preuve, démontrant les propriétés anti-arrhythmiques de mepivacaine et constituant une raison valable de poursuivre l'évaluation de substances apparentées afin de trouver de meilleurs agents anti-arrhythmiques.

UNTERSUCHUNGEN ÜBER DIE ANTI-ARRHYTHMISCHE WIRKUNGEN VON MEPIVACAINE UND LIGNOCAINE

ZUSAMMENFASSUNG
Bei Hunden wurde die Brusthöhle geöffnet. Die anti-arrhythmische Wirkung von 2 mg/kg Mepivacain und Lignocain wurde durch die Erhöhung der end-diastolischen ventriculären Reizschwelle bestimmt. Sowohl Mepivacain als auch Lignocain erhöhten diese Reizschwelle (EDCST) bedeutend. Die maximale Erhöhung der EDVST stellte sich innerhalb von 2 Minuten nach der Injektion ein und betrug im Durchschnitt 0,013 mA (13 mikro A) bei Mepivacain und 0,022 mA (22 mikro A) bei Lignocain. Der frühere Wirkungseintritt von Lignocain verglichen mit Mepivacain war eindrucksvoll. Nach 4 Minuten betrug die Abklingrate ungefähr 0,001 mA/min. für beide Substanzen. Die experimentellen Untersuchungen beweisen erneut die antiarrhythmischen Eigenschaften von Mepivacain und rechtfertigen die Auswertung von Substanzen mit verwandten Eigenschaften auf der Suche nach besseren antiarrhythmischen Mitteln.

BOOK REVIEW


The Biennial Western Conference on Anesthesiology has been an outstanding event in the United States since 1949, and it has now achieved a massive reputation as a forum on which either existing knowledge is expounded with clarity and scholarship, or new material is presented for the first time. This book is an edited account of the Conference in 1967 and fully lives up to this reputation. The list of speakers is impressive while the subject matter shows the considerable interest of anaesthetists in fundamental pharmacological mechanisms. Ellis Cohen of San Francisco, for example, describes with clarity the now classic experiments of Water and Lilli and demonstrates the value of this method in clarifying the site of action of curare-like drugs. Cohen also describes elsewhere in this volume the use of radio isotopes in the study of anaesthetic drug distribution and metabolism. He is brief, concise, and informative, and shows clearly his interest and mastery of this subject. J. F. Nunn, at the time of the Conference, of Leeds, writes on oxygen and carbon dioxide in his usual clear and authoritative manner. He discusses the toxicity of oxygen in relationship to its use as a therapeutic agent. His other contribution on carbon dioxide follows orthodox lines but is none the less extremely readable and clear. Of the other authors, Greene of Yale University considers both the metabolic pathways involving anaesthetic drugs, and drug interaction. He discusses in some detail the importance of enzyme induction to the anaesthetist, and both the possible good and bad effects of this phenomenon.

This collection of papers is quite outstanding in its ability to inform the clinician on matters exceedingly relevant to his work, but which lie perhaps a little outside his usual sphere of comprehension. The diagrams are clear while the binding and printing are of a high standard. This book is recommended to all anaesthetists and indeed other clinicians who wish to keep a little further abreast of this subject than is provided by the usual books and journals.

W. W. Mushin