LIDOCAINE IN EXPERIMENTAL VENTRICULAR FIBRILLATION:

ENDOTRACHEAL vs INTRAVENOUS USE

by

LINDA KATHLEEN BROWN

B.S.(Pharm.), The University of British Columbia (1977)

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

Division of Pharmacology and Toxicology
of the Faculty of Pharmaceutical Sciences

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

APRIL 1982

© Linda Kathleen Brown, 1982
In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of FACULTY OF PHARMACEUTICAL SCIENCES

The University of British Columbia
1956 Main Mall
Vancouver, Canada
V6T 1Y3

Date April 27/82
ABSTRACT

The endotracheal (ET) route for the administration of selected drugs has been proposed as an effective alternate route of drug administration during emergency situations when an intravenous (IV) line cannot be established. Lidocaine may be beneficial in the treatment of ventricular fibrillation (VF) resulting from acute myocardial infarction, although this hypothesis has not been confirmed in the literature. The efficacy of lidocaine in the treatment of ventricular fibrillation due to acute coronary artery ligation was examined, as well as the use of the endotracheal route as an alternative to IV injection.

Rabbits were anesthetized with sodium pentobarbital or halothane, intubated with an endotracheal tube, and animals receiving pentobarbital were mechanically respired. Ventricular fibrillation was produced by occlusion of the left circumflex coronary artery, or by subsequent reperfusion of ischemic myocardium.

Endotracheal administration of 2mg/Kg lidocaine (2mg/ml in normal saline) resulted in lower peak plasma lidocaine concentrations initially compared with IV injection, but more sustained levels in the therapeutic range for lidocaine (p<0.05). Administration of lidocaine either IV or ET during ventricular fibrillation resulted in a significant increase (p<0.05) in plasma lidocaine concentrations during the first minute compared with controls. During ventricular fibrillation there was no significant difference between plasma lidocaine levels following IV or ET administration.
Administration of lidocaine 2mg/Kg endotracheally (in normal saline) during VF resulted in a significant decrease in the duration of fibrillation compared with untreated and normal saline controls (p < 0.001).
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>vii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td></td>
</tr>
<tr>
<td>1. The Endotracheal Route for Lidocaine Administration</td>
<td>1</td>
</tr>
<tr>
<td>a) The Rationale for Endotracheal Drug Administration</td>
<td>1</td>
</tr>
<tr>
<td>b) Endotracheal Absorption of Drugs</td>
<td>3</td>
</tr>
<tr>
<td>2. The Antifibrillatory Efficacy of Lidocaine</td>
<td>11</td>
</tr>
<tr>
<td>a) Overview</td>
<td>11</td>
</tr>
<tr>
<td>b) Mechanisms of Arrhythmogenesis</td>
<td>13</td>
</tr>
<tr>
<td>c) Electrophysiological Effects of Lidocaine in Normal and Ischemic</td>
<td>19</td>
</tr>
<tr>
<td>Myocardium</td>
<td></td>
</tr>
<tr>
<td>d) Effects of Lidocaine Seen Clinically</td>
<td>22</td>
</tr>
<tr>
<td>3. Rationale and Purpose of the Present Study</td>
<td>25</td>
</tr>
<tr>
<td>MATERIALS AND METHODS</td>
<td></td>
</tr>
<tr>
<td>1. Plasma Lidocaine Level Studies</td>
<td>28</td>
</tr>
<tr>
<td>a) Animal Experiments</td>
<td>28</td>
</tr>
<tr>
<td>b) Lidocaine Assay</td>
<td>30</td>
</tr>
<tr>
<td>2. Coronary Artery Ligation/Ventricular Fibrillation Studies</td>
<td>34</td>
</tr>
<tr>
<td>3. Analyses and Statistics</td>
<td>41</td>
</tr>
<tr>
<td>4. Drugs and Chemicals</td>
<td>42</td>
</tr>
<tr>
<td>RESULTS</td>
<td></td>
</tr>
<tr>
<td>1. Plasma Lidocaine Level Studies</td>
<td>43</td>
</tr>
<tr>
<td>a) Endotracheal vs Intravenous</td>
<td>43</td>
</tr>
<tr>
<td>Lidocaine in Distilled Water</td>
<td></td>
</tr>
<tr>
<td>During Halothane Anesthesia</td>
<td></td>
</tr>
<tr>
<td>b) The Effect of Pentobarbital or</td>
<td>43</td>
</tr>
<tr>
<td>Halothane Anesthesia on the Endotracheal Absorption of Lidocaine</td>
<td></td>
</tr>
<tr>
<td>in Distilled Water</td>
<td></td>
</tr>
</tbody>
</table>
c) Plasma Lidocaine Levels Following Endotracheal Instillation of Lidocaine in Either Distilled Water or Normal Saline During Pentobarbital Anesthesia........................................... 49

d) Absorption of Lidocaine Following Endotracheal Administration of Lidocaine in Normal Saline During Closed Chest Controls, Open Chest Controls, and Ventricular Fibrillation......... 56

e) Plasma Lidocaine Levels Following Intravenous Injection of Lidocaine in Normal Saline During Open Chest Controls and Ventricular Fibrillation............... 60

f) Plasma Lidocaine Levels Following Either Intravenous Injection or Endotracheal Instillation of Lidocaine to Open Chest Controls................................. 64

g) Plasma Lidocaine Levels Following Endotracheal Instillation or Intravenous Injection of Lidocaine During Ventricular Fibrillation................................. 69

h) Plasma Lidocaine Levels Following Endotracheal Administration of Lidocaine 2mg/Kg in Distilled Water Followed by 1mg/Kg Every Five Minutes........... 74

2. Antifibrillatory Efficacy of Endotracheal Lidocaine........................................... 74

a) The Effect of Endotracheal Lidocaine on Duration of Ventricular Fibrillation...... 74

b) Tendency for Ventricular Fibrillation: Three Classifications............................... 80

c) Occlusion vs Reperfusion Ventricular Fibrillation............................................... 89

DISCUSSION.................................................................................................................. 96

REFERENCES.................................................................................................................. 108
LIST OF TABLES

Table I. Calculated first-order rate constants and plasma half-lives for intravenous injection and endotracheal instillation of lidocaine in distilled water ...........................................48

Table II. Calculated first-order rate constants and plasma half-lives for endotracheal instillation of lidocaine in distilled water and normal saline ...........................................57

Table III. Area under the curve, fraction of dose absorbed and clearance of lidocaine following intravenous or endotracheal administration during either ventricular fibrillation or open chest controls ...........................................63

Table IV. Duration of ventricular fibrillation following endotracheal administration of lidocaine, normal saline, or no treatment ...........................................78

Table V. Percent occlusion of right ventricular, left ventricular, and total ventricular mass in untreated controls, normal saline controls, and in lidocaine-treated animals ...........................................79

Table VI. Duration and frequency of ventricular fibrillation in short ventricular fibrillation and long ventricular fibrillation categories ...........................................81

Table VII. Comparison of percent occlusion of left ventricular, right ventricular, and total ventricular mass with tendency to fibrillate ...........................................87

Table VIII. Comparison of the incidence of ventricular arrhythmias following coronary artery ligation with tendency to fibrillate ...........................................88

Table IX. Comparison of percent occlusion of left ventricular, right ventricular, and total ventricular mass in ventricular fibrillation occurring during an occlusion or reperfusion phase ...........................................95
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Principle of homogeneous enzyme immunoassay</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>Schematic representation of the position of the ligating suture in the heart</td>
<td>36</td>
</tr>
<tr>
<td>2a</td>
<td>Cross-sectional representation of the position of the ligating suture</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>Plasma lidocaine levels following endotracheal instillation or intravenous injection of lidocaine in distilled water during halothane anesthesia</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Log plasma lidocaine concentration following endotracheal instillation or intravenous injection of lidocaine in distilled water during halothane anesthesia</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>Plasma lidocaine concentrations following endotracheal instillation of lidocaine in distilled water during either halothane or pentobarbital anesthesia</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Plasma lidocaine concentrations following endotracheal instillation of lidocaine in either normal saline or distilled water</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>Log plasma lidocaine concentration vs time following endotracheal instillation of lidocaine in either normal saline or distilled water</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>Plasma lidocaine levels following endotracheal administration of lidocaine in normal saline during ventricular fibrillation with cardiac massage, open chest controls and closed chest controls</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>Plasma lidocaine levels following intravenous injection of lidocaine in normal saline during ventricular fibrillation and open chest controls</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>Plasma lidocaine levels following endotracheal instillation of lidocaine in normal saline or intravenous injection of lidocaine in normal saline</td>
<td>66</td>
</tr>
<tr>
<td>11</td>
<td>Log plasma lidocaine concentrations vs time following intravenous injection of lidocaine in normal saline or endotracheal instillation of lidocaine in normal saline</td>
<td>68</td>
</tr>
</tbody>
</table>
Figure 12. Plasma lidocaine levels observed following either intravenous injection of lidocaine in normal saline or endotracheal instillation of lidocaine in normal saline during ventricular fibrillation with cardiac massage ...............71

Figure 13. Log plasma lidocaine concentrations vs time following either intravenous injection of lidocaine in normal saline or endotracheal instillation of lidocaine in normal saline .....................73

Figure 14. Plasma lidocaine levels following endotracheal administration of a 'loading dose' followed by a 'maintenance dose' every 5 minutes ............................................76

Figure 15. Blood pressure and ECG recordings during ventricular fibrillation with manual heart massage ......................................................84

Figure 16. Blood pressure and ECG recordings during a ventricular fibrillation episode which lasted 25 seconds and terminated spontaneously .................................................86

Figure 17. Comparison of blood pressure before and for 10 minutes after coronary artery ligation in animals in which no ventricular fibrillation, short ventricular fibrillation or long ventricular fibrillation occurred ........91

Figure 18. Changes in heart rate following coronary artery occlusion in No VF, Short VF and Long VF experiments .................................................93
ACKNOWLEDGEMENTS

I would like to express my gratitude to Dr. Jack Diamond for his guidance and support, and for the opportunity to pursue this project.

I would especially like to thank Pamela Livingstone, to whom I owe a great deal of thanks for her assistance both in the lab and in the preparation of this manuscript.

My sincere gratitude also goes to Dr. David Hunt and Dr. Les Vertesi, without whose enthusiasm and encouragement this project may never have been started.

I would also like to thank Jo-anne Maxey, Evelyn Chu and Lynn Pollock for their assistance.

This work was supported by the British Columbia Health Care Research Foundation and the British Columbia Heart Foundation, whose assistance is greatly appreciated.

I would also like to express my appreciation to Syva Diagnostics Ltd. for their technical assistance.
INTRODUCTION

1. The Endotracheal Route for Lidocaine Administration

   a) The Rationale for Endotracheal Drug Administration

   Advanced pre-hospital care has expanded rapidly throughout North America and Europe in the past ten years (Cobb et al, 1975; Schaffer and Cobb, 1975). In British Columbia, Advanced Life Support (ALS) personnel have been providing emergency pre-hospital care in selected communities since 1975 (Vertesi, 1978). On-site evaluation and treatment of many medical and surgical emergencies are performed by highly trained ambulance personnel, employees of the Emergency Health Services Commission of British Columbia. These teams are able to establish intravenous catheters, perform endotracheal intubation, and administer direct-current countershock and selected drugs during cardiac arrest and other life-threatening emergencies.

   The subject of drug administration via appropriate and efficacious routes during these situations has only been addressed recently. Administration of pharmacologic agents during cardiac arrest has most frequently been accomplished via the peripheral intravenous (IV) route, since peripheral IV cannulas can usually be rapidly and safely established and provide direct access of the drug to the patient's circulation (American Heart Association, 1980). More recently, it has been shown that during cardiopulmonary resusitation (CPR) in humans, injection of Cardio-Green® dye via peripheral IV resulted in reduced arterial concentrations and delayed appearance of peak
levels compared with central injection via the subclavian vein (Kuhn et al, 1981). Other recent work in dogs (Barsan et al, 1981) showed that central IV injection of lidocaine during CPR resulted in higher peak levels of the drug than peripheral IV injection.

A delayed appearance of injected agents in the central circulation during cardiac arrest may reflect slow venous return and therefore may lead to a delayed response to the drug. This particular aspect of IV drug administration has not been extensively investigated, and further work in this area is necessary before conclusive statements may be made. At the present time, the peripheral IV route is by far the most common route of drug administration both in emergency pre-hospital care and in the emergency room (American Heart Association, 1980).

The use of the peripheral IV route for drug administration may not always be possible during cardiac arrest. During CPR, intense peripheral vascular constriction results in poor peripheral perfusion, and insertion of an IV catheter may technically be difficult or at times impossible (Greenberg, M. et al, 1979).

Statistics from the Advanced Life Support Program in British Columbia (Emergency Health Services Academy, 1982) show that in a series of 1198 patients, 68% of IV lines were established upon the first attempt, 87% after the second attempt, and 95% were successful following the third attempt. Since each additional attempt at starting an IV is time consuming and since the rapidity with which drug therapy is instituted is critical, alternate routes of drug administration should be considered.
Intravenous injection via central catheter could provide a reliable method of drug delivery during cardiovascular collapse. During pre-hospital cardiac arrest, however, insertion of a central IV cannula either via the subclavian or external jugular vein may also be difficult, and at times unsafe. This procedure is associated with a risk of pneumothorax or perforation of the carotid artery, and is best performed under well-lit controlled conditions (American Heart Association, 1980).

Intracardiac (IC) injection may also be used for administering drugs during cardiac arrest, however, this technique is associated with the risk of pneumothorax, hemothorax, pericardial tamponade, myocardial laceration and coronary artery laceration (Goldberg, 1974). The intracardiac route for drug administration is therefore advocated when no other methods are available or appropriate.

The endotracheal route for selected drug administration has been proposed as an effective alternate route when a peripheral IV line cannot be quickly established and prolonged attempts to start an IV may delay definitive treatment unnecessarily (Redding et al, 1967; Elam, 1977; Roberts et al, 1978; Greenberg et al, 1979b; Roberts et al, 1979a; Roberts et al, 1979b). Endotracheal intubation is usually performed routinely, even before attempting to establish an IV line, and would be available for administration of drugs if satisfactory absorption of drugs via that route could be documented.

b) **Endotracheal Absorption of Drugs**
Absorption of certain drugs from the trachea, bronchi, bronchioles, and alveoli has been well documented (Redding et al, 1967; Elam, 1977; Greenberg et al, 1979)\(^b\). Epinephrine (adrenaline), isoproterenol, lidocaine and atropine are considered to be essential drugs in emergency cardiac care and it has been proposed that they may be effective when administered via the endotracheal route (Redding et al, 1967; Elam, 1977; Roberts et al, 1978; Greenberg et al, 1979\(^a\); Roberts et al, 1979\(^a\); Roberts et al, 1979\(^b\)).

Roberts et al (1978, 1979\(^a\)) compared the blood levels and pharmacologic effects obtained when epinephrine was given by either the intravenous or endotracheal route in anesthetized dogs. Endotracheal instillation was performed by introducing epinephrine diluted in 5 ml normal saline into an endotracheal tube, occluding the end of the tube for five seconds to prevent reflex coughing of the solution, and then performing five quick inflations of the lungs with an Ambubag\(^R\). Intravenous injections were performed into a peripheral leg vein. Maximum concentrations of epinephrine were achieved at 15 seconds following both IV injection and endotracheal (ET) instillation, although the peak level achieved via the IV route was approximately ten times that achieved with the ET route. The time course of epinephrine in the blood following ET instillation was found to differ from that following IV injection: at five minutes following IV injection, only 20% of the initial concentration of epinephrine could be found, whereas with the ET route at five minutes, 80% of the initial concentration remained. Similar results were obtained when the pharmacologic effects of
epinephrine were compared when the drug was given by the two routes.

These data suggest that in dogs, rapid absorption of epinephrine occurs from the lungs, trachea, and bronchi, following ET administration, and that the marked sustained elevation in blood levels following ET instillation may reflect some sort of depot, reservoir, or sustained release mechanism. Roberts et al (1979b) have subsequently reported the successful use of endotracheal epinephrine in two patients with cardiorespiratory collapse.

In 1967, Redding et al examined the effectiveness of epinephrine, given via different routes, in reversing hypoxia-induced cardiac arrest in dogs. The effects of the drug were compared when it was given by IV, intramuscular (IM), or intracardiac (IC) injection, or by endotracheal instillation. Endotracheal instillation was performed by giving epinephrine in 1 mL and 10 mL distilled water, or in 10 mL normal saline.

The results indicate that epinephrine was equally effective in restoring circulation when injected IV or when instilled via the ET route. The data further suggest that delivery of the drug is enhanced when it is diluted in water as compared with normal saline, since the mean time to return of circulation following epinephrine in water was significantly less than following epinephrine in saline. There was no difference between the time to return of circulation or number of dogs responding to 1 mg epinephrine given IV or ET (in 10 mL distilled water).

In 1977, Elam examined the intrapulmonary route for atropine, epinephrine, and lidocaine during hypoxia-induced
cardiac arrest in dogs. His results indicate that intrapulmonary instillation of the drugs through a catheter produced a more rapid and more sustained ECG response than IV administration via the femoral vein. Plasma levels of the drugs were not monitored, therefore therapeutic response, measured as ECG changes, was the only method used to determine onset and duration of action by both routes.

Absorption of local anesthetics from the trachea, bronchi, bronchioles and lungs was documented as early as 1958, when Campbell and Adriani reported significant absorption producing blood levels comparable to those attained by intravenous injection. The anesthetics studied were tetracaine, procaine, cocaine, and benzocaine. In contrast to later work, they found that blood levels attained were a function of total dose, and not of the concentration of solution used. They also determined that absorption was more rapid from the trachea than from the pharynx, and higher peak levels were attained when the animals (dogs) were in an upright position than in the prone position. This study was conducted to examine the possibility of systemic toxicity arising from the careless or improper use of local anesthetics in the upper respiratory tract.

In 1961, Bromage and Robson investigated the absorption of lidocaine into the blood following IV, IM, epidural, and endotracheal administration to anesthetized patients. Intravenous lidocaine was given to seven patients as an infusion (9.3 - 100 mg/min) to a total dose of 9.7 -16.3 mg/Kg. Systemic toxicity was manifested by an acute drop in blood pressure and decreased tidal volume. Convulsions followed these signs if the infusion was not terminated. Lidocaine was applied as a 4% spray
to the larynx and trachea prior to endotracheal intubation. Doses varied from 3.5 to 10.5 mg/Kg and were administered in divided amounts over 2-10 minutes. The rate of absorption varied widely, with peak blood concentrations reached between 5-25 minutes after administration.

The large variation in peak blood levels and rates of absorption demonstrated may be due to variation in dosage, site of administration, and duration of the application. As with intravenous administration, it seems likely that rapid endotracheal administration of a bolus amount would produce a more rapid and higher peak blood level than intermittent spraying over a ten minute period.

Since this investigation, many reports have focused on the potential toxicity of lidocaine when applied topically to mucous membranes, larynx, trachea, bronchi, and alveoli. Most reports show prolonged and delayed absorption of lidocaine from the respiratory tract. Peak arterial and venous plasma concentrations of 3.2 μg/mL and 2.5 μg/mL respectively have been demonstrated 2 - 5 minutes after 3 mg/Kg of a 10% solution was administered to the trachea and bronchi in anesthetized patients (Pelton et al, 1970).

Chu et al (1975) demonstrated peak plasma levels of lidocaine in venous blood 15 - 20 minutes following topical anesthesia of the trachea using a special cannula to spray the solution. The average dose was 3.3 mg/Kg, and peak plasma levels were 2 - 5.6 μg/mL. The solution was sprayed into the trachea prior to intubation of patients undergoing elective surgery. The mean time to peak plasma level was 15 - 20 minutes following ET administration and 2 minutes after IV injection.
Similar results were reported using 2 mg/Kg sprayed onto the larynges and tracheas of anesthetized patients (Viegas and Stoelting, 1975). The authors reported peak plasma concentrations of $1.7 \pm 0.2 \mu g/mL$, 9 - 15 minutes after lidocaine administration. In patients who were intubated with endotracheal tubes lubricated with viscous lidocaine, peak plasma concentrations were $2.4 \pm 0.3 \mu g/mL$, 4 - 15 minutes after administration of the same dose of lidocaine.

Curran et al (1975) also noted delayed absorption of lidocaine from the larynx and trachea, and further determined that absorption from the laryngeal area is decreased compared with absorption from the trachea. Peak plasma levels of $0.4 - 2.5 \mu g/mL$ were obtained at 10 - 20 minutes from the larynx, whereas peak levels of $1.9 - 8 \mu g/mL$ were reached at 5 - 15 minutes from the trachea. This finding is not unexpected due to the higher degree of vascularity of the tracheal area compared to the larynx.

Uptake of lidocaine given via intermittent positive pressure breathing (IPPB) and ultrasonic nebulizer has been investigated (Chinn et al, 1977). Plasma levels did not exceed $1.1 \mu g/mL$ although doses used were 280 mg via ultrasound and 400 mg via IPPB.

Similar plasma levels were obtained using a metered dose applicator (a fine spray) and using 50 mg or 100 mg only (Scott et al, 1976). They further reported that higher plasma levels were obtained when patients were paralyzed and ventilated, than when they had spontaneous respirations. It was felt that artificial ventilation may force some of the drug deeper into the pulmonary tree, whereas spontaneous respiration allows some of the...
administered drug to be exhaled or coughed out.

The slow uptake of lidocaine noted following administration as a fine spray to the upper respiratory tract is in marked contrast to the rapid ECG results obtained by Elam (1977) following instillation of a solution via a catheter into the pulmonary area. The latter study demonstrates that epinephrine, lidocaine, and atropine may be effective when given via the intrapulmonary route, and that this route may provide as rapid and more prolonged an effect in cardiorespiratory collapse than the IV route. It does not, however, examine the question of suitable dosages and appropriate pharmacological responses. The objective of cardiopulmonary resuscitation is to restore effective pumping action to the heart, and the use of ECG response alone as the primary criteria for therapeutic effect does not totally answer this question.

It appears that the use of lidocaine via the endotracheal route may be of benefit when an IV line cannot be established. Although there is considerable controversy in the literature regarding the rate of absorption and amount absorbed, it is clear that lidocaine is absorbed from the larynx, trachea, bronchi, and lungs. There is evidence to suggest that deep instillation of lidocaine into the lungs will produce more rapid and higher peak plasma levels than topical application to the laryngeal area. It also appears that water may be a more appropriate vehicle than normal saline, although this should be confirmed.

Due to the large variation reported in rate and extent of lidocaine absorption, it is necessary to further examine the plasma levels obtained when the drug is given experimentally in
a situation analogous to that encountered clinically. In cardiac arrest, the hemodynamic status of the body differs greatly from the normal situation (Voorhees et al, 1980). Peripheral perfusion is often very poor, with the majority of circulating blood volume in the central circulation. Instillation of a drug into the lungs may result in more rapid uptake into the central circulation where its action is desired, than intravenous injection into a peripheral vein.

Due to the potentially serious adverse effects which may occur when plasma lidocaine levels exceed 6 μg/ml (Bromage and Robson, 1961; Benowitz and Meister, 1978), it is important to closely determine the dosage necessary in any given situation. The pharmacokinetics of intravenous lidocaine have been accurately determined (Benowitz and Meister, 1978), allowing for safe and rapid administration of the drug via this route. The same data is necessary for the endotracheal route, if the drug is to be used effectively and safely in this manner.
2. The Antifibrillatory Efficacy of Lidocaine

a) Overview

Acute myocardial infarction (AMI) is one of the leading causes of morbidity and mortality in Canada and the United States (Canadian Heart Foundation, 1980). By far the most dangerous consequence of myocardial ischemia is the production of lethal arrhythmias and sudden death. In 1980, acute myocardial infarction resulted in death in approximately 50,000 patients in Canada alone (Canadian Heart Foundation, 1980). Of those patients suffering cardiorespiratory arrest, ventricular fibrillation is the causative arrhythmia in 50%-80% of cases, and either asystole, electromechanical dissociation, or severe bradycardia are the cause of the remainder (Vertesi, 1978).

Although prompt antiarrhythmic therapy may abolish arrhythmias and perhaps decrease the incidence of ventricular fibrillation (Lie et al, 1974), many patients still develop VF either prior to arrival of advanced pre-hospital care personnel, prior to arrival at hospital, or before appropriate antiarrhythmic therapy has been instituted.

Electrical defibrillation via direct-current counter-shock is the treatment of choice to reverse ventricular fibrillation (American Heart Association, 1980). This treatment is not always successful, however, particularly when VF has been established for a period of time (Liberthson et al, 1974; Eisenberg et al, 1980).

Many drug protocols have been devised for resuscitation
from cardiac arrest. Drug therapy initially evolved empirically with development of treatment regimens based on scientific hypotheses and subjective observations. Due to the difficulty in performing controlled human experiments during cardiac arrest, changes or advances in drug therapy have come about primarily as a result of animal experiments and subjective observations, with few controlled human studies.

In the American Heart Association's 'Standards and Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC) (1980), lidocaine is recommended as the drug of choice for the suppression of ventricular ectopic beats and ventricular tachycardia. It is also recommended in the treatment of ventricular fibrillation unresponsive to electrical defibrillation alone. Since not all episodes of ventricular fibrillation can be successfully terminated with electrical defibrillation, and since ventricular fibrillation continues to occur either prior to or despite institution of appropriate therapy, careful evaluation of current protocols and their efficacy is mandatory. Although evidence suggests that lidocaine may be helpful in terminating ventricular fibrillation, this has not been clearly demonstrated in controlled clinical trials. The following is a survey of the literature regarding the known antiarrhythmic and electrophysiological properties of lidocaine, and the rationale for further experiments to document the extent of its antifibrillatory efficacy in vivo.

Although complex electrophysiological documentation of the effects of lidocaine on the fibrillating heart are beyond the scope of this study, the following discussion will deal in some depth with mechanisms of arrhythmogenesis and the electro-
physiological actions of lidocaine. These data will be presented as support for the possibility that lidocaine may possess antifibrillatory activity in established ventricular fibrillation.

b) **Mechanisms of Arrhythmogenesis**

Several models have been developed to study underlying mechanisms involved in the electrophysiological events accompanying acute myocardial infarction (Wit and Friedman, 1975). Arrhythmia production and sudden death as a result of occlusion of a coronary artery have been clearly demonstrated in animal experiments where acute surgical occlusion of a coronary artery has resulted in electrophysiologic sequelae which are similar to those reported in man during acute myocardial infarction. Many patients in whom sudden death has occurred, however, show no significant degree of occlusion of coronary blood flow (Bashe et al, 1975). Temporary spasm of a coronary artery has been demonstrated clinically in man, and may be a factor in sudden death in patients in whom no significant degree of coronary artery occlusion can later be found (Oliva and Breckinridge, 1977). Coronary arterial spasm was seen in 40% of myocardial infarctions due to coronary artery disease. Spasm was often seen to be superimposed on an atherosclerotic obstruction already present. Relief of the spasm resulted in return of patency of the artery in some patients.

In order to mimic the clinical situation, animal models have been developed in which temporary occlusion of a coronary artery is followed by reperfusion. Both occlusion
and reperfusion of coronary arterial blood flow have been shown to be highly arrhythmogenic in many animal species, including dogs, cats, and rats (Battle et al, 1974; Axelrod et al, 1975; El-Sherif et al, 1975; Levites et al, 1975; Kane et al, 1979; Kaplinsky et al, 1979; Murdock et al, 1980; Kaplinsky et al, 1981).

Occlusion of the left anterior descending coronary artery in dogs has consistently resulted in the production of ventricular arrhythmias within a few minutes of occlusion (Axelrod et al, 1975; El-Sherif et al, 1975; Levites et al, 1975; Kaplinsky et al, 1979; Murdock et al, 1980; Kaplinsky et al, 1981). These arrhythmias usually peak in frequency within about 4 - 8 minutes and then abate. Spontaneous ventricular fibrillation has been reported in 65% of animals following this occlusion procedure (Fujimoto et al, 1981), although the frequency with which this event occurred in other studies varied greatly from 1%-40% (Battle et al, 1974; Kaplinsky et al, 1979; Kaplinsky et al, 1981; Ouyang et al, 1981).

Reperfusion of ischemic myocardium in the dog has also been shown to be highly arrhythmogenic, resulting in the production of ventricular arrhythmias immediately upon release of the ligature (Levites et al, 1975; Murdock et al, 1980) and subsequent ventricular fibrillation in up to 60%-65% of animals (Battle et al, 1974; Kaplinsky et al, 1981). Production of arrhythmias upon occlusion and release has also been demonstrated in the cat (Corr et al, 1978; Penkoske et al, 1978) with an overall mortality due to ventricular fibrillation of 29% following occlusion and 25% following reperfusion.
Occlusion and reperfusion arrhythmias have been noted to have distinctive characteristics with respect to onset, frequency and duration. Arrhythmias due to coronary artery occlusion have been noted to develop gradually, peak within 4 - 8 minutes and then abate in about 10 - 12 minutes (Corr et al, 1978; Penkoske et al, 1978; Murdock et al, 1980). Some investigators have noted a second phase of arrhythmias which occurs from 12 - 30 minutes following ligation (Kaplinsky et al, 1979) although other studies in cats using occlusion periods of the same duration have not noted this (Corr et al, 1978; Penkoske et al, 1978).

Reperfusion arrhythmias, however, have been shown to occur almost immediately upon release of the ligature or within one minute of release, and abate rapidly within the following 1 - 2 minutes (Battle et al, 1974; Axelrod et al, 1975; Penkoske et al, 1978; Murdock et al, 1980). Kaplinsky et al (1981), however, also demonstrated a second phase of arrhythmias occurring within 2 - 7 minutes after reperfusion.

Mechanisms responsible for the production of arrhythmias upon occlusion or reperfusion of a coronary artery are thought to be complex and involve many factors. The contribution of neurohormonal, biochemical and electrophysiological factors have yet to be completely defined. In general though, it is felt that arrhythmias can occur via two different electrophysiological processes, re-entry and enhanced automaticity (Han, 1969). Re-entry is proposed to occur when an electrical impulse is blocked along one pathway, travels along an alternate route, and then eventually re-excites more proximal tissue by travelling in a retrograde fashion along the
original blocked route. This may occur as a result of a reduction in conduction velocity in one segment of myocardium relative to another, or by differences in refractory periods in adjacent tissue.

Enhanced automaticity or spontaneous depolarization may occur as a result of an increase in slope of phase 4 diastolic depolarization (in cardiac tissue with those intrinsic properties), an increase (less negative) in the maximum diastolic potential at the end of repolarization, or a decrease (more negative) in the electrical threshold for action potential development. These concepts have been recently reviewed by several authors (Wit and Friedman, 1975; Ribner et al., 1979; Vera and Mason, 1981).

Acute occlusion of a coronary artery has been shown to result in a reduction in ventricular fibrillation threshold which paralleled appearance of ventricular arrhythmias and susceptibility to both spontaneous and electrically-induced ventricular fibrillation (Battle et al., 1974; Axelrod et al., 1975; Corbalan et al., 1976).

Both conduction delay and a decrease in refractory period have been shown to occur within ischemic myocardial tissue following coronary artery occlusion (Levites et al., 1975; Penkoske et al., 1978; Kaplinsky et al., 1979; Murdock et al., 1980). These changes did not occur in non-ischemic myocardial tissue. Marked fractionation of electrical activity as recorded by epicardial and subepicardial electrodes has also been observed and coincides with increased arrhythmia frequency. The fractionation of electrical activity reflects non-homogeneous depolarization of myocardial cells, probably
from slow conducting tissue (El-Sherif et al, 1975; Kaplinsky et al, 1979; Murdock et al, 1980).

Demonstration of fractionation of electrical activity, conduction delay and a decrease in refractory period in ischemic myocardial tissue have led most investigators to promote re-entry as the most likely mechanism for arrhythmia production following coronary artery occlusion.

Re-entry has been demonstrated clinically in man in the genesis of supraventricular tachycardia (Goldreyer and Bigger, 1971) and ventricular fibrillation (Josephson et al, 1978).

The evidence for a mechanism for arrhythmias following coronary artery reperfusion is not so clear. Ventricular fibrillation threshold decreases within approximately 3 minutes following occlusion of a coronary artery in most animal models (Battle et al, 1974; Axelrod et al, 1975; Corbalan et al, 1976). This threshold returns to normal in approximately 10 minutes. Upon reperfusion, the threshold for ventricular fibrillation has been shown to drop almost immediately to levels seen following occlusion, and this reduction is of brief duration. Kaplinsky et al (1981) reported the association of immediate reperfusion arrhythmias with the reappearance of nonhomogeneous, fragmented electrical activity. These conditions could provide conditions suitable for re-entry. They also noted a delayed period of arrhythmias beyond the time when conduction abnormalities had returned to control levels, and associated this with augmented automaticity. Augmented automaticity demonstrated by overdrive suppression and enhanced idio-ventricular rates has been suggested by Penkoske et al (1978)
as a possible mechanism of arrhythmia production during reperfusion. In addition, localized areas of depressed conduction velocity exist, indicating heterogeneous recovery after reperfusion. It is possible that Kaplinsky (1981) and co-workers were able to define more clearly during reperfusion a temporal sequence of re-entry followed closely by augmented automaticity.

Re-entry as a mechanism for reperfusion arrhythmias has also been proposed by Murdock et al (1980), who demonstrated nonhomogeneous recovery of conduction which coincided with a return of arrhythmias.

The role of humoral and biochemical parameters on arrhythmogenesis may be very complex. Adrenergic influences during induced myocardial ischemia have been observed, including enhanced sympathetic afferent discharge (Brown, 1967). Both phentolamine and propranolol have been shown to reduce the ventricular fibrillation threshold changes which occur during coronary artery occlusion (Corbalan et al, 1976). These effects were not seen following reperfusion, suggesting that adrenergic mechanisms may not be as significant at that time.

Regional cyclic AMP levels have been measured and compared with local electrophysiologic activity following coronary artery occlusion (Corr et al, 1978). Alterations in intramyocardial conduction time correlated well with onset of arrhythmias. Coronary occlusion also resulted in an increase in cAMP levels in ischemic tissue which was maximal at 15 minutes and paralleled an increase in arrhythmias. Cyclic AMP was also elevated in the normal myocardium following occlusion, but to a significantly lower extent than in ischemic
tissue. Spontaneous ventricular fibrillation was significantly correlated with elevated cAMP levels. Pretreatment with propranolol caused a significant reduction in cAMP levels and a lower incidence of arrhythmias and ventricular fibrillation.

Increased washout of metabolic waste products resulting from impaired blood flow and altered cellular permeability have also been proposed as mechanisms for arrhythmogenesis during coronary artery reperfusion. It has been observed that prolongation of occlusion time results in an increased incidence of induced ventricular fibrillation upon reperfusion (Corbalan et al, 1976). It is possible that there may be a minimum occlusion time required for some of these biochemical alterations to occur.

Increased 'washout' of potassium and lactate from ischemic myocardium has been reported during reperfusion (Lang et al, 1974). These metabolic products may be released due to disruption of cellular membrane integrity and may contribute to localized electrophysiological changes in the myocardium.

c) Electrophysiological Effects of Lidocaine in Normal and Ischemic Myocardium

Lidocaine has been shown to further slow conduction velocity in ischemic cardiac tissue without effect on normal tissue (Kupersmith, 1979). Since conduction in ischemic myocardium is already slowed, thereby providing a mechanism for re-entry, further slowing of impulses in this region may result in bidirectional block and termination of re-entry. Lazzara
et al (1978) observed that lidocaine consistently reduced conduction in isolated ischemic cardiac cells, and that this change in conduction coincided with the disappearance of abnormal spontaneous beats. This impaired conduction was totally extinguished by lidocaine as well as by tetrodotoxin. They concluded that arrhythmias may result from depression of the fast sodium channels in ischemic cells resulting in slowed conduction. Membrane responsiveness (upstroke velocity of phase 0 in relation to resting membrane potential) was also impaired in ischemic cells and was further reduced by lidocaine. This may also contribute to the observation that lidocaine extinguishes conduction in ischemic cells which previously exhibited delayed conduction and re-entry. The effects of lidocaine in abolishing already depressed fast responses have also been reported by Brennan et al (1975).

Another mechanism by which lidocaine may exert its antiarrhythmic effects is through alterations in refractory period. Lidocaine has been shown to prolong the effective refractory period (ERP) in ischemic cardiac tissue without significantly changing action potential duration (APD) (Kupersmith, 1979). The effects seen in normal tissue were a decrease in APD but no effect on ERP. The overall result, therefore, was a decrease in the ratio of APD/ERP to approximately 1.0 in the ischemic zone, with a smaller reduction occurring in the normal zone. This change in refractoriness in tissue known to generate arrhythmias may also explain some of the antiarrhythmic properties of lidocaine.

Automaticity has been shown to be altered by lidocaine through a retardation of spontaneous phase 4 depolarization
(Bigger and Mandel, 1970; Rosen et al., 1973) without reducing the resting membrane potential (Lazzara et al., 1975). Han and colleagues (1974) demonstrated the ability of lidocaine to suppress ectopic beats due to enhanced automaticity and re-entry following myocardial ischemia in the dog.

The reduction in ventricular fibrillation threshold (VFT) accompanying coronary artery occlusion has been shown to be abolished by lidocaine (Spear et al., 1972; Borer et al., 1976). Administration of lidocaine in these studies was also associated with a reduction in the incidence of spontaneous ventricular fibrillation.

The possibility that lidocaine may affect VFT during myocardial ischemia has also been investigated by Kramer and coworkers (1981), who found no difference in threshold values between control and lidocaine-treated groups. The discrepancies between results may be due to differences in stimulus frequency and intensity used to determine VFT.

Pre-treatment with lidocaine has been shown to be effective in reducing the incidence of arrhythmias and ventricular fibrillation following coronary artery ligation in rats (Kane et al., 1979). It has also been shown to elevate VFT and afford protection against ouabain-induced arrhythmias in isolated rabbit and guinea pig hearts (Almotrefi and Baker, 1980; Almotrefi and Baker, 1981).

Boudoulas and coworkers (1978a) have found that lidocaine exerted a protective effect on canine ischemic myocardium. Following coronary artery occlusion, ST-segment elevation commonly seen during ischemia was reduced by lidocaine, and coronary sinus CPK was shown to increase in the control
group more than in the lidocaine-treated group. They postulated that this protection may result from the negative inotropic effect of lidocaine. Boudoulas et al (1978) have also reported that lidocaine decreased ischemic injury and necrosis following coronary occlusion.

Pretreatment with lidocaine 10 minutes prior to a 40 minute coronary artery occlusion (in dogs) has been shown to result in a three-fold reduction in infarct size, a reduction in ventricular arrhythmias upon occlusion and release, decreased rate of rise of left ventricular developed pressure and increased left ventricular end-diastolic pressure (Nasser et al, 1980). Coronary artery occlusion was associated with decreased mitochondrial respiration in the center of infarcted tissue which was not altered by lidocaine therapy. Since regional myocardial blood flow was lowest in the lidocaine-treated groups, the authors proposed that lidocaine did not exert its effects through negative inotropic mechanisms but rather through preservation of myocardial cell membrane integrity.

In an uncontrolled study, Carden and Steinhaus (1956) reported successful resuscitation from ventricular fibrillation in 21 of 23 dogs following intraventricular administration of lidocaine. Lidocaine dosage was 15mg/Kg and response was seen in a mean time of 7 minutes (range 2 - 27 minutes).

d) **Effects of Lidocaine Seen Clinically**

Lidocaine was first synthesized in Sweden in 1943 and was used for many years as a local anesthetic agent. In 1950, Southworth et al reported the successful use of lidocaine
to reverse ventricular fibrillation which resulted from cardiac catheterization.

In 1967, Lown proposed the concept that premature ventricular contractions (PVCs) were warning arrhythmias which would ultimately lead to ventricular fibrillation or ventricular tachycardia. Suppression of these ectopic beats with anti-arrhythmic therapy was therefore presumed to be a logical step in the prevention of the more serious subsequent arrhythmias. The terms 'warning arrhythmias' or 'premonitory arrhythmias' generally referred to frequent ventricular ectopic beats or PVCs (greater than 5/minute), multifocal or paired ectopics, and those occurring on or near the preceding T wave. Lidocaine has been demonstrated to be very effective in terminating ventricular tachycardia and in abolishing or reducing the number and frequency of PVCs when plasma levels of 1.5 - 5.5 μg/mL are obtained (Gianelly et al, 1967; Jewitt et al, 1968; Spracklen et al, 1968).

Lidocaine, therefore, has been used routinely to suppress ventricular ectopic beats during the acute phase of myocardial infarction and presumably to prevent VF or ventricular tachycardia. Plasma lidocaine levels greater than 6 μg/mL may be associated with toxicity, such as muscular irritability, convulsions, myocardial depression, and coma (Gianelly et al, 1967; Benowitz and Meister, 1978).

More recently, the concept that VF is preceded by warning arrhythmias, and that antiarrhythmic therapy at that time will prevent VF in those patients, has been questioned. It has been observed that 25%-40% of patients did not exhibit warning arrhythmias prior to VF, and that premonitory arrhythmias occur
as frequently in patients who do not develop VF as in those patients who do (Lie et al, 1975; Ribner et al, 1979).

Furthermore, many 'warning arrhythmias' may go undetected during routine surveillance in a coronary care unit, resulting in delayed antiarrhythmic therapy (Lown et al, 1975).

Attention has since been focused on the concept of prophylaxis against VF in all patients with acute myocardial infarction. Lidocaine prophylaxis has received considerable attention in the literature.

Lie et al, (1974), in a double-blind, randomized trial in a series of 212 consecutive patients, assessed the efficacy of lidocaine in preventing VF in acute myocardial infarction. Their findings indicate that lidocaine in the dosage given was highly effective ($p < 0.002$) in preventing VF. These findings were supported by other workers (Valentine et al, 1974; Wyman and Hammersmith, 1974; Szeplaki et al, 1976).

Although prompt treatment with antiarrhythmic drugs may decrease the incidence of VF, many patients still develop VF either prior to arrival of a pre-hospital advanced life support unit (ALS), prior to arrival at hospital, or before definitive antiarrhythmic drug therapy has been instituted. Electrical defibrillation via direct-current countershock is the treatment of choice to reverse the fibrillation, but this is not always successful. In a series of 301 patients treated by the ALS rescue squad from the Miami Fire Department, only 199 could be defibrillated despite the use of conventional cardiac arrest drug therapy. Furthermore, of those defibrillated, approximately 40% had recurrence of VF. Approximately 50% of those defibrillated died prior to arrival at hospital (Liberthson et al, 1974). Eisenberg
et al (1980) reported that in 36 cases of out-of-hospital ventricular fibrillation, 27 patients remained in ventricular fibrillation after the first defibrillation attempt.

Both epinephrine and lidocaine are currently used in cardiac arrest protocols in the management of ventricular fibrillation (American Heart Association, 1980; Redding, 1977). The question as to whether lidocaine is useful in restoring effective cardiac contractions from VF is not clear. A review of the literature revealed no controlled studies in the use of lidocaine alone in the management of VF. Nevertheless, it has been the concept in cardiac arrest drug therapy that lidocaine and/or epinephrine be used in the treatment of VF unresponsive to defibrillation, since withholding drugs in this situation will certainly not be of value.

3. Rationale and Purpose of the Present Study

Statistics from the Vancouver Advanced Life Support Program indicate that approximately 13% of patients treated in the pre-hospital setting fail to have an IV line established after two attempts (Emergency Health Services Academy, 1982). These patients, therefore, cannot receive adequate drug therapy until the IV line is in place, unless alternate routes of drug administration are available.

It is possible that lidocaine may be effective when administered in the form of a solution via an endotracheal tube. The rate and extent of absorption need to be determined during both normal cardiovascular status and ventricular fibrillation. Lidocaine is currently in widespread use in the
treatment and prevention of ventricular fibrillation and tachycardia. Considerable effort has been directed towards prevention of these arrhythmias, and it appears that lidocaine may be effective when given prior to the onset of VF. Lidocaine appears to be effective in the treatment of ventricular tachycardia.

Prevention of VF is of vital concern during the initial stages of acute myocardial infarction. However, significant numbers of patients are in VF when seen by an emergency ALS crew, or develop VF before any definitive treatment is instituted. Defibrillation and correction of acid-base balance are of primary concern in this situation. It appears that despite the use of electrical defibrillation, approximately 1/3 - 1/2 of patients are not able to be defibrillated successfully. Evidence in the literature suggests that lidocaine may abolish ventricular arrhythmias by eliminating re-entrant pathways and by reducing augmented automaticity. It is therefore possible that lidocaine may assist electrical defibrillation in terminating ventricular fibrillation.

The value of lidocaine in the termination of ongoing VF has not been established. Although epinephrine and lidocaine are used in this situation, the efficacy of either agent has not been demonstrated conclusively in controlled clinical trials. It appears that the efficacy of lidocaine in the treatment of ventricular fibrillation due to acute myocardial infarction is a question which has yet to be answered.

It is the aim of this study to investigate the efficacy of lidocaine when administered via an endotracheal tube during experimentally-induced ventricular fibrillation. Onset, peak
and duration of plasma lidocaine levels will be examined following both endotracheal and intravenous administration in a rabbit model.
MATERIALS AND METHODS

1. Plasma Lidocaine Level Studies

a) Animal Experiments

White New Zealand rabbits of either sex weighing 2.0 - 3.5 Kg. were anesthetized with either halothane via inhalation or intravenous sodium pentobarbital.

Halothane was administered initially in a concentration of approximately 4%. When deep pain reflexes were absent the rabbits were intubated orally with a Magill type endotracheal tube (size 3.0 - 4.0 I.D., National Catheter Corp.) using a Welch Allyn laryngoscope and pediatric size Miller blade (size 01). Anesthesia was maintained with 1.0 - 1.5% halothane and rabbits were allowed to breathe spontaneously. Halothane concentration was regulated using two flowmeters (Roger Gilmont Instruments Inc.). One flowmeter delivered 95% O₂/5% CO₂ while the other passed O₂/CO₂ through a chamber containing halothane liquid.

Pentobarbital (30 - 60 mg/Kg) was injected via the marginal ear vein using a 21 gauge butterfly infusion set (Abbott Venisystems) kept patent using normal saline with heparin (5 units/ml). Supplemental pentobarbital was occasionally required during long experiments.

Pentobarbital-anesthetized rabbits were placed in a supine position on an operating tray and an endotracheal tube was placed via tracheotomy in the same antero-posterior
position as would be achieved via oral intubation. The rabbits were respired at a rate of 26 per minute and tidal volume of 25 - 35 ml (C.F. Palmer Respirator).

Arterial blood pressure (BP) was recorded from the carotid artery using a Gould Statham P23Db physiological pressure transducer. A three-way stopcock was attached to the carotid artery cannula for sampling of arterial blood for plasma lidocaine determinations. Lead II of a three-lead electrocardiogram (ECG) was monitored using Grass needle electrodes. Both ECG and blood pressure were recorded continuously on a Grass Instruments 2-Channel Polygraph.

Rectal temperature was monitored with a Yellow Springs Instruments Model 47 scanning telethermometer and temperature was maintained between 37°C - 39°C using an infrared heating lamp. Normal rabbit body temperature is 39.4°C (Kaplan, 1979).

For endotracheal lidocaine studies a solution of lidocaine 2 mg/ml in either distilled water or normal saline was instilled directly into the endotracheal tube, followed by four quick lung inflations using a pediatric Laerdal bag. Unless otherwise stated, the dosage used for all experiments was 2 mg/kg lidocaine HCl. Following instillation of the solution the endotracheal tube was either reconnected to the respirator or the rabbit was allowed to resume spontaneous respirations, depending on the anesthetic used.

For intravenous experiments, either a 2 mg/ml solution of lidocaine in distilled water was injected within five
seconds into the rabbit marginal ear vein or a 20 mg/ml solution of lidocaine in normal saline was injected into a distal hind leg vein at the same rate. The leg vein was isolated surgically and cannulated with polyethylene tubing (PE-90). Following injection of either lidocaine solution the tubing was flushed with 0.25 ml normal saline.

Following either endotracheal instillation or intravenous injection of lidocaine, 0.5 ml arterial blood samples were withdrawn from the carotid artery cannula at 15 seconds, 30 seconds, 1 minute, 2, 3, 4, 10, 20 and 30 minutes.

Samples were placed in 1.5 ml polypropylene microcentrifuge tubes (VWR Scientific Inc.) containing approximately 1.5 mg disodium EDTA per tube.

The samples were centrifuged in an Eppendorf microcentrifuge for one minute at 8000 x g, and the plasma was stored in a refrigerator (4-6°C) for future lidocaine assay.

Unless otherwise stated, plasma lidocaine level studies were performed in animals in which no further surgical procedures had been performed. "Open Chest" and "Ventricular Fibrillation" surgical procedures are described in section II and were employed for some studies where indicated.

b) LIDOCAINE ASSAY

Plasma samples were assayed for lidocaine within seven days of the experiment using EMIT enzyme immunosassay marketed by Syva Diagnostics Ltd., Montreal (Pape et al, 1978; Rubenstein, 1978) (Figure 1). Preliminary studies were conducted in the lab to ascertain that stability of the samples
Figure 1

Principle of homogeneous enzyme immunoassay. When the enzyme-ligand conjugate is complexed to the antibody (left), the enzyme substrate is excluded from the active site and enzyme activity is reduced. The presence of ligand releases a portion of the enzyme conjugate, which is then active (right).

Copyright 1978 Syva Diagnostics Ltd., Montreal (with permission)
over this time period lay within $\pm 5\%$ of samples assayed immediately following experiments.

Equipment used for the assay procedure consisted of a Gilford Stasar III spectrophotometer, a Syva Model 1500 Pipetter-Diluter, a Syva CP-5000 Microprocessor, Emit$^R$-cad Lidocaine Assay Kits, Emit$^R$-cad Lidocaine Control, and 1.5 ml disposable autoanalyzer cups (conical bottoms).

Each Emit$^R$ assay kit consisted of Antibody/Substrate Reagent A, Enzyme Reagent B, six lidocaine calibrators containing 0, 1.0, 2.0, 3.0, 5.0 and 12.0 $\mu$g/ml lidocaine, and 0.055M tris-HCl buffer solution (pH 7.9). All solutions were prepared prior to use with the addition of distilled water. Reconstituted Antibody/Reagent A contained a standardized preparation of immunized sheep gamma globulin, glucose-6-phosphate and NAD, monoethylglycinexylidide (MEGX) and preservative in 0.055M tris HCl buffer at pH 5.0. Reconstituted Enzyme Reagent B contained glucose-6-phosphate dehydrogenase - labelled lidocaine and preservatives in 0.55M tris HCl buffer at pH 7.9.

A standard curve was run at the start of each assay. Standard procedure for either calibrators or unknown samples was as follows:

The pipetter-diluter was programmed to withdraw 50 $\mu$l of lidocaine sample (unknown or calibrator), Antibody/Substrate Reagent A, or Enzyme Reagent B and dispense it with 250 $\mu$l tris HCl buffer solution into an autoanalyzer cup. Initially two serial dilutions of
unknown or calibrator were performed, followed by the addition of 1:5 dilutions of Reagent A and then Reagent B to the second lidocaine dilution. The reaction mixture was aspirated immediately into the spectrophotometer flow cell, activating the microprocessor to time and record absorbance measurements at 15 and 45 seconds after aspiration (expressed as a change in absorbance over 30 seconds, $\Delta A$).

Duplicate absorbance measurements were made on the 0 $\mu$g/ml calibrator ($\overline{AA}_0$) and the difference ($\Delta A - \overline{AA}_0$) between this reading and the reading for the other calibrators ($\Delta A$) was determined by the microprocessor in order to plot a standard curve. Calibration of the standard curve was checked with a known lidocaine concentration (4$\mu$g/ml). The absorbance measurements of unknown samples were used in the same manner ($\Delta A - \overline{AA}_0$) to determine concentrations by use of the standard curve. Duplicate lidocaine determinations were made on each plasma sample.

Plasma lidocaine levels greater than 13$\mu$g/ml (outside assay limits) were determined by performing an additional 1:5 dilution of the plasma sample prior to addition of Reagents A & B.

2. **Coronary Artery Ligation / Ventricular Fibrillation Studies**

White New Zealand rabbits weighing 2.0-3.5 Kg were anesthetized with intravenous pentobarbital and prepared as
Figure 2

Schematic representation of the position of the suture placed around the left circumflex coronary artery.

Figure 2a

Cross-sectional representation of placement of the ligating suture before and after ligation was secured.
described in section 1. The chest was opened with a medial incision through the sternum and retractors were used to enlarge the chest opening. The thymus gland was either partially removed or clamped to the chest wall to provide clear visualization of the heart. The pericardium was opened medially and attached to the chest wall with 4-0 silk suture (Ethicon, Inc.) if necessary, to provide a cradle for the heart.

Using 4-0 silk black braided cardiovascular sutures (Ethicon, Inc.) a tie was placed in the apex of the left ventricle to assist in manipulation of the heart. The left circumflex branch of the left coronary artery was visualized by lifting the left atrial appendage with forceps and rotating the heart slightly to the right. A cardiovascular 4-0 silk suture was then placed through the myocardium and around the artery as diagrammed in Figures 2 and 2a. The suture ends were passed through a piece of polyethylene tubing for later use in clamping off the artery. When possible, the suture was placed proximal to division of the circumflex artery into two branches.

When the ligature was in place the heart was allowed to recover for at least 10 - 20 minutes or until blood pressure and ECG returned to pre-thoracotomy levels. Ligation of the artery was accomplished by pulling both ends of the suture through the tubing and clamping tightly with hemostatic forceps (Figure 2a). Occlusion of the artery could be visualized by blanching of part of the left ventricle, often the apex and posterior wall, and was usually accompanied by a drop in arterial blood pressure.
Occulsion of the artery was maintained for 15 minutes at which time the ligature was loosened and a 5 minute reperfusion phase allowed to occur. At the end of the reperfusion phase the ligature was resecured. A maximum of three cycles of occlusion (15 minutes) and reperfusion (5 minutes) were performed.

Ventricular fibrillation occurred during both occlusion and reperfusion phases, although it did not occur in every experiment. Each experiment fell into one of three distinct categories depending on the frequency and length of fibrillation:

1. No ventricular fibrillation: The heart did not fibrillate at any time during the experiment.

2. Short ventricular fibrillation: Ventricular fibrillation persisted for less than 2 minutes and terminated spontaneously (mean 0.6 minutes, range 0.2 - 1.8 minutes).

3. Long ventricular fibrillation: Ventricular fibrillation persisted longer than 2 minutes (mean 9.7 minutes, range 6.3 - 12.5 minutes). This group was used for both plasma lidocaine level studies during ventricular fibrillation and lidocaine efficacy studies.

Blood pressure, ECG and frequency of arrhythmias were monitored at various times, for comparison of these parameters with tendency to fibrillate in the three categories.

When ventricular fibrillation did occur the heart was
allowed to fibrillate for 15 seconds with no intervention. Manual pumping of the heart would then be started to maintain mean arterial blood pressure between 25-50 mmHg. Artificial circulation would be continued for 2 minutes of ventricular fibrillation unless the heart started to beat again on its own. If conversion to spontaneous cardiac rhythm occurred within this two minute period, the arrhythmia would be included in a "short ventricular fibrillation" category and the experiment continued in the appropriate occlusion/reperfusion cycle.

When ventricular fibrillation occurred during an occlusion phase the ligature was kept secured for the duration of the fibrillation and if it occurred during reperfusion the tie was left loose.

Further episodes of ventricular fibrillation would be managed in the same manner depending on their duration.

Plasma lidocaine level studies during ventricular fibrillation were instituted when fibrillation had proceeded for at least two minutes. Lidocaine was administered either endotracheally or intravenously and carotid artery blood samples were drawn at appropriate times as detailed in section 1. Circulation was maintained by means of cardiac massage until the onset of spontaneous cardiac rhythm. Plasma lidocaine level studies in sham-operated open chest controls were treated in the same manner but with the ligation left unsecured and no cardiac massage necessary.

Lidocaine efficacy studies were performed only when
ventricular fibrillation had persisted for 2 minutes. After 2 minutes of ventricular fibrillation either 2 mg/kg lidocaine (2 mg/ml in normal saline) or 1 ml/kg normal saline was administered endotracheally in a blind, randomized fashion. Cardiac massage was maintained until the return of spontaneous cardiac rhythm or for the duration of the experiment. Untreated control experiments were performed in the same manner except no treatment was given at 2 minutes of ventricular fibrillation.

If spontaneous circulation resumed within ten minutes after administration of either lidocaine, saline, or no treatment, artificial circulation was stopped and blood pressure and ECG were recorded. Subsequent cardiovascular status was monitored for 30 minutes. If ventricular fibrillation persisted, at 10 minutes following administration of lidocaine, normal saline or no treatment, electrical defibrillation was attempted (0.5 joules) to a maximum of 2 defibrillation attempts (Mennen-Greatback Electronics Inc. DC Defibrillator). If defibrillation was successful the cardiovascular status was monitored for 30 minutes as above.

At the end of each experiment, the heart was removed and perfused with 20ml normal saline on a modified Langendorf-type apparatus. With the ligation secured, the heart was then perfused slowly with 20ml Methyl Green Biological Stain (0.5 mg/ml) to delineate the occluded areas of the myocardium. Occluded areas were excised, weighed and expressed as percent wet weight of left ventricular, right ventricular and total ventricular mass.
3. Analyses and Statistics

Plasma lidocaine values were calculated by the Syva CP 5000 microprocessor in relation to a standard curve for lidocaine. Samples were assayed in duplicate and the mean value entered as one data point. All values were plotted as the mean ± standard error of the mean (S.E.M.) for the indicated number of experiments.

The Student's t-test for unpaired data was used to determine statistical significance between treatment groups. Data were considered to be significantly different at p<0.05 for a 2-tailed test.

First-order rate constants for elimination ($k$) were determined from the slope of the back-extrapolated elimination portion of the log concentration vs time curve. Absorption-distribution (endotracheal) and distribution (intravenous) rate constants ($\alpha$) were calculated from the slope of the line calculated by the method of residuals. Slope, y-intercept, and correlation coefficient ($r$) were determined using log linear least squares regression analysis.

Calculation of the area under the curve for the first ten minutes following drug administration ($\text{AUC}_{10}^{\text{ET}}$) was done by the trapezoidal rule method.

Fraction of an endotracheal dose absorbed in ten minutes ($f_{10}^{\text{ET}}$) was calculated by the formula

$$f_{10}^{\text{ET}} = \frac{\text{AUC}_{10}^{\text{ET}}}{\text{AUC}_{10}^{\text{IV}}}$$
Clearance of lidocaine in ten minutes ($\text{Cl}_{10}$) was calculated using the formula

$$\text{Cl}_{10} = \frac{f_{10} \times \text{dose}}{\text{AUC}_{10}}$$

These parameters are not true values since they assess conditions during the first ten minute of each experiment only. The calculated values should therefore be interpreted cautiously.

4. **Drugs and Chemicals**

Disodium ethylenediamine tetraacetic acid (Disodium EDTA or EDTA) - Sigma Chemical Co.

Halothane (Fluothane$^R$) - Ayerst Laboratories.

Lidocaine HCl - Dottbonapace Co., Italy, and I.M.S. Ltd., Montreal.

Pentobarbital sodium - B.D.H. Chemical Co.
RESULTS

1. Plasma Lidocaine Level Studies

   a) Endotracheal vs Intravenous Lidocaine in Distilled Water During Halothane Anesthesia

   Figure 3 shows arterial plasma lidocaine levels obtained following either endotracheal instillation or intravenous injection of 2mg/Kg lidocaine (2mg/ml in distilled water). The experiments were performed under halothane anesthesia and injection was made via the marginal ear vein. Administration of lidocaine endotracheally resulted in significantly higher plasma concentrations at 15 seconds and 1 minute although there was no significant difference at or following the 2 minute point.

   A semi-logarithmic plot of plasma lidocaine concentration vs time is shown in Figure 4. Following both intravenous injection and endotracheal instillation, lidocaine was shown to exhibit first-order pharmacokinetic behavior. Calculated rate constants and half-lives for distribution and elimination are summarized in Table I. The combined absorption-distribution rate constant ($\alpha$) for endotracheal lidocaine had a calculated value approximately 70% that of intravenous injection. Elimination rate constants ($\beta$) were similar for both routes.

   b) The Effect of Pentobarbital or Halothane Anesthesia on the Endotracheal Absorption of Lidocaine in Distilled Water
Figure 3

Plasma lidocaine levels vs time following endotracheal (ET) instillation or intravenous (IV) injection of 2mg/Kg lidocaine (2mg/ml in distilled water) during halothane anesthesia. Numbers of experiments are indicated. All points represent mean plasma levels \( \pm \) S.E.M. of the number of experiments indicated.

* significantly greater than IV at \( p < 0.05 \).
Figure 4

Log plasma lidocaine concentrations vs time following endotracheal (ET) instillation or intravenous (IV) injection of 2mg/Kg lidocaine (2mg/ml in distilled water) during halothane anesthesia. All points represent mean plasma concentrations of the number of experiments indicated.

* significantly greater than IV at $p < 0.05$. 
Table 1  Calculated first-order absorption-distribution (\( \alpha_{ET} \)), distribution (\( \alpha_{IV} \)), and elimination (\( \beta \)) rate constants and plasma half-lives for intravenous injection and endotracheal instillation of 2mg/Kg lidocaine (2mg/ml) in distilled water.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Lidocaine 2mg/kg IV</th>
<th>Lidocaine 2mg/kg ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>1.77 min(^{-1})</td>
<td>1.23 min(^{-1})</td>
</tr>
<tr>
<td></td>
<td>(r=-0.9789)</td>
<td>(r=-0.9973)</td>
</tr>
<tr>
<td>( \beta )</td>
<td>2.03 x 10(^{-2})min(^{-1})</td>
<td>1.99 x 10(^{-2})min(^{-1})</td>
</tr>
<tr>
<td></td>
<td>(r=-0.9906)</td>
<td></td>
</tr>
<tr>
<td>( t\frac{1}{2} (\alpha) )</td>
<td>0.347 min</td>
<td>0.563 min</td>
</tr>
<tr>
<td>( t\frac{1}{2} (\beta) )</td>
<td>32.7 min</td>
<td>34.8 min</td>
</tr>
</tbody>
</table>

\( a \) - data calculated from Figure 4.
Figure 5 shows plasma lidocaine concentrations observed following endotracheal instillation of lidocaine 2mg/ml in distilled water during either halothane or pentobarbital anesthesia. Animals anesthetized with halothane were allowed to breathe spontaneously while those anesthetized with pentobarbital were mechanically respired. Mean plasma lidocaine concentrations were greater at all time points during halothane anesthesia, although the differences were not statistically significant.

c) Plasma Lidocaine Levels Following Endotracheal Instillation of Lidocaine in Either Distilled Water or Normal Saline During Pentobarbital Anesthesia

Figure 6 shows the effect of using either normal saline or distilled water as the vehicle for lidocaine administration on lidocaine absorption via the endotracheal route. The dosage was 2mg/kg for both groups. Administration of lidocaine 2mg/ml in distilled water resulted in initial plasma lidocaine concentrations which were greater than those observed following administration of lidocaine 2mg/ml in normal saline. This difference was statistically significant (p< .05) at only 30 seconds after lidocaine administration. After 2 minutes, higher plasma lidocaine concentrations were observed when lidocaine was administered in normal saline than when distilled water was used as the vehicle. These differences were not statistically significant.

Figure 7 represents a semi-logarithmic plot of plasma lidocaine concentration vs time following endotracheal
Figure 5

Plasma lidocaine concentrations vs time following endotracheal instillation of 2mg/Kg lidocaine (2mg/ml in distilled water) during either halothane or pentobarbital anesthesia. Numbers of experiments are indicated and all points represent mean plasma levels ± S.E.M. There was no significant difference (p<0.05) between the two groups.
Figure 6

Plasma lidocaine concentrations vs time following endotracheal instillation of 2mg/Kg lidocaine (2mg/ml) in either normal saline or distilled water. All animals were anesthetized with pentobarbital. Numbers of experiments are indicated and all points represent mean plasma levels \( \pm S.E.M. \).

* significantly greater than normal saline at \( p < 0.05 \).
Log plasma lidocaine concentration vs time following endotracheal instillation of 2mg/Kg lidocaine (2mg/ml) in either normal saline or distilled water. All animals were anesthetized with pentobarbital. All points represent mean plasma levels ± S.E.M. of the number of experiments indicated.
administration of lidocaine in either normal saline or distilled water. This plot shows a rapid absorption-distribution phase for lidocaine in distilled water which is log linear, allowing calculation of a first-order absorption-distribution rate constant (α) and elimination rate constant (β) (Table II). The lidocaine in normal saline curve is not log linear during either the absorption-distribution or elimination phases up to 30 minutes, therefore a best estimate of these rate constants was obtained. This was done by (a) assuming that elimination of lidocaine after administration in normal saline occurred in a manner parallel with its elimination following administration in distilled water, and (b) calculating the absorption-distribution rate constant from this parallel line.

Absorption of Lidocaine Following Endotracheal Administration of Lidocaine in Normal Saline During Closed Chest Controls, Open Chest Controls and Ventricular Fibrillation

Figure 8 shows the time course of plasma lidocaine levels following endotracheal administration of lidocaine 2mg/ml in normal saline in closed chest controls, open chest controls and open chest animals during ventricular fibrillation. All animals were anesthetized with pentobarbital. Administration of lidocaine endotracheally to sham-operated open chest controls resulted in slightly higher plasma lidocaine concentrations over the first three minutes than administration to closed chest controls, although the difference was not significant.

When lidocaine in normal saline was administered endotracheally during ventricular fibrillation with cardiac
Table II  Calculated\(^{a}\) first-order absorption-distribution 
\((\alpha_{ET})\) and elimination \((\beta)\) rate constants and 
plasma half-lives for endotracheal instillation 
of 2mg/Kg lidocaine (2mg/ml) in normal saline 
and distilled water.

<table>
<thead>
<tr>
<th>Vehicle of Administration</th>
<th>Lidocaine 2mg/ml in Distilled Water</th>
<th>Lidocaine 2mg/ml in Normal Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)</td>
<td>0.741 min(^{-1})</td>
<td>0.786 min(^{-1})</td>
</tr>
<tr>
<td>(\beta)</td>
<td>2.53 x 10(^{-2}) min(^{-1})</td>
<td>2.65 x 10(^{-2}) min(^{-1})</td>
</tr>
<tr>
<td>(t_{\frac{1}{2}}(\alpha))</td>
<td>0.935 min</td>
<td>0.882 min</td>
</tr>
<tr>
<td>(t_{\frac{1}{2}}(\beta))</td>
<td>27.4 min</td>
<td>26.2 min</td>
</tr>
</tbody>
</table>

\(^{a}\) - data calculated from Figure 7.
Plasma lidocaine levels vs time following endotracheal administration of 2mg/Kg lidocaine (2mg/ml in normal saline) during ventricular fibrillation with cardiac massage, open chest (sham-operated) controls and closed chest controls. All animals were anesthetized with pentobarbital. All points represent mean plasma levels ± S.E.M. of the number of experiments indicated.

* significantly greater than open chest controls at p < 0.05.
ET

- Ventricular fibrillation
- Open chest control
- Closed chest control

Plasma lidocaine (µg/ml)

<table>
<thead>
<tr>
<th>n=5</th>
</tr>
</thead>
</table>

Time (min)

0 1 2 3 4 5 6 7 8 9 10
massage, a marked increase in plasma lidocaine concentration was observed over all time points. The increase was significant \((p < 0.05)\) at 15 seconds, 30 seconds and 1 minute post-administration.

Calculated area under the curve to 10 minutes \((\text{AUC}_{10})\), fraction of dose absorbed in 10 minutes \((f_{10})\) and clearance of lidocaine over the initial 10 minutes \((\text{Cl}_{10})\) are reported in Table III. \(\text{AUC}_{10}\) was increased during ventricular fibrillation and \(\text{Cl}_{10}\) was decreased. Amount of lidocaine absorbed was 71% and 72% in controls and ventricular fibrillation, respectively.

e) **Plasma Lidocaine Levels Following Intravenous Injection of Lidocaine in Normal Saline During Open Chest Controls and Ventricular Fibrillation**

Figure 9 shows plasma lidocaine levels observed following intravenous injection of lidocaine 20mg/ml in normal saline during ventricular fibrillation with cardiac massage or to open chest (sham-operated) controls. Injection was made via distal hindleg vein and animals were anesthetized with pentobarbital. Plasma lidocaine levels were greater at all times during ventricular fibrillation although this was significant \((p < 0.05)\) only at one minute.

Table III shows area under the curve to 10 minutes \((\text{AUC}_{10})\), fraction of the dose absorbed in 10 minutes \((f_{10})\) and clearance of lidocaine in the initial 10 minutes \((\text{Cl}_{10})\) for open chest controls and ventricular fibrillation. \(\text{AUC}_{10}\) was increased during ventricular fibrillation and \(\text{Cl}_{10}\) was decreased.
Figure 9

Plasma lidocaine levels vs time following intravenous injection of 2mg/Kg lidocaine (20mg/ml in normal saline) during ventricular fibrillation and open chest controls. All animals were anesthetized with pentobarbital and injection was made via a distal hindleg vein. All points represent mean plasma levels ± S.E.M. of the number of experiments indicated.

* significantly greater than open chest controls at p<0.05.
IV

- Ventricular Fibrillation
- Open Chest Controls

Plasma Lidocaine (ug/ml)

Time (min)

n=4
Table III
Area under the curve ($\text{AUC}_{10}$), fraction of dose absorbed ($f_{10}$) and clearance ($\text{Cl}_{10}$) of lidocaine during first 10 minutes following intravenous$^a$ or endotracheal$^b$ administration to either ventricular fibrillation or open chest controls.

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine 2mg/kg IV</th>
<th>Lidocaine 2mg/kg ET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>VF</td>
</tr>
<tr>
<td>$\text{AUC}_{10}$ ($\mu g \cdot \text{min/m}l$)</td>
<td>25.8</td>
<td>65.8</td>
</tr>
<tr>
<td>$f_{10}$</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>$\text{Cl}_{10}$ (ml/min)</td>
<td>186</td>
<td>87</td>
</tr>
</tbody>
</table>

$^a$ Lidocaine 20mg/ml in normal saline into distal hindleg vein

$^b$ Lidocaine 2mg/ml in normal saline
f) **Plasma Lidocaine Levels Following Either Intravenous Injection or Endotracheal Instillation of Lidocaine to Open Chest Controls**

Plasma lidocaine levels observed following endotracheal (ET) instillation of lidocaine 2mg/ml in normal saline, or intravenous (IV) injection of lidocaine 20mg/ml in normal saline, are shown in Figure 10. Figure 11 shows a semi-logarithmic plot of this data. These comparisons were obtained by rearranging data from sections (d) and (e). The dosage of lidocaine used was 2mg/kg for both routes.

All animals were anesthetized with pentobarbital and injection was made via a distal hindleg vein. Injection of lidocaine resulted in peak plasma levels at 15 and 30 seconds which were significantly greater (p<0.05) than those obtained following endotracheal instillation.

These levels decreased rapidly, however, and at 2 minutes, the plasma levels following endotracheal administration were significantly greater than those obtained from intravenous injection (p<0.05). There were no significant differences between plasma levels at any other time points.

Calculated area under the curve, fraction of dose absorbed and clearance in the first 10 minutes are compared in Table III. Area under the curve was smaller during endotracheal administration than during intravenous injection and the fraction of the dose absorbed endotracheally was 71%. Clearance of lidocaine in the first 10 minutes was only slightly larger following endotracheal administration than following IV injection.
Figure 10

Plasma lidocaine levels vs time following endotracheal instillation of 2mg/Kg lidocaine (2mg/ml in normal saline) or intravenous injection of lidocaine (20mg/ml in normal saline). Animals were anesthetized with pentobarbital and were open chest (sham-operated) controls. Injection was made via a distal hindleg vein. All values represent mean plasma levels ± S.E.M. of the number of experiments indicated.

* significantly greater than endotracheal at p < 0.05.

** significantly greater than intravenous at p < 0.05.
Open Chest Controls

- ET
- IV

Plasma Lidocaine (μg/ml)

Time (min)

n = 4
n = 5
Figure 11

Log plasma lidocaine concentrations vs time following intravenous (IV) injection of 2mg/Kg lidocaine (20mg/ml in normal saline) or endotracheal (ET) instillation of 2mg/Kg lidocaine (2mg/ml in normal saline). Animals were open chest (sham-operated) controls and were anesthetized with pentobarbital. Injection was made via a distal hindleg vein. Numbers of experiments are indicated and all values represent mean plasma levels.

* significantly greater than ET at p < 0.05.

** significantly greater than IV at p < 0.05.
g) **Plasma Lidocaine Levels Following Endotracheal Instillation or Intravenous Injection of Lidocaine During Ventricular Fibrillation**

Figure 12 shows plasma lidocaine levels observed during ventricular fibrillation with cardiac massage following either endotracheal instillation of lidocaine 2mg/ml in normal saline or intravenous injection of lidocaine 20mg/ml in normal saline. Figure 13 shows a semi-logarithmic plot of this data. The dosage used in all cases was 2mg/Kg and IV injection was made via a distal hindleg vein. All animals were anesthetized with pentobarbital. These comparisons were obtained by re-arranging data from sections (d) and (e).

Although intravenous injection resulted in higher plasma lidocaine levels over all time points, the differences were not statistically significant.

When only experiments in which spontaneous conversion to normal sinus rhythm occurred were considered, the differences between the intravenous and endotracheal routes were larger. (Three out of four animals administered lidocaine via the intravenous route converted from ventricular fibrillation to normal sinus rhythm in a mean time of $1.4 \pm 0.1$ minutes). Conversion to normal sinus rhythm occurred in all animals administered lidocaine via the endotracheal route in a time of $1.4 \pm 0.4$ minutes post administration. A separate curve demonstrating plasma lidocaine levels from those animals which did show conversion following intravenous lidocaine is shown in Figure 12. The distribution phase of lidocaine following IV injection was shortened when conversion to spontaneous cardiac
Figure 12

Plasma lidocaine levels vs time following either intravenous injection of 2mg/Kg lidocaine (20mg/ml in normal saline) or endotracheal instillation of 2mg/Kg lidocaine (2mg/ml in normal saline) during ventricular fibrillation with cardiac massage. Also shown is data from only those intravenous experiments in which spontaneous conversion to normal sinus rhythm occurred. Animals were anesthetized with pentobarbital. All points represent mean plasma levels ± S.E.M. of the number of experiments indicated. Intravenous injection was accomplished via a distal hindleg vein.
Lidocaine in Ventricular Fibrillation

- ET
- IV
- IV $\rightarrow$ NSR

Plasma Lidocaine (ug/ml)

Time (min)

n=3
n=4
n=5
Log plasma lidocaine concentrations vs time following either intravenous (IV) injection of 2mg/kg lidocaine (20mg/ml in normal saline) or endotracheal (ET) instillation of 2mg/kg lidocaine (2mg/ml in normal saline). Intravenous injection was made via distal hindleg vein and animals were anesthetized with pentobarbital. Also shown is data from only those intravenous experiments in which spontaneous conversion to normal sinus rhythm occurred. All values represent mean plasma levels of the number of experiments shown.
Log plasma lidocaine (ug/ml)
output occurred.

Comparison of area under the curve (AUC\textsubscript{10}), fraction of dose absorbed (f\textsubscript{10}) and clearance in 10 minutes (Cl\textsubscript{10}) are shown for intravenous and endotracheal lidocaine during ventricular fibrillation in Table III. Ventricular fibrillation increased AUC\textsubscript{10} proportionately both intravenous and endotracheal lidocaine and Cl\textsubscript{10} was the same for both routes.

h) **Plasma Lidocaine Levels Following Endotracheal Administration of Lidocaine 2mg/Kg in Distilled Water Followed by 1mg/Kg Every Five Minutes**

Figure 14 shows plasma lidocaine concentrations observed following a "loading dose" of 2mg/Kg lidocaine endotracheally in distilled water and a "maintenance dose" of 1mg/Kg endotracheally every five minutes. The solution strength was 2mg/ml and the anesthetic used was pentobarbital. Administration of "maintenance doses" every five minutes resulted in accumulation of both peak and trough plasma levels over the 20 minute period. Trough concentrations had accumulated significantly by 20 minutes (p<0.05).

2. **Antifibrillatory Efficacy of Endotracheal Lidocaine**

a) **The Effect of Endotracheal Lidocaine on Duration of Ventricular Fibrillation**

Table IV shows the length of time ventricular fibrillation persisted following endotracheal instillation of 2mg/Kg
Figure 14

Plasma lidocaine levels vs time following endotracheal administration of a 2mg/kg "loading dose" followed by a 1mg/kg "maintenance dose" every 5 minutes. The solution used was lidocaine 2mg/ml in distilled water and animals were anesthetized with pentobarbital. Values are the mean plasma levels ± S.E.M. of three experiments.

* significantly greater than trough level at 5 minutes (p < 0.05).
Plasma Lidocaine (ug/ml)
lidocaine (2mg/ml in normal saline), 1ml/Kg normal saline, or no treatment. In all cases, the hearts were manually pumped as described in the methods.

Administration of lidocaine 2 minutes after the start of ventricular fibrillation significantly reduced the duration of fibrillation compared to either untreated or normal saline controls (p<0.001).

There was no significant difference in the duration of VF between untreated and normal saline controls. The effect of lidocaine on VF was significant regardless of whether the fibrillation occurred during an occlusion or reperfusion phase.

Table V shows percent occlusion of left, right and total ventricular mass in the untreated controls, normal saline controls, and lidocaine-treated group. There was no significant difference in percent occlusion between any of the treatment groups.

When possible, cardiovascular status was monitored for 30 minutes after conversion to spontaneous cardiac rhythm in normal saline controls and lidocaine-treated animals. Of the six animals receiving lidocaine, all resumed spontaneous rhythm within 1.2 minutes of receiving the drug (mean 0.7 ± 0.1 minute). Three of those animals survived to 30 minutes post-conversion with adequate blood pressure and ECG.

Two animals survived less than 10 minutes, with inadequate cardiac output (electro-mechanical dissociation) as the cause of death. One animal was terminated at 10 minutes with adequate BP and ECG (prior to institution of the 30 minute protocol).

In the normal saline control group, three animals had
Table IV
Duration of ventricular fibrillation following ET administration of lidocaine (2mg/Kg) in normal saline, normal saline (1ml/Kg) or no treatment (minutes). Ventricular fibrillation persisted for 2 minutes prior to initiation of protocol. Numbers of experiments are indicated in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>Untreated Controls</th>
<th>Normal Saline Controls (1ml/Kg)</th>
<th>Untreated &amp; Normal Saline Controls Combined</th>
<th>Lidocaine 2mg/Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusion</td>
<td>8.4 ± 1.1 (n=3)</td>
<td>10.0 (n=1)</td>
<td>8.8 ± 0.8 (n=4)</td>
<td>0.7 ± 0.1* (n=3)</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>6.3 ± 1.2 (n=2)</td>
<td>7.2 ± 1.1 (n=4)</td>
<td>6.9 ± 0.8 (n=6)</td>
<td>0.8 ± 0.2* (n=3)</td>
</tr>
<tr>
<td>Total</td>
<td>7.6 ± 0.9 (n=5)</td>
<td>7.8 ± 1.0 (n=5)</td>
<td>7.7 ± 0.6 (n=10)</td>
<td>0.7 ± 0.1* (n=6)</td>
</tr>
</tbody>
</table>

* significantly shorter than untreated controls, normal saline controls or both at p<0.001.

a - times corrected (-2' min) to allow for 2 minutes of ventricular fibrillation prior to administration of lidocaine or normal saline.

b - experiments where ventricular fibrillation occurred during 15 minute occlusion phase.

c - experiments where ventricular fibrillation occurred during 5 minute reperfusion phase.
Table V
Percent occlusion\textsuperscript{a} of right ventricular, left ventricular and total ventricular mass in untreated controls, normal saline controls\textsuperscript{b} and lidocaine-treated group\textsuperscript{c}.

<table>
<thead>
<tr>
<th>Percent Occlusion</th>
<th>Untreated Controls (n=5)</th>
<th>Normal Saline Controls (1ml/Kg) (n=5)</th>
<th>Untreated &amp; Normal Saline Controls Combined (n=10)</th>
<th>Lidocaine 2mg/Kg ET in Normal Saline (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Ventricle</td>
<td>5.9 ± 3.9</td>
<td>6.8 ± 3.2</td>
<td>6.4 ± 2.4</td>
<td>7.8 ± 3.2</td>
</tr>
<tr>
<td>Left Ventricle</td>
<td>46.1 ± 2.9</td>
<td>40.4 ± 2.4</td>
<td>43.3 ± 2.0</td>
<td>44.6 ± 5.6</td>
</tr>
<tr>
<td>Total Ventricle</td>
<td>36.0 ± 3.3</td>
<td>31.3 ± 2.0</td>
<td>33.6 ± 2.0</td>
<td>35.4 ± 4.9</td>
</tr>
</tbody>
</table>

\textsuperscript{a} - no significant difference in percent occlusion between any of the groups.

\textsuperscript{b} - normal saline 1ml/Kg endotracheally.

\textsuperscript{c} - 2mg/Kg lidocaine (2mg/ml in normal saline) endotracheally.
spontaneous conversion to "normal sinus rhythm" and two animals were electrically defibrillated (0.5 watt-seconds, DC counter-shock) 10 minutes after normal saline administration. Four animals survived a further 30 minutes with adequate blood pressure and ECG, and one was terminated at 5 minutes with acceptable cardiovascular status.

b) Tendency for Ventricular Fibrillation: Three Classifications

All coronary artery ligation experiments fell into one of three categories: Short Ventricular Fibrillation (Short VF), Long Ventricular Fibrillation (Long VF) or No Ventricular Fibrillation (No VF) (as reported in methods).

All control experiments in which ventricular fibrillation occurred fell into two distinct categories with respect to duration of ventricular fibrillation (Table VI). In one group, (Short VF), fibrillation lasted for less than two minutes (mean 0.56 ± 0.7 minute, range 0.18-1.83 minutes, n=10) and in the other group, (Long VF), fibrillation lasted for approximately 10 minutes (mean 9.5 ± 0.07, range 6.5-12.5 minutes, n=16). All hearts which fibrillated for longer than two minutes did so for at least 6.5 minutes (unless treated with lidocaine) and were used in the lidocaine efficacy experiments.

Also shown in Table VI are the number of fibrillation episodes per animal in the Short and Long VF categories. There was a tendency for multiple episodes of fibrillation to occur in the Short VF category. Many of these occurred during a reperfusion phase of the experiment. In all animals studied, only one Long VF
Table VI

Duration and frequency of ventricular fibrillation in short ventricular fibrillation and long ventricular fibrillation categories.

<table>
<thead>
<tr>
<th></th>
<th>Number of Animals</th>
<th>Number of VF Episodes</th>
<th>VF Frequency (# per experiment)</th>
<th>Duration of VF Mean (min)</th>
<th>S.E.</th>
<th>Range (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short VF:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion(^a)</td>
<td>7</td>
<td>9</td>
<td>1.3</td>
<td>0.62±0.18</td>
<td>0.17-1.83</td>
<td></td>
</tr>
<tr>
<td>Reperfusion(^b)</td>
<td>4</td>
<td>24</td>
<td>6.0</td>
<td>0.54±0.08</td>
<td>0.17-1.83</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>11</td>
<td>33</td>
<td>3.0</td>
<td>0.56±0.07</td>
<td>0.17-1.83</td>
<td></td>
</tr>
</tbody>
</table>

| **Long VF:**   |                   |                       |                                 |                           |      |             |
| Occlusion      | 4                 | 4                     | 1.0                             | 11.0±1.0                  | 8.8-12.5 |
| Reperfusion    | 6                 | 6                     | 1.0                             | 8.9±0.9                   | 6.5-11.5 |
| **Total**      | 10                | 10                    | 1.0                             | 9.7±0.7                   | 6.5-12.5 |

\(^a\) - VF occurred during an occlusion phase.

\(^b\) - VF occurred during a reperfusion phase.
episode occurred per experiment although one animal had multiple short fibrillations prior to establishing a long fibrillation.

Figure 15 shows typical ECG and blood pressure tracings obtained during ventricular fibrillation with open-chest manual heart massage. A mean systolic BP of 50mm Hg was usually obtained with this method and massage was performed at a rate of approximately 130 compressions per minute. When the chart speed was increased to 10mm/sec and massage was temporarily stopped, the ECG tracings show ventricular fibrillation and the blood pressure tracing demonstrates the absence of cardiac output. This tracing was taken from an experiment where fibrillation lasted for 10 minutes after administration of 1ml/Kg normal saline endotracheally.

Figure 16 shows typical ECG and BP tracings obtained during a short fibrillation episode (less than 2 minutes). Shown are the period of fibrillation followed by spontaneous conversion to a regular heart beat.

Table VII shows percent occlusion of left, right and total ventricular mass in the No VF, Short VF and Long VF categories. There was no significant difference in occluded areas between the Short VF, Long VF and No VF groups.

The incidence of ventricular arrhythmias in the No VF group, or prior to ventricular fibrillation in the Short VF and Long VF groups is shown in Table VIII.

Fifty-seven percent of hearts which did not fibrillate demonstrated ventricular arrhythmias during the experimental protocol. The incidence of arrhythmias was greater prior to short or long fibrillation episodes, 90% and 75% respectively. Where multiple short fibrillation episodes occurred during one
Figure 15

Blood pressure and ECG recordings during ventricular fibrillation with manual heart massage. The chart speed was increased to 10mm/sec from 10mm/min every minute to demonstrate ventricular fibrillation and lack of cardiac output.
Blood pressure and ECG recordings during a ventricular fibrillation episode which lasted 25 seconds and terminated spontaneously. The tracing was run at a chart speed of 10mm/second except for the area indicated by the dark bar to the right of the tracing, where the chart speed was 10mm/minute.
Table VII

Comparison of percent occlusion of left ventricle, right ventricle and total ventricular mass with tendency to fibrillate.

<table>
<thead>
<tr>
<th>% Area Occluded</th>
<th>% Right Ventricle</th>
<th>% Left Ventricle</th>
<th>% Total Ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Ventricular Fibrillation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.9 ± 1.8</td>
<td>36.4 ± 4.1</td>
<td>28.2 ± 3.4</td>
</tr>
<tr>
<td>Short Ventricular Fibrillation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.8 ± 1.9</td>
<td>46.7 ± 4.6</td>
<td>36.0 ± 4.1</td>
</tr>
<tr>
<td>Long Ventricular Fibrillation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.9 ± 1.9</td>
<td>43.8 ± 2.3</td>
<td>34.3 ± 2.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ventricular fibrillation did not occur at any time during the experiment.

<sup>b</sup> Ventricular fibrillation lasted for less than 2 minutes.

<sup>c</sup> Ventricular fibrillation lasted longer than 2 minutes. Includes all animals in control groups and group treated with lidocaine.
Table VIII

Comparison of the incidence of ventricular arrhythmias following coronary artery ligation with tendency to fibrillate.

<table>
<thead>
<tr>
<th>Number of Animals</th>
<th>Number of Animals with Ventricular Arrhythmias</th>
<th>% with Arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Ventricular Fibrillation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Short Ventricular Fibrillation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Long Ventricular Fibrillation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16</td>
<td>12</td>
</tr>
</tbody>
</table>

<sup>a</sup> - ventricular fibrillation did not occur at any time during the experiment.

<sup>b</sup> - VF lasted for less than 2 minutes. Arrhythmias reported only prior to first fibrillation.

<sup>c</sup> - VF lasted longer than 2 minutes. Includes all animals in control groups and group treated with lidocaine.
experiment, only the time prior to the first fibrillation was noted for arrhythmias.

Figures 17 and 18 compare the changes in blood pressure and heart rate which occurred during the first ten minutes after coronary artery occlusion in the No VF, Short VF and Long VF categories.

In all three groups, the largest drop in blood pressure occurred during the first two minutes after occlusion of the artery (Figure 17), after which blood pressure appeared to stabilize. There was no significant difference in blood pressure between the three groups at any time points.

Heart rate was shown to decline following coronary artery ligation in animals in which ventricular fibrillation occurred (Figure 18). There was no appreciable change in heart rate in animals in which ventricular fibrillation did not occur. The largest change in heart rate occurred over the first two minutes of occlusion in the Long VF category. There was a significant difference (p < 0.05) in heart rate at ten minutes between animals where no fibrillation or long fibrillation occurred.

c) Occlusion vs Reperfusion Ventricular Fibrillation

Table IX shows the percent occlusion of left, right, and total ventricular mass in experiments where ventricular fibrillation (longer than two minutes) occurred during an occlusion or reperfusion phase. There were no significant differences in these measurements between the two groups. Measurements of the occluded areas were performed with the ligatures secured in all
Figure 17

Comparison of blood pressure before and for 10 minutes after coronary artery ligation in animals in which no ventricular fibrillation, short ventricular fibrillation (less than 2 minutes), or long ventricular fibrillation occurred (longer than 2 minutes). Values shown are mean systolic and diastolic pressures for the number of animals indicated. There was no significant difference in blood pressure between the three groups at any time point.
Figure 18

Changes in heart rate following coronary artery occlusion in No VF, Short VF (less than 2 minutes), and Long VF (greater than 2 minutes) experiments. Values expressed are mean heart rate ± S.E.M. of the number of experiments indicated.

* significantly less than no ventricular fibrillation at \( p \leq 0.05 \).
• No VF
• Short VF
• Long VF

Heart Rate (beats/min)

Pre-ligation
2 min
5 min
10 min
Post-ligation

n=7
n=10
n=16
experiments, as described in the methods.

There were no significant differences in pre-ligation, post-ligation or pre-fibrillation blood pressures and heart rates between animals where VF occurred during occlusion or reperfusion phases. Ventricular arrhythmias occurred prior to VF in five out of seven animals where VF (longer than two minutes) occurred during occlusion, and in seven out of nine animals where it occurred during reperfusion. During Short VF experiments, ventricular arrhythmias preceded the first fibrillation episode in all seven animals where it occurred during occlusion and in two out of three where it occurred during a reperfusion phase.
Table IX
Comparison of percent occlusion of left ventricle, right ventricle and total ventricular mass in ventricular fibrillation (>2 min) occurring during an occlusion or reperfusion period.\(^a\)

<table>
<thead>
<tr>
<th>% Area Occluded</th>
<th>Phase Where VF Occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Occlusion Phase(^b)</td>
</tr>
<tr>
<td>% Right Ventricle</td>
<td>8.4 ± 3.3</td>
</tr>
<tr>
<td>% Left Ventricle</td>
<td>45.6 ± 2.6</td>
</tr>
<tr>
<td>% Total Ventricle</td>
<td>36.1 ± 2.7</td>
</tr>
</tbody>
</table>

\(^a\) - no significant difference between occlusion and reperfusion groups.

\(^b\) - VF occurred during occlusion phase.

\(^c\) - VF occurred during reperfusion phase.
DISCUSSION

The present study indicates that lidocaine is rapidly and extensively absorbed following administration via an endotracheal tube in the rabbit. These data are in agreement with those of Elam (1977) where a prompt ECG response to ET lidocaine was noted in hypoxia-induced cardiac arrest in dogs.

Others have previously reported similar results using ET epinephrine, where rapid but prolonged responses (Redding et al, 1967; Elam, 1977; Roberts et al, 1978) and sustained plasma levels (Roberts et al, 1979a) were observed.

Results of the present study showed lower peak plasma levels following ET lidocaine when compared to IV (Figures 10 & 11), but slower decline in plasma levels, so that at two minutes the ET plasma level was significantly greater than the IV level. This delayed absorption may be due to a depot or reservoir of drug in the alveoli, as suggested by Roberts et al (1978; 1979a) for epinephrine. They observed even more prolonged ET absorption of epinephrine than we observed with lidocaine, perhaps due to local vasoconstriction of lung vasculature through stimulation of \( \alpha \)-receptors by epinephrine.

Results obtained in early experiments (Figures 3 & 4) are perhaps somewhat misleading. Using IV injection as a standard, the percent of lidocaine absorbed via the ET route was calculated to be 132% based on measurement of the area under the curve. These data are clarified in Figures 10 & 12 where percent of the ET dose absorbed over ten minutes was shown to be approximately 70% of an IV dose. It is possible that greater
and more prolonged plasma levels were seen with the ET route than with the IV route due to the initial method used to administer the IV injection. Lidocaine was injected as a 2mg/ml solution in a dosage of 2mg/Kg via the marginal ear vein. This volume (1ml/Kg) may parallel a relatively large volume injection in man, approximately 50 - 100ml based on comparison of total blood volume. When given rapidly a volume of this size may distribute rapidly throughout the circulation, resulting in a smaller peak plasma level than seen following a small volume IV bolus injection. Furthermore, due to the time required to inject a relatively large volume, the true peak plasma lidocaine level probably occurred prior to taking the first sample at 15 seconds.

Delayed absorption of ET lidocaine was reflected in a first-order rate constant (α_{ET}) which was approximately 70% of the value calculated for the IV route. It should be noted that α_{ET} in this case is a reflection of both absorption and distribution which were not separated, and is not a pure distribution rate constant. Following IV injection absorption is complete, hence α_{IV} in this case is a true reflection of the distribution of lidocaine in this model.

Elimination rate constants (β) for the two routes of administration were found to be similar (Figure 4, Table I). This suggests that absorption via the ET route was virtually complete within approximately ten minutes. Absorption - distribution, distribution, and elimination half-lives were extremely short in this model, due to rapid circulation times in the rabbit. This accounts in part for the large standard errors obtained during the first 15 - 30 seconds of sampling
in most experiments.

Spontaneous or artificial ventilation had no significant effect on plasma lidocaine levels following ET instillation although during spontaneous respiration higher plasma levels were generally seen. This is in contrast to the report by Scott et al (1976), where higher plasma lidocaine levels were noted in patients who were paralyzed and ventilated. Differences in ventilation methods and drug administration may account for this discrepancy.

Endotracheal administration of epinephrine in distilled water has been shown to have a shorter onset of action compared with administration in normal saline (Redding et al, 1967). Data shown in Figure 6 suggest a similar phenomenon for lidocaine, although there was a significant difference only at 30 seconds. Absorption of distilled water from the alveoli has been shown to occur at a faster rate than absorption of normal saline (Courtice and Phipps, 1946). As shown by Redding et al (1967) and confirmed by these data, the duration of effect of the drug may be prolonged when normal saline is the vehicle, without a change in the efficacy of the drug. For these reasons, and the potential for normal saline to be a more physiologic medium than distilled water, it was decided to use lidocaine in normal saline for further endotracheal studies.

Lidocaine is an oil soluble compound (Merck Index, 1968) and therefore has the potential to diffuse well across the lipid alveolar membrane. This may partly explain why there is not a large difference between its absorption in water or normal saline.

Calculated pharmacokinetic parameters for ET lidocaine
in normal saline and distilled water (Table II) are rough estimates at best due to the lack of time points beyond 30 minutes. They do, however, illustrate a slightly prolonged absorption - distribution phase when the assumption is made that final elimination should occur in a parallel fashion.

The small elevation in ET lidocaine levels above controls which occurred upon opening the chest cavity (Figure 8) is presumably due to changes produced in intrathoracic pressure by this procedure.

Of interest is the large elevation in plasma lidocaine levels observed during ventricular fibrillation (Figures 8 & 9). It may be postulated that the circulatory changes which accompany cardiac arrest (with cardiac massage) could result in a prolonged distribution phase and confinement of adequate circulating blood flow to the central circulation. This may have produced the abnormally high plasma lidocaine levels which persisted for a longer period of time than in controls. These changes in drug distribution are reflected in the decreased ten - minute clearances ($C_{10}$) calculated during ventricular fibrillation (Table III).

Barsan et al (1981) also reported peak plasma lidocaine levels which were elevated well into the toxic range following either peripheral venous or central venous injection in dogs receiving CPR during cardiac arrest. These observations emphasize the need for similar clinical studies in man, since current cardiac arrest dosage regimens may indeed produce drug levels which are higher than one would otherwise assume. In fact, an assumption is often made during cardiac arrest drug therapy that lack of clinical response may be due in part to
poor circulating levels of the drug in question; additional
doses may then be given.

Ventricular fibrillation (with cardiac massage) did
not alter the amount of lidocaine absorbed via the endotracheal
route (Table III) during the first ten minutes after drug
administration. Based on this observation, plus the fact that
during ventricular fibrillation peak plasma lidocaine levels
were observed 30 seconds after administration of the drug, one
could assume that adequate circulation to the lungs is maintained
in this condition.

The 'depot' effect following endotracheal administration
of lidocaine was also observed during ventricular fibrillation
(Figures 12 & 13). Compared with IV injection, distribution
was prolonged and initial peak plasma levels were not as high.
This may have some therapeutic advantage since administration
via this route may avoid initial toxic levels and prolong the
time in the therapeutic range.

Endotracheal administration of lidocaine every five
minutes resulted in slow and steady accumulation of both peak
and trough plasma lidocaine levels (Figure 14). It may be
assumed from this that if smaller doses had been given more
frequently, a pseudo 'steady state' plasma level could have
been achieved within the therapeutic range.

After both IV and ET administration of lidocaine
the final elimination (β) phase occurred in a parallel fashion.
Since 70% of the original ET dose had been absorbed by 10
minutes, one might postulate that extra - hepatic metabolism
or storage could account for the remaining 30% of the dose.
Post et al (1978) has demonstrated accumulation of lidocaine in
perfused rat lungs. The significance of accumulation of lidocaine in lung tissue is not clear at this time, although lidocaine endotracheal spray has been used for topical anesthesia for many years without evidence of lung toxicity.

Endotracheal administration of lidocaine during prolonged ventricular fibrillation had a profound effect on reducing the duration of the arrhythmia regardless of whether fibrillation resulted from occlusion or reperfusion of the coronary artery (Table IV). Without exception, ventricular fibrillation reverted to an organized cardiac rhythm within 1.2 minutes of lidocaine administration (mean 0.7 ± 0.1 min.). This is in contrast to control experiments where fibrillation persisted for 6.5 - 12.5 minutes (mean 7.7 ± 0.6 min.). The mean duration of ventricular fibrillation in control experiments is, in fact, artificially shortened since most arrhythmias were terminated at ten minutes with electrical defibrillation if spontaneous conversion to an organized heart beat had not occurred.

Comparison of percent ventricular mass to which blood flow was occluded (Table V) shows that the response to lidocaine was not biased in any way by smaller occluded zones in those animals.

No further episodes of ventricular fibrillation occurred in any animals after conversion to regular cardiac rhythm (in the lidocaine efficacy studies). Even non lidocaine-treated animals appeared to be relatively arrhythmia-free once an organized heart beat had begun.

In most animal models of coronary occlusion in the
literature, there appear to be two definite periods of susceptibility to ventricular fibrillation. In this model, it appeared that occlusion-induced fibrillation always occurred within ten or fifteen minutes of occlusion, and reperfusion fibrillation occurred almost as soon as the ligature was released.

Since conclusion of this study, Harrison (1981) has reported a trial of lidocaine in out-of-hospital counter-shock refractory ventricular fibrillation. Patients not responding to two electrical countershocks plus intravenous sodium bicarbonate were given either lidocaine plus further therapy as ordered by physicians (epinephrine, calcium chloride, sodium bicarbonate), or further therapy with no antiarrhythmic drug. The authors reported no difference in percent of patients remaining in ventricular fibrillation upon arrival at the hospital and there was no significant difference in other drugs used between the two groups.

A number of aspects of this study are open to criticism, however. Only one 100mg IV bolus of lidocaine was given during any resuscitation attempt, and the authors do not state the mean time in this group from initiation of the resuscitation attempt to arrival at the hospital. Other details which are not given are the time sequence with respect to lidocaine administration and any subsequent cardiac rhythms. It is not stated whether patients still in fibrillation upon arrival at the hospital had exhibited any other cardiac rhythms during the preceding resuscitation attempt. The study was not randomized; patients were selected by the ordering physician with respect to lidocaine administration. The
authors were unable to determine the criteria used in these cases for the use of lidocaine. This report does, however, address the question of antiarrhythmic therapy of countershock-refractory ventricular fibrillation, and raises some very appropriate concerns with regard to current therapy.

Firstly, appropriateness of all agents used should be assessed, with respect to both immediate response and long-term survival of patients. Secondly, dosages of drugs currently used should be examined for both efficacy and toxicity. As shown in the current study, plasma levels of lidocaine during cardiac arrest may in fact be much higher initially than often presumed. Since the circulation time in a small animal such as a rabbit differs greatly from that of man, a direct parallel cannot be drawn with respect to rate and extent of appearance of lidocaine in the blood during cardiac arrest.

Bretylium therapy in the treatment of cardiac arrest has recently been evaluated by Nowak et al (1981). They reported greater survival in patients receiving bretylium (39%) than those receiving placebo (9%) for ventricular fibrillation. All other drug therapy was administered according to American Heart Association (1980) guidelines. Of note is the fact that lidocaine was used more frequently in the group who received bretylium, and isoproterenol was used more often in the placebo group. These trends may have predisposed patients to increased (or decreased) survival.

Lidocaine has also been compared recently with bretylium in the management of out-of-hospital ventricular fibrillation (Haynes et al, 1981). After one electrical defibrillation attempt, approximately 24% of patients had
converted to an organized rhythm in both groups, whereas follow­
ing either lidocaine (100mg) or bretylium (500mg) intravenously
plus an average of 1.6 additional defibrillatory shocks, 89% of patients receiving bretylium and 93% of patients receiving
lidocaine had converted to an organized rhythm. The percent of
patients in the lidocaine and bretylium - treated groups who
were subsequently discharged home was 26% and 34% respectively,
which is somewhat in contrast to the number discharged home in
Harrison's (1981) study (2-11%).

It appears that further evaluation of lidocaine as an
adjunct to the management of ventricular fibrillation needs to
be performed. Certainly the data from the present study
indicate that lidocaine may posess some antifibrillatory
efficacy, at least in the model used. It was not possible
in this animal model to assess only fibrillation episodes
refractory to electrical defibrillation since all hearts were
easily defibrillated electrically. It therefore became
necessary to assess the efficacy of lidocaine as a chemical
defibrillator alone, and not as an adjunct to electrical
defibrillation.

The three clinical studies mentioned herein are the
first reported attempts to directly address the issue of
antiarrhythmic therapy in the treatment of defibrillation -
refractory ventricular fibrillation. Further work in this
area is definitely required before decisions concerning the most
appropriate agents, dosages and routes of administration can be
made.

In the animal model used in this study, certain trends
were observed concerning duration of ventricular fibrillation.
It was noted that fibrillation appeared to occur more often in animals in which a certain area of myocardium had been occluded (Table VII). Although the difference in percent of left ventricular and percent of total ventricular mass occluded between the No VF and Long VF groups is not statistically significant \((p=0.104\) and \(p=0.128\) respectively), a trend appeared to exist in which hearts with a larger occluded area were more likely to fibrillate. It is interesting to speculate that in a small animal heart such as the rabbit heart perhaps a relatively large area (40-45%) of ischemic left ventricle is required for the production and maintenance of re-entrant pathways.

During preliminary experiments, two distinct patterns developed with respect to the amount of time fibrillation persisted (Table VI). It became obvious that the lidocaine efficacy study could only be carried out on animals where the arrhythmia had persisted for at least two minutes, since spontaneous defibrillation often occurred prior to that time. Other authors have not reported these two distinct trends in ventricular fibrillation, possibly since their study designs would not necessarily reveal such trends.

Short ventricular fibrillation episodes occurred more frequently during reperfusion than during occlusion (Table VI), and once an episode of short fibrillation had occurred in an animal, a long fibrillation episode was unlikely to occur. It is possible that the areas of damaged myocardium generating these short arrhythmias were less able to sustain the abnormal conduction necessary to produce a prolonged episode of
ventricular fibrillation.

As reported in other trials in the literature, reperfusion of previously ischemic myocardium was found in this study to be highly arrhythmogenic, often resulting in ventricular fibrillation within one minute of reperfusion. This was in contrast to occlusion arrhythmias which tended to develop over a period of minutes after occlusion, finally degenerating into ventricular fibrillation. No other differences were noted between the two phases. Areas of occlusion were the same in both groups undergoing a long ventricular fibrillation episode (Table IX).

In summary, these studies suggest that lidocaine may be effective in terminating ventricular fibrillation due to acute myocardial infarction. Since ventricular fibrillation in man is managed with electrical defibrillation plus drug therapy, the significance of these findings in relation to the clinical situation remains unclear.

This study indicates that lidocaine may have similar efficacy in ventricular fibrillation whether given intravenously or endotracheally since plasma levels achieved are comparable. Further studies are required, however, before any definitive conclusions can be drawn. The intravenous route is still the route of choice for administration of drugs during cardiac arrest. These data simply lend support to the hypothesis that the endotracheal route may be an effective alternate route for lidocaine administration, should access to an IV line be delayed.
CONCLUSIONS

1. In the rabbit, lidocaine is absorbed as rapidly following endotracheal administration as following intravenous injection, with approximately 70% of an endotracheal dose absorbed over 10 minutes.

2. Following endotracheal administration lower peak plasma lidocaine levels and slightly prolonged distribution were observed compared with peripheral intravenous injection.

3. Following both intravenous and endotracheal administration during ventricular fibrillation, peak plasma lidocaine levels are greater and initial distribution is prolonged, compared with controls.

4. Administration of lidocaine endotracheally during persistent ventricular fibrillation due to acute coronary artery ligation significantly shortens the duration of fibrillation.
REFERENCES


