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GLASS, STEVEN JAMES

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THE EFFECT OF CIMETIDINE, RANITIDINE, AND HALOTHANE ON LIDOCAINE PHARMACOKINETICS IN MAN

by

Steven James Glass

A Thesis Submitted to the Faculty of the COMMITTEE ON TOXICOLOGY (GRADUATE) In Partial Fulfillment of the Requirement For the Degree of

MASTER OF SCIENCE

In the Graduate College

THE UNIVERSITY-OF ARIZONA

1983
STATEMENT BY AUTHOR

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This thesis has been approved on the date shown below:

John Bentley, M.D.
Assistant Professor of Anesthesiology

Date
To my children
for their love and understanding
and to Jenny
whose time and patience made this thesis possible
ACKNOWLEDGMENTS

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF ILLUSTRATIONS</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>viii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>x</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Drug-drug Interactions</td>
<td>1</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>1</td>
</tr>
<tr>
<td>Effects of Cimetidine on Hepatic Metabolism</td>
<td>5</td>
</tr>
<tr>
<td>Effects of Cimetidine on Hepatic Blood Flow</td>
<td>7</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>8</td>
</tr>
<tr>
<td>Effects of Ranitidine on Hepatic Metabolism</td>
<td>8</td>
</tr>
<tr>
<td>Effects of Ranitidine on Liver Blood Flow</td>
<td>9</td>
</tr>
<tr>
<td>Halothane</td>
<td>10</td>
</tr>
<tr>
<td>Effects of Halothane on Hepatic Drug Metabolism</td>
<td>10</td>
</tr>
<tr>
<td>Effects of Halothane on Liver Blood Flow</td>
<td>11</td>
</tr>
<tr>
<td>Alpha1-acid Glycoprotein</td>
<td>13</td>
</tr>
<tr>
<td>Lidocaine Kinetics and Liver Blood Flow</td>
<td>13</td>
</tr>
<tr>
<td>Statement of the Problem</td>
<td>16</td>
</tr>
<tr>
<td>MATERIALS AND METHODS</td>
<td>17</td>
</tr>
<tr>
<td>Chemicals</td>
<td>17</td>
</tr>
<tr>
<td>Ranitidine/Cimetidine Study</td>
<td>20</td>
</tr>
<tr>
<td>Lidocaine Protocol</td>
<td>21</td>
</tr>
<tr>
<td>Halothane/Nitrous Narcotic Study</td>
<td>22</td>
</tr>
<tr>
<td>Halothane Analysis</td>
<td>24</td>
</tr>
<tr>
<td>Analytical</td>
<td>24</td>
</tr>
<tr>
<td>Lidocaine Metabolites</td>
<td>32</td>
</tr>
<tr>
<td>Alpha1-acid Glycoprotein</td>
<td>32</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>33</td>
</tr>
<tr>
<td>Statistics</td>
<td>40</td>
</tr>
<tr>
<td>RESULTS</td>
<td>42</td>
</tr>
<tr>
<td>Cimetidine–Ranitidine Study</td>
<td>42</td>
</tr>
<tr>
<td>Morphological Characteristics</td>
<td>42</td>
</tr>
<tr>
<td>H2 Receptor Blockers and Lidocaine Concentration</td>
<td>42</td>
</tr>
<tr>
<td>Pharmacokinetic Data</td>
<td>45</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS--Continued

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha₁-acid Glycoprotein Levels and Vdₜₜ.</td>
<td>51</td>
</tr>
<tr>
<td>Halothane Study</td>
<td>51</td>
</tr>
<tr>
<td>Morphological Characteristics</td>
<td>51</td>
</tr>
<tr>
<td>Lidocaine Concentration and Dose.</td>
<td>54</td>
</tr>
<tr>
<td>End Tidal Halothane Levels.</td>
<td>54</td>
</tr>
<tr>
<td>Metabolite Pharmacokinetics</td>
<td>57</td>
</tr>
<tr>
<td>Lidocaine Pharmacokinetics</td>
<td>60</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>65</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>81</td>
</tr>
</tbody>
</table>
LIST OF ILLUSTRATIONS

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>A diagram depicting the major route of lidocaine metabolism.</td>
<td>15</td>
</tr>
<tr>
<td>2.</td>
<td>Chemical structures of lidocaine and its analogues MEGX and EMGX.</td>
<td>18</td>
</tr>
<tr>
<td>3.</td>
<td>Chemical structures of cimetidine and ranitidine.</td>
<td>19</td>
</tr>
<tr>
<td>4.</td>
<td>A spectrophotometric scan of lidocaine showing a peak absorbance at about 210.</td>
<td>26</td>
</tr>
<tr>
<td>5.</td>
<td>A chromatogram of an HPLC separation of lidocaine and major metabolite MEGX during the cimetidine-ranitidine study.</td>
<td>27</td>
</tr>
<tr>
<td>6.</td>
<td>Typical lidocaine calibration curve extracted from plasma (r = 0.9999).</td>
<td>29</td>
</tr>
<tr>
<td>7.</td>
<td>A sample chromatogram resulting from HPLC separation of lidocaine, the internal standard EMGX and MEGX during the halothane study.</td>
<td>31</td>
</tr>
<tr>
<td>8.</td>
<td>Sample gel demonstrating the single radial immunodiffusion technique used to determine the concentration of AAG in human serum.</td>
<td>34</td>
</tr>
<tr>
<td>9.</td>
<td>Serum lidocaine concentration-time plot for one subject who showed the greatest effect.</td>
<td>50</td>
</tr>
<tr>
<td>10.</td>
<td>Comparison of alpha₁-acid glycoprotein levels and steady-state volume of distribution for the subjects participating in the cimetidine-ranitidine study.</td>
<td>53</td>
</tr>
<tr>
<td>11.</td>
<td>Serum lidocaine concentration-time plot for patient number 4, who received the nitrous-narcotic anesthetic technique.</td>
<td>63</td>
</tr>
<tr>
<td>12.</td>
<td>Serum lidocaine concentration-time plot for patient number 5, who received halothane anesthesia.</td>
<td>64</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anthropometric data for subjects participating in the cimetidine-ranitidine study.</td>
<td>43</td>
</tr>
<tr>
<td>2. Comparison of lidocaine concentrations and dose between the different treatment groups in the cimetidine-ranitidine study.</td>
<td>44</td>
</tr>
<tr>
<td>3. Comparison between treatment groups of pharmacokinetic parameters obtained from the model independent method in the cimetidine-ranitidine study.</td>
<td>47</td>
</tr>
<tr>
<td>4. Comparison between treatment groups obtained from SPSS-NONLIN fitted to a two compartment model in the cimetidine-ranitidine study.</td>
<td>48</td>
</tr>
<tr>
<td>5. Comparison between treatment groups of pharmacokinetic parameters obtained from SPSS-NONLIN fitted to a two/three compartment combination model in the cimetidine-ranitidine study.</td>
<td>49</td>
</tr>
<tr>
<td>6. Serum alpha_1-acid glycoprotein levels (mg/dl) following the various pretreatments in the cimetidine-ranitidine study.</td>
<td>52</td>
</tr>
<tr>
<td>7. Comparison of morphological characteristics for the patients participating in the halothane study.</td>
<td>55</td>
</tr>
<tr>
<td>8. Lidocaine concentration and dose compared between halothane and nitrous-narcotic treatment groups during the halothane study.</td>
<td>56</td>
</tr>
<tr>
<td>9. End tidal levels of halothane obtained throughout the surgical procedure for patients receiving halothane anesthesia.</td>
<td>58</td>
</tr>
<tr>
<td>10. Pharmacokinetic data obtained from the halothane and nitrous-narcotic treatment groups for the major metabolite for lidocaine, MEGX during the halothane study.</td>
<td>59</td>
</tr>
<tr>
<td>Table</td>
<td>Page</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>11. Halothane data summary comparing the pharmacokinetic parameters between halothane and nitrous-narcotic treatment groups.</td>
<td>61</td>
</tr>
</tbody>
</table>
ABSTRACT

Alterations in lidocaine pharmacokinetics by ranitidine and cimetidine were compared in a double blind, double dummy cross over study, while the ability of halothane to alter the disposition of lidocaine was tested in patients receiving halothane or nitrous-narcotic anesthesia. Lidocaine concentrations were determined during and up to five hours following drug administration. Pharmacokinetic parameters were determined from serum concentration-time data for each individual. Cimetidine treatment caused decreased lidocaine $C_l_s$ and $V_d_{ss}$, while ranitidine treatment resulted in no significant changes in these pharmacokinetic parameters. Halothane anesthesia caused decreases in both $C_l_s$ and $V_d_{ss}$. The clinical implications of these studies is that drug interactions involving widely used drugs, such as cimetidine and halothane, may occur if the potential for these interactions is not realized.
INTRODUCTION

Drug-drug Interactions

Drug interactions, where one drug affects the disposition or effect of another, are important in clinical medicine, since toxicity may result. These alterations may come about at many levels, including absorption, distribution, excretion, or protein binding of the compound. These interactions may be detected using a branch of pharmacology known as pharmacokinetics, which is the study of the time course of drug disposition and effect. Usually mathematical relationships are required to formulate models to interpret such data. In any case, using parameters such as the terminal elimination half-life ($t_{1/2} \beta$), the volume of drug distribution ($V_d$), and total systemic clearance ($Cl_s$) alterations in drug disposition can be detected. By definition, $t_{1/2} \beta$ is the time required for drug concentration to decrease by 50%. Alterations in $t_{1/2} \beta$ may be due to changes in $Cl_s$ or $V_d$ through the relationship:

$$t_{1/2} \beta = \frac{(0.693)(V_d)}{Cl_s}$$

$V_d$ is the theoretical volume into which a drug distributes, while $Cl_s$ is the volume of blood from which all drug is removed by the organs of elimination per unit time. Changes in $V_d$ can result if drug is displaced from protein binding sites in the blood or tissue through the relationship:
\[ V_d = V_{\text{blood}} + \frac{\text{unbound drug in blood} \times V_{\text{tissue}}}{\text{unbound drug in tissue}} \]

where \( V_{\text{blood}} \) is the volume of the blood compartment and \( V_{\text{tissue}} \) is the volume of the tissue compartment. Changes in \( C_l_s \) may be detected through the relationship:

\[ C_l_s = \frac{\text{Div}}{\text{AUC}} \]

where Div is the intravenous dose of the drug, and AUC is the area under the serum concentration-time curve for the drug.

\( C_l_s \) may be termed hepatic clearance \( (C_l_H) \), if elimination of the drug is carried out solely by the liver. This is the case for many drugs, and as such their clearance can be described by the following mathematical formula:

\[ C_l_s = C_l_H = Q \cdot \left[ \frac{f_B \cdot C_{l\text{int}}}{Q + f_B \cdot C_{l\text{int}}} \right] \]

where \( Q \) is equal to liver blood flow, \( f_B \) is equal to the fraction of drug that is unbound in blood, and \( C_{l\text{int}} \) is equal to intrinsic clearance -- a pharmacokinetic term which is the inherent ability of the liver to irreversibly remove drug in the absence of any blood flow limitations. Alterations in protein binding cause changes in \( f_B \), while alterations in hepatic metabolism change \( C_{l\text{int}} \). The term in brackets above is also known as the extraction ratio \( (E) \), so that the formula could also be written:

\[ C_l_H = Q \cdot E \]
Drugs that are metabolized by the liver can be termed high and low clearance based upon their initial value of Cl_{int}. Such drugs as warfarin, theophylline, or aminopyrine are termed low clearance drugs because their clearance is dependent upon the activity of the drug metabolizing enzymes in the liver, and very little upon the rate of liver blood flow. In other words, a doubling of the metabolic activity of the liver presumably through induction, will result in an approximately equal increase in the extraction ratio due to the small initial value of Cl_{int}, which will result in a proportional increase in Cl_{H}. An increase in Q will have very little effect on low clearance drugs because their small initial value of Cl_{int} and small E will counteract any increase in Q within physiological limits. On the other hand, high clearance drugs such as lidocaine and propranolol will be very little affected by increases in Cl_{int} due to their large initial value of Cl_{int}; however, the clearance of these drugs will be largely affected by changes in Q (Wilkinson and Shand, 1975).

Certain drugs such as cimetidine, a potent H_{2} receptor blocker used to treat peptic and duodenal ulcers, and halothane, a volatile anesthetic, have been reported to cause alterations in both hepatic metabolism and liver blood flow, so that these compounds have the potential to cause decreased hepatic disposition of both high and low clearance drugs (Gelman, 1976; Wood and Wood, 1982; Somogyi and Gugler, 1982).
Ranitidine, another $H_2$ receptor blocker, has been implicated in reducing liver blood flow, so that this drug also may alter the clearance of drugs with high $Cl_H$ (Feeley and Guy, 1982; Heagerty, Castleden, and Patel, 1982). In this regard, lidocaine, a prototype high clearance drug, theoretically can be used as a pharmacokinetic tool to test the ability of these compounds to alter liver blood flow. That is, changes in liver blood flow caused by cimetidine, ranitidine and halothane would be expected to cause large alterations in the clearance of lidocaine.

Because of their close relationship, both the clearance and volume of distribution of lidocaine may potentially be affected by the concentration of alpha$_1$-acid glycoprotein (AAG). This protein is the major serum binding protein of lidocaine and also many other basic drugs. The serum concentration of this acute reactive protein increases in response to stress, inflammatory disease, malignant tumors, and various hematological disorders (Kawai, 1973). Cimetidine, ranitidine or halothane could potentially affect the volume of distribution or clearance of lidocaine by affecting the levels of AAG and hence lidocaine protein binding.

Thus, lidocaine can be used as a prototype high clearance drug to test potential drug interactions involving cimetidine, ranitidine and halothane, employing pharmacokinetic modeling.
Cimetidine

Cimetidine (Tagamet) is a potent $H_2$ receptor antagonist, which is widely prescribed to treat peptic and duodenal ulcers due to its ability to decrease gastric acid secretion. The drug was first introduced into the U.S. in August, 1977, and has since become the most widely prescribed drug in America (Duncan and Parsons, 1980).

The usual therapeutic dosage of oral cimetidine to treat peptic ulcer disease is 300 mg, with the dose interval being every six hours. Peak blood levels occur 60-90 minutes after oral administration, and correlate directly with the administered dosage. Approximately 70% of the drug is recovered in urine within 24 hours of administration, and the terminal elimination half-life is about two hours in patients without renal dysfunction (Brogden et al., 1978). The principal reason for concern about this drug is its ability to alter the disposition of many high (lidocaine and propranolol) and low (antipyrine) clearance drugs (Somogyi and Gugler, 1982).

Effects of Cimetidine on Hepatic Metabolism

Cimetidine has been found to alter the kinetics of many low clearance drugs both in vitro and in vivo. In vitro, cimetidine decreases the metabolism of aminopyrine, benzo(a)pyrene, meperidine and pentobarbital in rat or human liver microsomes (Puurunen, Sotaniemi and Pelkonen, 1980;
Drew, Rowell and Grygiel, 1981; Knodell et al., 1982). In vivo, cimetidine decreases the clearance of many drugs, including diazepam, theophylline, warfarin and librium (Klotz and Reimann, 1980; Serlin et al., 1981; Desmond et al., 1980; Jackson et al., 1981a). Also cimetidine prevents acetaminophen toxicity in both rats and man, indicating that the metabolism of this analgesic was inhibited (Mitchell et al., 1981; Jackson, 1982). Lastly, Abernethy et al. (1982) reported no change in the half-life or clearance of lorazepam or acetaminophen, both of which depend upon phase II conjugation for clearance and elimination. The crux of these studies is that cimetidine causes decreased metabolism of many drugs in both animal and human studies, which could lead to toxic manifestations.

The mechanism for cimetidine's inhibition of hepatic metabolism lies in the ability of the drug to form a ligand with cytochrome P-450, the major system of drug metabolizing enzymes in the liver (Rendic et al., 1979). The ligand interaction between cimetidine and cytochrome P-450 is presumably between the nonbonded nitrogen electrons in the imidazole ring of cimetidine and the heme moiety of cytochrome P-450, specifically at the site where oxygen binds for drug metabolism to take place (Rogerson, Wilkinson and Hetarski, 1977). Cimetidine's inability to bind to cytochrome P-448 is indicated by the lack of inhibition of
benzo(a)pyrene hydroxylation in liver microsomes isolated from rats pretreated with 3-methylcholanthrene (Pelkonen and Puurunen, 1980).

Effects of Cimetidine on Hepatic Blood Flow

Cimetidine has been reported to cause reduced hepatic blood flow by a variety of methods used to measure blood flow through this organ, including indocyanine green clearance, electromagnetic flow devices, and propranolol disposition (Feeley, Wilkinson and Wood, 1981; Heagerty et al., 1981; Jackson, 1981). Reducing hepatic blood flow should decrease the clearance of flow limited drugs, such as lidocaine. This could result in higher blood concentrations and possible toxicity. This concept is supported by the results of Feeley et al. (1982a) who found reduced total systemic clearance as well as a decreased volume of distribution of lidocaine in subjects who took a single dose of 600 mg cimetidine.

Cimetidine appears to reduce hepatic blood flow by blocking histamine$_2$ receptors in the hepatic arteries, since the drug prevents histamine-induced increases in flow through the common hepatic arteries (Charbon, Brouwers and Sala, 1980). Since total hepatic blood flow is the sum of the flow to the portal vein (70%) and the hepatic artery (30%), a reduction in the hepatic arterial flow caused by cimetidine could lead to a significant but small reduction
in total liver blood flow (Somogyi and Gugler, 1982).

In conclusion, cimetidine has been shown to alter the disposition and pharmacokinetics of a variety of substrates, probably through both reduction of hepatic metabolism as well as liver blood flow.

**Ranitidine**

Ranitidine (Zantac), a recently introduced H₂-receptor antagonist, is reportedly five times more potent than cimetidine with fewer side effects (Peden et al., 1979). The chemical structure of ranitidine differs from cimetidine in that the former has a furan ring and no cyanide functional group. The drug is widely used in Europe to treat gastric and duodenal ulcers, but has not been released on the U.S. drug market. The usual clinical dosage is 150 mg administered by mouth twice daily, but can be increased to a total of 900 mg per day given in divided doses. The half-life of the drug is about three hours, but is highly dependent upon the dose (Bogues, et al, 1980).

**Effects of Ranitidine on Hepatic Metabolism**

Ranitidine's effects on hepatic drug metabolism have been studied using a variety of compounds both in vitro and in vivo. The in vitro effects of ranitidine have been tested using both rat and human liver microsomal preparations, and two different substrates, meperidine and pentobarbital. Microsomal metabolism of these drugs was not
impaired by ranitidine (Knodell et al., 1982). The in vivo effects of ranitidine have been studied in human volunteers using antipyrine, aminopyrine, theophylline and warfarin. No significant alteration of the kinetics of these compounds was caused by ranitidine (Henry et al., 1980; Serlin, Sibeou and Breckenridge, 1981; Breen et al., 1982).

**Effects of Ranitidine on Liver Blood Flow**

The effects of ranitidine on liver blood flow might be similar to those of cimetidine, since they are both $H_2$ receptor antagonists. However, the effect or lack of effect of ranitidine on hepatic blood flow is unclear because of conflicting reports in the literature. Indocyanine green clearance was decreased in subjects administered 150 mg of ranitidine twice a day compared to control patients who did not receive ranitidine (Feeley and Guy, 1982b; Garg et al., 1982). However, Grainger et al. (1982) disagree with these findings, suggesting that large intersubject variability in indocyanine green clearance could negate the small decreases in the clearance reported in this study. Other studies found no significant alterations by ranitidine in the kinetics of propranolol and lidocaine, which have high hepatic extraction ratios, and hence are probably dependent on liver blood flow for their clearance (Heagerty, Caselden and Patel, 1982; Feeley and Guy, 1983).
In summary, ranitidine does not inhibit hepatic drug metabolism, and may or may not decrease liver blood flow.

**Halothane**

Halothane is a gaseous anesthetic agent, which has become one of the most widely used general anesthetics in the world since its introduction in 1956. However, the use of halothane in this country has declined with the introduction of other gaseous anesthetics (Hughes, Campbell and Fitch, 1980). The effects of halothane on hepatic drug metabolism and liver blood flow have been well documented with the latter receiving more attention (Deutsch, 1967; Larson et al., 1971; Juhl and Einer-Jensen, 1974).

**Effects of Halothane on Hepatic Drug Metabolism**

Halothane has been shown to depress the metabolism of many low clearance drugs such as antipyrine in rat liver microsomal preparations (Brown, 1971). The metabolism of a large number of compounds, including pentobarbitone, diazepam and ketamine was found to be depressed during in vivo animal studies (Kanto and Pihlajamake, 1973; Pearson, Bogan and Sanford, 1973; White et al., 1976). Also, the hexobarbital sleeping time was found to be significantly increased in rats pretreated with 2% halothane for one hour once daily for five days, indicating decreased metabolism of the drug (Reitbrock, Lazarus and Otterbein, 1972). Furthermore, aminopyrine metabolism in rats is impaired by halothane in a
dose related manner, and this effect persists for 24 hours after administration of the anesthetic (Wood and Wood, 1982). In summary, these studies conclude that halothane inhibits hepatic drug metabolism both in vivo and in vitro, and these effects may persist for an extended period of time.

Halothane inhibits drug metabolism presumably by binding to hepatic microsomal cytochrome P-450 (Brown, 1971). In addition, metabolism of a variety of substrates was found to be inhibited in the presence of halothane (Hallen and Johansson, 1975). Halothane can also compete with microsomal metabolism of a variety of compounds, since it is also metabolized by the mixed function oxidase system (Kanto and Pihlajamaki, 1973).

**Effects of Halothane on Liver Blood Flow**

A great deal of study has been devoted to halothane's effect on liver blood flow because many different types of drugs are administered during anesthesia, the metabolism of which may be affected by decreases in hepatic perfusion rate. Hepatic blood flow was found to decrease using a variety of methods in both animals and humans during halothane anesthesia.

As early as 1966, halothane anesthesia was reported to cause decreased hepatic blood flow in human subjects using an indocyanine green clearance technique (Epstein et al., 1966). Numerous animal studies using dogs and monkeys
were conducted that substantiate the results found in these studies (Amory, Steffenson and Forsyth, 1971; Juhl and Einer-Jensen; 1974; Hughes, Campbell and Fitch, 1980). Furthermore, Gelman found that surgical opening of the abdomen potentiated the reduction in liver blood flow caused by halothane (Gelman, 1976). The results of these studies suggest that halothane causes reduced liver blood flow in both man and animals and that intra-abdominal surgery may also decrease liver perfusion. The proposed mechanism for this effect includes decreased cardiac output due to the negative inotropic actions of halothane as well as halothane associated reduced splanchnic vascular resistance (Larson et al., 1974). The splanchnic vasculature receives about 25% of the cardiac output, while the portal vein, which terminates in the liver, receives about 80% of the splanchnic blood flow. Therefore, a significant reduction in cardiac output could ultimately result in a significant reduction in liver blood flow (Strunin, 1977). Redistribution of organ blood flow due to decreased cardiac output and decreased vascular resistance was found in rabbits anesthetized with halothane. This finding suggests that an altered clearance might be found in drugs that are highly dependent upon rate of blood flow to the liver for their metabolism (Wyler and Weisser, 1972).

In summary, halothane, like cimetidine, has been shown to alter the disposition and kinetics of a large
number of compounds. This effect probably occurs as a result of both impaired hepatic metabolism and blood flow.

**Alpha_1-**acid Glycoprotein

Alpha_1-**acid glycoprotein** (orosomucoid) is an acute reactive globulin, which may be isolated from either serum or plasma (Schmid, 1975). This alpha globulin has recently been shown to be the major binding protein for a variety of basic drugs, including propranolol and imipramine (Piafsky and Borga, 1977). Protein binding of lidocaine in serum has also been shown to be highly dependent upon levels of alpha_1- acid glycoprotein in human subjects (Routledge et al., 1980). The importance of these studies is the free concentration of basic drugs correlates well with the concentration of alpha_1-**acid glycoprotein**. An increase in the levels of this protein results in a decrease in the free concentration of the drug. As noted previously, both the volume of distribution and Cl_s may be altered by changes in the free concentration of drug in the blood.

**Lidocaine Kinetics and Liver Blood Flow**

Alteration in lidocaine kinetics may be used to indicate changes in liver blood flow because the antiarrhythmic and local anesthetic drug is metabolized almost solely by the liver and the compound has a high intrinsic clearance and extraction ratio, which means that lidocaine is highly dependent upon hepatic blood flow for its metabolism.
(Benowitz and Meister, 1978). In addition, lidocaine $\text{Cl}_s$ and hepatic blood flow have been found to be correlated (Zito and Reid, 1978). However, the inhibition of hepatic drug metabolism by SKF-525A caused a significant reduction in lidocaine clearance in the cat, so that hepatic clearance of this drug may depend on both hepatic blood flow and metabolism. If this is the case, lidocaine clearance can not be used as a marker of liver blood flow (Lautt and Skelton, 1977). A possible solution to this problem would be to simultaneously measure a major lidocaine metabolite during the study, so that metabolism and liver blood flow effects can be separated. Figure 1 diagrams lidocaine's major route of metabolism, and monoethylglycinexylidine (MEGX) is one metabolite that can be readily measured in serum. Thus concentrations of MEGX, determined along with those of lidocaine, may shed some light on the effect of cimetidine, ranitidine and halothane on lidocaine pharmacokinetics and metabolism.
Figure 1. A diagram depicting the major route of lidocaine metabolism.

MEGX = monoethylglycinexylididene;
GX = glycinexylididene.
Statement of the Problem

The potential for toxic drug interactions in clinical medicine is important, especially when drugs are extensively used as is the case with halothane and cimetidine. Considerable evidence suggests that both of these drugs have the propensity to cause drug-drug interactions when administered concomitantly with other drugs. In contrast, ranitidine is unlikely to have this effect. Thus, the purpose of this study is to investigate the potential for cimetidine, ranitidine, and halothane to alter the disposition of lidocaine, a prototype high hepatic clearance drug.
MATERIALS AND METHODS

Approval from the University of Arizona Human Subjects Committee for the cimetidine-ranitidine study (HSC # 80-13) prepared by Edward Jackson, M.D. was received on December 23, 1981. John Bentley, M.D. submitted the protocol for the halothane study (HSC # 82-10), which was approved on February 4, 1982.

Chemicals

Lidocaine base, monoethylglycinexylidine (MEGX) and ethylmethylglycinexylidine (EMGX) (Figure 2), were kindly supplied by Astra Pharmaceuticals (Worcester, MA). The purity of lidocaine, MEGX and EMGX was determined using gas chromatography-mass spectrometry using a solid probe injection technique. The fragmentation pattern for the sample matched a library spectrum for lidocaine with a parent ion of 234 mu, as well as characteristic ion fragments at 72, 86, 105, 120 and 148 mu. The molecular ions for EMGX (220) and MEGX (206), as well as characteristic ion fragments for these lidocaine metabolites were seen upon separate analysis. Cimetidine and ranitidine (Figure 3), as well as the placebos, were kindly provided by Glaxo, Inc. (Research Triangle Park, NC).
Figure 2. Chemical structures of lidocaine and its analogues MEGX and EMGX.
Figure 3. Chemical structures of cimetidine and ranitidine.
Ranitidine/Cimetidine Study

Subjects

Six healthy male volunteers participated in this study. The age and height were recorded at the beginning of the study, and the weights were determined before each lidocaine infusion, since the total dose was based on weight. A baseline laboratory study consisting of complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, serum transaminases, serum alkaline phosphatase, serum bilirubin, serum albumin, and serum glucose were determined before and after the study. All values obtained were within normal limits. Smokers were excluded from this study because of the potential effects on lidocaine metabolism and protein binding (McNamara et al., 1980). None of the subjects had a history of ingestion of drugs which may have potential effects on hepatic metabolism. No alcohol or other drugs were ingested for 48 hours prior to the study.

Study Design

A double-blind, double-dummy crossover design was used to assign subjects to treatment groups. Each subject acted as his own control with the pharmacokinetics of lidocaine determined before the administration of the potential moderators. Each subject was randomly assigned to ranitidine-placebo-cimetidine or cimetidine-placebo-ranitidine groups, and each person ingested one type of tablet every
12 hours (ranitidine 200 mg or placebo) and another type of tablet every 6 hours (cimetidine 300 mg or placebo) totaling 6 tablets daily for each of the 3 treatment periods. Both the subjects and investigators were unaware of the identity of the tablets until the analytical procedures were completed. The last dose of each study drug was taken one hour before lidocaine infusion. Each lidocaine treatment was separated by at least one week.

**Lidocaine Protocol**

All studies were performed in the morning to avoid any diurnal variations. Each subject received a constant infusion of lidocaine (2 mg/kg) intravenously over a 10 minute period using an IVAC infusion pump (IMED Corp., San Diego, CA). The subjects remained in a sitting position throughout the study because of the effect of posture on liver blood flow (Nies, Shand and Wilkinson, 1976; George, 1979; Daneshmend, Jackson and Roberts, 1981). Blood samples were drawn from an indwelling intravenous catheter at 3, 6 and 9 minutes during the infusion, and 1, 2, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes after the infusion was completed. A 2 ml volume of blood was drawn and discarded prior to obtaining the sample to avoid the effect of heparin on drug protein binding (Wood, Shand and Wood, 1979). Serum was separated and collected into polycarbonate tubes (West Coast Scientific, Berkeley, CA) in
order to avoid the effects of Vacutainer® tubes on protein binding of lidocaine (Stargel et al., 1979). The serum samples were stored at \(-20^\circ\) C until analyzed.

Halothane/Nitrous Narcotic Study

Patients

Six patients participated in this study of the effects of halothane on lidocaine pharmacokinetics. All patients underwent surgery that did not involve opening of the abdomen because of the effects of laparotomy on liver blood flow (Gelman, 1976). Three of the patients underwent surgical procedures for arthroscopy, two of the patients had an operation for inguinal hernia, while the remaining patient had an arthrotomy. None of the patients had any complications during surgery; however, patient number 3 had difficulty waking up after halothane surgery. The age, height, weight and sex were recorded for each patient.

Study Design

Each of the patients, regardless of the anesthetic technique, received an IV solution of 5% dextrose in Ringers lactate for the administration of various medications during the surgical procedure. In addition, all patients were monitored routinely with an electrocardiogram, blood pressure cuff, and a precordial stethoscope.

The protocol for anesthesia in all patients involved preoxygenation with 100% oxygen (6 L/min) for 3 minutes followed by pretreatment with gallamine (20 mg IV), a
neuromuscular relaxant which prevents fasciculations caused by succinylcholine, another type of muscle relaxant used during anesthetic induction. Anesthesia was induced with thiopental (dose range = 275-500 mg IV) followed by succinylcholine for muscle relaxation. Mask ventilation was begun with 60% nitrous oxide and 40% oxygen. The patients receiving halothane anesthesia were ventilated by mask with 1-2% inspired halothane as set on the anesthesia machine, while the patients receiving nitrous narcotic anesthesia were dosed with from 3-7 ml of a 50 µg/ml concentration of fentanyl titrated until the desired clinical response was observed. A 20 gauge teflon IV catheter (Critikon, Inc., Tampa, FL) was started in the contralateral arm to the IV solution in all patients. A blank sample of blood at zero time (B₀) was drawn, and then lidocaine HCl (3 mg/kg) was administered as an IV bolus. Two minutes after lidocaine administration the patient was intubated with a 7 or 8 French endotracheal tube. Pancuronium bromide was used for muscle relaxation, and ventilation was mechanically controlled. Near the termination of anesthesia and surgery, neostigmine and atropine were used to reverse neuromuscular blockade. Blood samples were drawn at 1, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, 210, 240, 300, 360, 420, and one case 540 minutes during and after the surgical procedure for lidocaine analysis. Serum was collected and frozen at -20°C until analytical procedures could be performed.
Halothane Analysis

End tidal samples of halothane were obtained from the patients receiving halothane anesthesia using a 5 ml gastight syringe (Precision Sampling Corp., Baton Rouge, LA), and an end tidal sampling device attached to the patients' endotracheal tube. The gas samples were processed using a Varian aerograph series 1400 gas-liquid chromatograph (Walnut Creek, CA) equipped with a 5 ft. x 1/8 in. (O.D.) stainless steel column packed with Varaport 30 100/120 mesh coated with a stationary phase consisting of 10% SE-30. The temperature parameters were oven 80°C, detector 160°C and injector 190°C. A thermal conductivity detector was used with a bridge current setting of 200 mA. The carrier gas used was helium set at a flow rate of 3 ml/min. The end tidal concentrations were quantitated by comparing peak heights of the samples to the peak height of a 1% standard (Matheson, East Rutherford, NJ) injected on the GC after each sample. The samples were injected onto a 50 μl injection loop, which was then vented onto the column.

Analytical

Serum lidocaine samples were analyzed using a Beckman model 332 gradient liquid chromatograph (Beckman Instruments, Fullerton, CA) operated isocratically, and equipped with a precolumn (Whatman Clifton, NJ) to saturate the mobile phase with silicate ions, a guard column.
(Upchurch Scientific, Oak Harbor, WA), and a microbondapak phenyl column (Alltech Associates, Deerfield, IL). A variable wave length detector was used to analyze lidocaine and its metabolites at a setting of 210 nm. A setting of 210 nm was chosen because a spectrophotometric scan of lidocaine showed a peak absorbance at 210 nm (Figure 4).

Quantitation of serum lidocaine levels was performed using peak areas obtained from an electronic integrator (Hewlett-Packard, Avondale, PA). Peak area quantitation was chosen because peak area gave the most consistent results, possibly due to the broad peaks obtained for the analysis. A sample chromatogram shows that lidocaine is well separated from the metabolite, MEGX, and both are fairly symmetrical with a resolved baseline (Figure 5). The peak areas were converted to micrograms per milliliter using linear regression analysis on peak areas obtained from a standard curve in the range of 5 μg/ml to 0.05 μg/ml.

Sample lidocaine concentrations less than 1 μg/ml make up data points for the terminal elimination phase of the pharmacokinetic disappearance curve; therefore, a linear regression formula was prepared using peak areas from the 0.05–1 μg/ml standards to convert these sample peak areas to concentration. The sample lidocaine peak areas corresponding to concentrations greater than 1 μg/ml were converted to concentration using a least squares formula fitted
Figure 4. A spectrophotometric scan of lidocaine showing a peak absorbance at about 210 nm. A double beam spectrophotometer was used with acetonitrile in the reference cell.
Figure 5. A chromatogram of an HPLC separation of lidocaine and major metabolite MEGX during the cimetidine-ranitidine study. The peaks are spatially separated and baseline resolved.
to the peak areas obtained from the whole standard curve. The linearity of the standard curve was such that concentrations could be extrapolated down to 0.05 \( \mu \text{g/ml} \) (Figure 6).

The samples were eluted from the phenyl column using an isocratic mobile phase consisting of 5% acetonitrile (UV grade, Burdick and Jackson, Muskegon, MI) to 95% water with 10 mM triethylamine phosphate as an ion pairing agent. The triethylamine phosphate was prepared with 35 ml triethylamine (Matheson, Coleman, and Bell Manufacturing Chemists, Norwood, OH) and 15.3 ml concentrated phosphoric acid, then made up to 250 ml with distilled deionized water and the pH adjusted to 2.85.

Extraction of lidocaine and its N-dealkylated metabolites was accomplished using a modification of a method by Nation et al. (1979). The procedure for lidocaine extraction was as follows: 0.1 ml of 1 N NaOH and 3 ml ethyl acetate (Burdick and Jackson, Muskegon, MI) were added to 1 ml of serum: The mixture was vortexed (Vortex Genie Scientific Industries, Springfield, MA) for one minute at a setting of 1.5 in order to promote mixing of the immiscible phases, and prevent an emulsion from forming. Then the mixture was centrifuged at 1650xg for 15 minutes. The ethyl acetate layer was transferred to a 15 ml conical tube containing 0.1 ml of 0.01 N \( \text{H}_2\text{SO}_4 \) (pH = 2.2). The mixture was vortexed at a setting of 5 for 1 minute, then centrifuged at 1650xg for 10 minutes. The ethyl acetate layer was
Figure 6. Typical lidocaine calibration curve extracted from plasma ($r = 0.9999$). The linearity was such that concentrations of 0.05 ug/ml could be measured reliably.
discarded and the acid layer was washed three times with hexane (Burdick and Jackson, Muskegon, MI) to remove any traces of ethyl acetate. A 30 \( \mu l \) aliquot of the acid layer was injected onto an Alltech model 210 injector with a 20 \( \mu l \) injection loop attached. The sample was then vented onto the column.

To increase sensitivity and detection limits for the halothane study, a micro-bondapak C-18 column (Alltech Associates, Deerfield, IL) was used in place of the phenyl column, the conical tubes were silanized to decrease variability between samples, the solvent composition and flow rate were changed (25% acetonitrile to 75% water and 1 ml/min), to optimize detection an internal standard (EMGX 1 \( \mu g/ml \)) was used, the standard curve was expanded from 16 \( \mu g/ml \)-0.025 \( \mu g/ml \) in order to cover a broader range of lidocaine concentrations and allow for measurements of lidocaine at later time points, and a fixed wavelength detector was used at a setting of 214 nm. A sample of a chromatogram obtained from this study shows that lidocaine is well separated from its metabolite (MEGX) and the internal standard (EMGX). In addition, the peak shapes are symmetrical and baseline resolved (Figure 7).

The reproducibility and linearity of the assay was tested by constructing three identical standard curves from 10-0.025 \( \mu g/ml \) and determining the coefficient of variation (CV) from the peak areas obtained from the chromatogram.
Figure 7. A sample chromatogram resulting from HPLC separation of lidocaine, the internal standard EMGX and MEGX during the halothane study. The peaks are well separated with a resolved baseline.
The CV was 0.23% at 10 \( \mu g/ml \) and 8.27% at 0.025 \( \mu g/ml \), and the linearity in each case was 0.99995. All of the samples for a given subject were analyzed as a batch with a standard curve to minimize assay error.

Lidocaine Metabolites

MEGX was added to plasma along with lidocaine for the purpose of constructing a standard curve. In the cimetidine-ranitidine study, the metabolite was added and reliably detected from 0.02-1 \( \mu g/ml \) with acceptable linearity. MEGX standard curves were constructed from 0.006-4.0 \( \mu g/ml \), and were detected with good reliability and linearity during the halothane study. MEGX was sufficiently separated from lidocaine and the internal standard in both assays such that no interference occurred. Glycinexylidine (GX) could be separated and detected in sample serum, but the half-life of this lidocaine metabolite is too long such that its pharmacokinetic disposition for this study would be meaningless.

Alpha\(_1\)-acid Glycoprotein

Alpha\(_1\)-acid glycoprotein (AAG) concentrations were kindly measured by Tetsuro Fukui, M.D., using serum obtained from a blood sample drawn before lidocaine infusion for the cimetidine-ranitidine study, according to a slightly modified method (Miles Laboratories, 1982). The modification was use of a different buffer to prepare the agar plates (Mancini,
Carbonara, and Heremans, 1965). The method involves a single radial immunodiffusion technique, and the procedure was as follows: agar plates were made containing the antisera for AAG (Miles Laboratories, Elkhart, IN) in a barbiturate buffer. Holes were punched in the agar after the gel hardened using a template in order to form wells where the sample could be placed. A 10 μl aliquot of the sample was placed in the well, and the plate was allowed to incubate at approximately 20°C for 48 hours to allow immunodiffusion to take place. The gel was then stained according to the technique explained in the pamphlet, and the diameter of the immunoprecipitin rings were measured. A calibration curve was constructed using standard reference sera in the concentration range of 50 to 150 mg/dl, and a linear regression formula was constructed from the points. The diameter of the sample precipitin ring could then be converted to mg/dl. A sample plate from a portion of the samples from the cimetidine-ranitidine study is depicted in figure 8. The same standard curve was used for many experiments because the rings did not enlarge to any significant extent using the endpoint diffusion method (Miles Qualityline, 1982).

Pharmacokinetics

The pharmacokinetic parameters for lidocaine were determined by two methods: SPSS-NONLIN, a computer modeling
Figure 8. Sample gel demonstrating the single radial immunodiffusion technique used to determine the concentration of AAG in human serum. The diameter of the circle is directly proportional to concentration in mg/dl, and the circle in the lower right represents 25 mg/dl.
program (Nie et al., 1979) and a model independent method of determining the volume of distribution at steady-state (Benet and Galeazzi, 1979). The NONLIN method is a digital computer program that is routinely employed for the linear least squares estimation of pharmacokinetic parameters, and for the simulation of the time course of drug disposition. The model independent method involves the use of statistical moment theory and a hand-held programmable calculator to determine pharmacokinetic constants. The SPSS-NONLIN method was used to calculate pharmacokinetics for the cimetidine-ranitidine study, and the values obtained were more variable than those obtained using the model independent method. The reason for the variation is due to the rapid distribution of lidocaine and slight errors in the time of blood collection during the early portion of lidocaine infusion. The resulting steep distribution curve and slight error in sample collection time caused the computer to add a third compartment or an early distribution phase, while causing large intercepts and variable slopes for the distributional phase. These large intercepts caused a large part of the variation in the data reported.

The estimated pharmacokinetic parameters that the computer model determines are the slopes and intercepts corresponding to the distribution and elimination phases from the pharmacokinetic disappearance curve. The SPSS-NONLIN program requires the input of limits for the initial
estimates, which were $A = 1.5$, $\alpha = 0.1$, $B = 1$, and $\beta = 0.007$ for the two compartment model, and $P = 1.0$, $\pi = 1.0$, $A = 1.5$, $\alpha = 0.1$, $B = 1.0$, and $\beta = 0.007$ for the three compartment model. The initial estimates may be converted to the half-life of elimination ($t_{1/2}$), area under the concentration-time curve (AUC), volume of distribution ($V_d$), and total systemic clearance ($Cl_s$) by employing commonly used pharmacokinetic formulas. The formula for determining $t_{1/2}$ is:

$$t_{1/2} = \frac{0.693}{\beta}$$

where 0.693 is the natural log of 2 and $\beta$ is the slope of the terminal elimination phase of the disappearance curve.

The equation used for determining the AUC is

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} \quad \text{or} \quad \frac{P}{\pi} + \frac{A}{\alpha} + \frac{B}{\beta}$$

where $A$ is the intercept of the distribution phase, $\alpha$ is the slope of the distribution phase, $B$ is the intercept of the terminal elimination phase, $P$ is the intercept of an added distribution phase, and $\pi$ is the slope of the line describing this additional distribution phase. The equation used to determine $V_d$ is:

$$V_d = \frac{Div}{AUC \cdot \beta}$$

where Div is the intravenous dose of the drug administered.

The formula used to determine $Cl_s$ is:

$$Cl_s = V_d \cdot \beta \cdot 1000 \quad \text{or} \quad Cl_s = \frac{Div}{AUC} \times 1000$$
Volume of the central compartment \((V_c)\) may be estimated through the following equation:

\[
V_c = \frac{D}{A + B} \quad \text{or} \quad \frac{D}{A + B + P}
\]

The SPSS-NONLIN method of determining the initial estimates \((A, B, \alpha, \text{ and } \beta)\) involved the use of DEC-20 and CYBER computer systems with initial estimate inputs, and the determination of the pharmacokinetic parameters involved the use of a computer program contained on a discette and an Apple II computer system. The data points for the time and concentration for each subject were fitted to a two and three compartment model to see which one gave the best "fit". The two compartment model equation is as follows:

\[
C = Ae^{-\alpha t} + Be^{-\beta t}
\]

where \(e\) is the base of the natural logarithm, \(t\) is equal to time, and \(C\) is equal to the serum concentration at time \(t\). The three compartment formula is as follows:

\[
C = Pe^{-\gamma t} + Ae^{-\alpha t} + Be^{-\beta t}
\]

the constants of which have been explained previously.

The zero-time intercepts following intravenous injection \((A_o, B_o \text{ and } P_o)\) may be obtained from the initial estimates following infusion \((A, B \text{ and } P)\) through the equations:

\[
A_o = \frac{AD\alpha}{K_o} \quad B_o = \frac{BD\beta}{K_o} \quad P_o = \frac{PD\gamma}{K_o}
\]
where \( D \) is the administered dose and \( K_0 \) is the infusion rate.

The computer was designated to print-out the sum of squares deviations for each of the different estimates obtained from the different models, so that the fit could be compared between them using an F test.

The second method of determining the pharmacokinetic parameters involves the calculation of the volume of distribution at steady-state (\( V_{dss} \)) without the use of compartments to describe the pharmacokinetics. A distinct advantage of this method is that a hand-held, programmable calculator may be used to determine the pharmacokinetic parameters. The \( V_{dss} \) may be calculated using the formula:

\[
V_{dss} = \frac{\int_0^\infty C_s t \, dt}{(\int_0^\infty C_s \, dt)^2} \cdot \text{Div or } V_{dss} = V_c \frac{K_21 \, K_12}{K_{21}}
\]

where \( \int_0^\infty C_s \, t \, dt \) is the area under the first moment of the AUC, \( V_c \) is the theoretical volume of the central space, and \( K_{12} \) and \( K_{21} \) are intercompartmental transfer rate constants between the central and peripheral compartments, which may be depicted like this:

![Diagram of pharmacokinetic compartments](image-url)
$V_d_{ss}$ determined for a lidocaine infusion requires correction back to time zero due to the effects of infusion on lidocaine distribution. The formula used in this correction is as follows:

$$V_d_{ss} = \frac{\text{dose} \cdot (\text{AUMC}) - T \cdot (\text{dose})}{(\text{AUC})^2} \cdot \frac{1}{2 \cdot \text{AUC}}$$

where AUMC equals area under the first moment curve and $T$ is equal to the duration of infusion (Perrier and Mayersohn, 1982). The AUMC and AUC may be determined using the trapezoidal rule (Gibaldi and Perrier, 1975). The AUMC calculated according to this rule would look like this:

$$\int_0^\infty C_s \cdot t \cdot dt = \sum_{i=0}^{\infty} \frac{(t_{i+1} + t_i) \cdot (C_i t_i + C_{i+1} t_{i+1})}{2}$$

The AUC calculated according to this rule would be similar, but only concentrations would be used, not concentration multiplied by time.

Lidocaine was administered as the HCl salt and determined in the standards as the base. A correction factor obtained by dividing the molecular weight of lidocaine base by the molecular weight of lidocaine HCl as follows:

$$\frac{\text{MW lidocaine base}}{\text{MW lidocaine HCl}} = 0.8654$$

can be used to convert the dose of lidocaine HCl administered to the base by multiplying by the correction factor.
The lidocaine concentration-time data obtained from the subjects and patients participating in both studies were plotted on semi-logarithmic paper, and the terminal elimination half-life was determined by log-linear regression analysis of the data points starting 60 minutes post injection. The pharmacokinetic parameters ($V_{dss}$, AUC and $Cl_s$) were determined using the model independent method of calculating steady-state volume of distribution (Benet and Galeazzi, 1979), described earlier.

Statistics

The sums of squared deviations obtained from the two and three compartment models were compared using the formula:

$$F = \frac{SS_j - SS_k}{SS_k} \times \frac{df_k}{df_j - df_k}$$

where $F$ is the statistical $F$ value, $SS_j$ is the sums of squared deviations for the $j$th set of parameters, $SS_k$ is the sums of squared deviations for the $k$th set of parameters, $df_j$ is the degrees of freedom for the $j$th set of parameters, and $df_k$ is the degrees of freedom for the $k$th set of parameters (Boxenbaum, Riegerman and Elashoff, 1974). The $F$ value obtained was compared to $F$ tables to determine significance at the 95% confidence interval.

Comparisons of the pharmacokinetic variables $t_{1/2}$, $V_{dss}$, $Cl_s$ were made using SPSS repeated measures analysis of variance. (Alpha = 0.05) (Nie et al., 1979).
The pharmacokinetic values showing significance through analysis of variance were tested using student's paired t-test to determine which of the values were different (2-tailed, alpha = 0.05).

A non-paired student's t-test at a confidence interval of 95% was used to determine statistical significance between the halothane and nitrous-narcotic treatment groups in the halothane study.
RESULTS

A study was conducted using lidocaine as a prototype high clearance drug to test the potential for drug interactions between two $H_2$ receptor antagonists. During a separate study, the ability of halothane to alter the disposition of lidocaine was also investigated.

Cimetidine-Ranitidine Study

Morphological Characteristics

The subject's age, weight and height were recorded, and the results are shown as mean ±S.D. (Table 1). All subjects were young males of medium weight. Examination of the mean weight of the subjects would indicate that the mean overall lidocaine dose that they should receive is 160 mg, if the total dose administered is 2 mg/kg.

$H_2$ Receptor Blockers and Lidocaine Concentration

Serum lidocaine concentrations as measured at the peak and end infusion were unaffected by pretreatment with either cimetidine or ranitidine (Table 2). Variations exhibited between the placebo and control groups, coupled with the variation in overall measurement, make small changes hard to detect. Lidocaine concentration does seem high in the cimetidine treatment group at end infusion even though it is not significant.
**Table 1.** Anthropometric data for subjects participating in the cimetidine-ranitidine study.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± S.D.(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>28 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 ± 10</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>182 ± 8</td>
</tr>
</tbody>
</table>

\(^a\) N = 6
Table 2. Comparison of Lidocaine concentrations and dose between the different treatment groups in the cimetidine-ranitidine study.

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Lidocaine concentration (ug/ml)(^a)</th>
<th>Peak</th>
<th>End Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>3.20 ± 0.76</td>
<td>3.15 ± 0.71</td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>2.94 ± 0.80</td>
<td>2.66 ± 0.60</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3.29 ± 0.99</td>
<td>2.93 ± 0.93</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.93 ± 0.83</td>
<td>2.75 ± 0.70</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Mean ± S.D., N = 6
Pharmacokinetic Data

Using the model independent method, a comparison was made of various factors between the four treatment groups. In the cimetidine-ranitidine study, the lidocaine clearance ($\text{Cl}_s$), steady-state volume of distribution ($\text{Vd}_{ss}$), half-life for elimination ($t_{\frac{1}{2}}$), and area under the serum concentration-time curve obtained using the model independent method were compared between the subjects in the study (Table 3).

Cimetidine pretreatment caused a significant reduction in $\text{Vd}_{ss}$ ($p < 0.05$), and a tendency towards decreased $\text{Cl}_s$ ($p = 0.06$). Large inter and intra subject variability in lidocaine disposition is depicted by large standard deviations. The variability is even more pronounced when a computer modeling program, which tries to fit the lidocaine concentration-time data to two or three compartment models, was used to determine pharmacokinetic constants (Tables 4 and 5). The two compartment model data seems to fit the data with the least variability when compared to the two/three compartment combination model data.

A pharmacokinetic disappearance curve for lidocaine after pretreatment with cimetidine, ranitidine, placebo, or control for one subject shows graphically what effect cimetidine can have on lidocaine disposition (Figure 9). After treatment with cimetidine, lidocaine $\text{Vd}_{ss}$ and $\text{Cl}_s$ were decreased. $\text{AUC}$ was increased, while $t_{\frac{1}{2}}$ was unaltered.
result in decreases in lidocaine $V_d^{ss}$ in this study perhaps because this drug is not as effective at $H_2$ receptors in the vasculature or a subtype population of $H_2$ receptors in the vasculature exist which are different from the $H_2$ receptor located in the gastric mucosa.

Decreases in lidocaine $V_d^{ss}$ secondary to halothane anesthesia might be the result of halothane associated cardiac depression (Epstein et al., 1966; Larson et al., 1974). Numerous animal studies document halothane anesthesia causes decreased cardiac output, as well as decreases blood flow to skeletal muscle and adipose tissue, the effect of which is dose dependent (Amory, Steffenson and Forsyth, 1971; Miller, Kistner and Epstein, 1980; Tranquilli et al., 1982). Reduced blood flow to skeletal muscle caused by halothane anesthesia reported in all of the animal studies could account for the reduced lidocaine $V_d^{ss}$ observed in our study. The mechanism whereby halothane causes reduced skeletal blood flow is not the same as that postulated for cimetidine, and in one animal study a speculation is made that reduced cardiac output caused by halothane's ability to cause cardiac depression is the reason for the reduced blood flow to all the tissues of the body (Wyler and Weisser, 1972). Benowitz and Meister (1978) made an appropriate observation that the rate of accumulation of drug in any tissue is directly related to the rate of blood flow to that tissue.
Table 3. Comparison between treatment groups of pharmacokinetic parameters obtained from the model independent method in the cimetidine-ranitidine study.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cimetidine</th>
<th>Ranitidine</th>
<th>Placebo</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_l_s$ (ml/min)</td>
<td>886 ± 215+</td>
<td>1143 ± 225</td>
<td>1087 ± 227</td>
<td>1011 ± 140</td>
</tr>
<tr>
<td>$V_{dss}$ (liters)</td>
<td>123 ± 20*</td>
<td>175 ± 38</td>
<td>156 ± 48</td>
<td>156 ± 39</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>112 ± 19</td>
<td>126 ± 20</td>
<td>121 ± 26</td>
<td>124 ± 27</td>
</tr>
<tr>
<td>AUC (µg·ml&lt;sup&gt;-1&lt;/sup&gt;·min)</td>
<td>161 ± 21</td>
<td>123 ± 16</td>
<td>133 ± 35</td>
<td>143 ± 21</td>
</tr>
</tbody>
</table>

+ p = 0.06 between the cimetidine treatment group and the other three groups.

* p < 0.05 between the cimetidine treatment group and the other three groups.

<sup>a</sup> mean ± S.D., N = 6
Table 4. Comparison between treatment groups obtained from SPSS-NONLIN fitted to a two compartment model in the cimetidine-ranitidine study.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cimetidine</th>
<th>Ranitidine</th>
<th>Placebo</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Cl}_S$ (ml/min)</td>
<td>785 ± 191</td>
<td>1071 ± 216</td>
<td>1026 ± 203</td>
<td>906 ± 135</td>
</tr>
<tr>
<td>$\text{Vd}_{ss}$ (liters)</td>
<td>66 ± 30.</td>
<td>102 ± 23</td>
<td>102 ± 48</td>
<td>109 ± 50</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>75 ± 25</td>
<td>88 ± 33</td>
<td>87 ± 14</td>
<td>109 ± 55</td>
</tr>
<tr>
<td>AUC ($\mu g \cdot ml^{-1} \cdot min$)</td>
<td>181 ± 24</td>
<td>132 ± 16</td>
<td>141 ± 37</td>
<td>160 ± 23</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean ± SD, N = 6
Table 5. Comparison between treatment groups of pharmacokinetic parameters obtained from SPSS-NONLIN fitted to a two/three compartment combination model in the cimetidine-ranitidine study.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cimetidine</th>
<th>Ranitidine</th>
<th>Placebo</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{l_s}$ (ml/min)</td>
<td>659 ± 270</td>
<td>785 ± 159</td>
<td>887 ± 183</td>
<td>689 ± 210</td>
</tr>
<tr>
<td>$V_{dss}$ (liters)</td>
<td>70 ± 36</td>
<td>93 ± 55</td>
<td>106 ± 39</td>
<td>90 ± 66</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>110 ± 31</td>
<td>119 ± 34</td>
<td>123 ± 35</td>
<td>125 ± 45</td>
</tr>
<tr>
<td>AUC (µg·ml·min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>234 ± 78</td>
<td>186 ± 70</td>
<td>164 ± 45</td>
<td>232 ± 99</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean ± SD, N = 6
Figure 9. Serum lidocaine concentration-time plot for one subject who showed the greatest effect. The various lines represent the terminal elimination phase of lidocaine disposition. The Vdss and Clss decreased for the cimetidine treatment group when compared to the other treatment groups; however, the t½ was unaltered.
The pharmacokinetic curves in Figure 9 show the effect that cimetidine has on AUC; it causes increases in this parameter. Since $V_d_{ss}$ and $Cl_s$ depend upon AUC, then cimetidine caused increases in AUC will directly affect the other pharmacokinetic parameters.

**Alpha\(_1\)-acid Glycoprotein Levels and $V_d_{ss}$**

Serum concentrations of alpha\(_1\)-acid glycoprotein (AAG) were measured in mg/dl from samples of blood drawn at the beginning of each lidocaine infusion. Neither cimetidine nor ranitidine pretreatment had any significant effect on mean AAG when compared by the various treatment groups (Table 6). Lidocaine $V_d_{ss}$ was plotted against AAG levels in mg/dl because of the effects of protein binding on this pharmacokinetic parameter (Figure 10). The data points show a large distribution over a range of $V_d_{ss}$ at AAG concentrations less than 100 mg. Concentrations of AAG greater than 100 mg appeared to limit the volume of distribution of lidocaine.

**Halothane Study**

Morphological Characteristics

The patient's age, height and weight were recorded the day prior to surgery. The age is the only characteristic which showed significance between the two treatment groups; however, the 4-year difference is not large enough
Table 6. Serum alpha₁-acid glycoprotein levels (mg/dl) following the various pretreatments in the cimetidine-ranitidine study.a

<table>
<thead>
<tr>
<th></th>
<th>Cimetidine</th>
<th>Ranitidine</th>
<th>Placebo</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>105 ± 27</td>
<td>94 ± 21</td>
<td>95 ± 17</td>
<td>99 ± 29</td>
</tr>
</tbody>
</table>

a Mean ± SD, N = 6
Figure 10. Comparison of alpha\textsubscript{1}-acid glycoprotein levels and steady-state volume of distribution for the subjects participating in the cimetidine-ranitidine study. Each point on the graph represents the data for one subject and one treatment. There were six subjects and four treatment groups. The V\textsubscript{dss} shows a tendency towards a decrease when alpha\textsubscript{1}-acid glycoprotein levels exceed 100 mg/dl.
to cause error due to age effects on liver blood flow (Table 7). The weight difference is not significant, but may be large enough as to have an effect on the pharmacokinetic data because the lidocaine was dosed according to weight. The dose is used in turn to calculate $Cl_s$ and $Vd_{ss}$, so the weight difference may contribute somewhat to the differences reported for the two treatment groups.

**Lidocaine Concentration and Dose**

Peak lidocaine concentrations in $\mu g/ml$ were compared between the two treatment groups and no significant difference was noted; however, the peak concentrations in the nitrous-narcotic treatment group showed considerable variability, which hampers the ability to discern a statistical significance (Table 8). The lidocaine dose was administered as a bolus intravenously, and was calculated according to the patient's weight as mentioned previously. A comparison of the lidocaine dose by treatment group shows no significant difference, but the halothane treatment group received a slightly smaller mean dose than the nitrous-narcotic treatment group.

**End Tidal Halothane Levels**

Patients receiving halothane anesthesia were monitored every 15 minutes to measure the halothane levels at the end of expiration. This method allows for an accurate
Table 7. Comparison of morphological characteristics for the patients participating in the halothane study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Halothane</th>
<th>Nitrous-Narcotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>33 ± 1 *</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 ± 13</td>
<td>83 ± 19</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 8</td>
<td>181 ± 7</td>
</tr>
</tbody>
</table>

* p < 0.05 between halothane and nitrous-narcotic groups

a Mean ± SD, N = 3/group
Table 8. Lidocaine concentration and dose compared between halothane and nitrous-narcotic treatment groups during the halothane study.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Lidocaine&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak Concentration (µg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>9.07 ± 1.68</td>
<td>189 ± 39</td>
<td></td>
</tr>
<tr>
<td>Nitrous-Narcotic</td>
<td>5.56 ± 3.79</td>
<td>252 ± 50</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean ± SD, N = 3/group
measure of the partial pressure of the anesthetic gas occurring in the arterial blood of the lungs. End tidal halothane values versus time are presented in Table 9 for each of the three patients, who received halothane anesthesia. The duration of anesthesia was shorter in each proceeding case with patient #3 receiving the longest duration of anesthesia, while patient #6 received the shortest duration. The end tidal halothane values seemed to decrease with time except for patient #5 where the level increased during anesthesia. This was due to not turning down the setting on the vaporizer after the patient reached equilibrium.

Metabolite Pharmacokinetics

A major lidocaine metabolite, MEGX, was measured during the halothane study for each of the patients in the two treatment groups. The data was plotted against time on semi-logarithmic paper, and the $t_{1/2}$ was determined. MEGX $t_{1/2}$ showed considerable variation between patients, and at least some of this variability can be attributed to the different lengths of the sampling period (Table 10). Close examination of the data will show that the $t_{1/2}$ in each of the patients receiving nitrous-narcotic anesthesia are approximately equal to the sample period length, which makes the calculation of accurate kinetic data difficult, if not impossible (Gibaldi and Perrier, 1975). The peak
Table 9. End tidal levels of halothane obtained throughout the surgical procedure for patients receiving halothane anesthesia. (All values are presented as percent (v/v) of gas used to balance the halothane standard).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Patient #3</th>
<th>Patient #5</th>
<th>Patient #6</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0.50</td>
<td>0.59</td>
<td>0.63</td>
</tr>
<tr>
<td>30</td>
<td>0.51</td>
<td>0.59</td>
<td>0.63</td>
</tr>
<tr>
<td>45</td>
<td>0.40</td>
<td>0.86</td>
<td>0.32 (48)</td>
</tr>
<tr>
<td>60</td>
<td>0.37</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>0.38</td>
<td>0.05 (72)*</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>0.36 (off)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>0.15 (extubated)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The numbers in parentheses indicate the time at which the halothane anesthesia was turned off and the patient was extubated.
Table 10. Pharmacokinetic data obtained from the halothane and nitrous-narcotic treatment groups for the major metabolite for lidocaine, MEGX during the halothane study.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>$t_{1/2}$ (min)</th>
<th>Peak conc. (µg/ml)</th>
<th>Time of peak conc. (min)</th>
<th>Time last sample drawn (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous-Narcotic</td>
<td>1</td>
<td>267</td>
<td>0.14</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>192</td>
<td>0.34</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>304</td>
<td>0.32</td>
<td>15</td>
</tr>
<tr>
<td>Halothane</td>
<td>3</td>
<td>284</td>
<td>0.56</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>174</td>
<td>0.32</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>147</td>
<td>0.32</td>
<td>15</td>
</tr>
</tbody>
</table>
concentration of MEGX appears to be comparable between the two treatment groups; however, patient #3 had a concentration of 0.56 \( \mu \)g/ml, which may have contributed to the anesthetic action of lidocaine particularly since this patient had difficulty awaking after surgery (Blumer, Strang and Atkinson, 1973). The time when the peak concentration of MEGX occurred was not different between the two patient groups; but this peak occurred at 45 minutes in patient #5 who received halothane. This may be related to the higher end-tidal halothane level in this patient measured at 45 minutes (Table 9).

Lidocaine Pharmacokinetics

Halothane anesthesia caused a significant decrease in lidocaine \( V_{d_{ss}} \) \((p < 0.001)\) and \( C_{l_s} \) \((p < 0.05)\), but \( t_{1/2} \) and AUC were not significantly different (Table 11). There appears to be about a twofold decrease in lidocaine \( C_{l_s} \) in patients undergoing halothane anesthesia when compared to those patients who received a nitrous-narcotic technique. The \( V_{d_{ss}} \) is decreased by about one-third due to halothane anesthesia. The duration of anesthesia did not seem to make much of a difference in halothane's effects on lidocaine pharmacokinetics (Table 9). The duration of halothane anesthesia ranged from 48-90 minutes in our study, and lidocaine pharmacokinetics in these patients appeared to be altered with even the short duration of anesthesia. It is
Table 11. Halothane data summary comparing the pharmacokinetic parameters between halothane and nitrous-narcotic treatment groups.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Halothane</th>
<th>Nitrous-Narcotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Cl_s$ (ml/min)</td>
<td>$678 \pm 119^*$</td>
<td>$1106 \pm 290$</td>
</tr>
<tr>
<td>$Vd_{ss}$ (liters)</td>
<td>$95 \pm 7^+$</td>
<td>$147 \pm 6$</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>$120 \pm 15$</td>
<td>$109 \pm 19$</td>
</tr>
<tr>
<td>AUC ($\mu g \cdot ml^{-1} \cdot min$)</td>
<td>$241 \pm 9$</td>
<td>$211 \pm 80$</td>
</tr>
</tbody>
</table>

* $p < 0.05$ between the halothane and nitrous-narcotic groups.

+ $p < 0.001$ between the halothane and nitrous-narcotic groups.

<sup>a</sup> Mean $\pm$ SD, N = 3/group
interesting to note the rapid onset of action that this volatile anesthetic has upon drug metabolism and kinetics.

A serum lidocaine concentration time curve for a patient from each of the two treatment groups illustrates the difference in the kinetic parameters even though the plots appear very similar (Figures 11 and 12). The two patients received equivalent doses of lidocaine, and had identical durations of anesthesia; however, $Cl_s$ decreased by a factor of one-fourth and $Vd_{ss}$ decreased by almost one-half. Lidocaine $t_\frac{1}{2}$ changed very little, but MEGX $t_\frac{1}{2}$ showed an increase in the patient who received nitrous-narcotic anesthesia. As explained previously, this may be an artificial result secondary to the length of the collection period.
Figure 11. Serum lidocaine concentration-time plot for patient number 4, who received the nitrous-narcotic anesthetic technique. The lines represent the best fit linear regression line that can be drawn for the data points obtained for lidocaine and its major metabolite MEGX. The pharmacokinetic parameters obtained through the model independent method are shown for comparison with those obtained for patient number 5, who received halothane anesthesia.
$C_s = 929 \text{ ml/min}$

$V_{dss} = 149 \text{ liters}$

$t_{1/2} = 117 \text{ min}$

$\text{MEGX } t_{1/2} = 304 \text{ min}$

$\text{Dose} = 221 \text{ mg}$
Figure 12. Serum lidocaine concentration-time plot for patient number 5, who received halothane anesthesia. The lines represent the best fit linear regression line that can be drawn for the data points obtained for lidocaine and its major metabolite MEGX. The pharmacokinetic parameters obtained through the model independent method are shown for comparison with those obtained for patient number 4, who received nitrous-narcotic anesthesia.
Cl\textsubscript{s} = 765 ml/min

Vd\textsubscript{ss} = 100 liters

t\textsubscript{1/2} = 109 min

MEGX t\textsubscript{1/2} = 187 min

Dose = 193 mg
Steady-state volume of distribution ($V_d_{ss}$) and total systemic clearance ($Cl_s$) were found to decrease in subjects pretreated with cimetidine and in patients receiving halothane anesthesia, while these parameters were unaffected in subjects treated with ranitidine. In order to discuss these findings in a clear, concise manner, the time course of distribution and clearance mechanisms need to be understood.

Lidocaine distribution has been investigated in the rat using radiolabelled microspheres and tritium labeled lidocaine (Katz, 1968; Keenaghan and Boyes, 1972). Also, a perfusion model simulation and tissue partition coefficients of lidocaine from the rhesus monkey were employed in a computer program to plot the tissue distribution of lidocaine versus time (Benowitz et al., 1974). The two methods used to determine the time course of lidocaine distribution agree fairly well despite use of two very different animal species. The rat studies determined that lidocaine is distributed very rapidly when the drug is administered as an intravenous bolus. A large portion of the lidocaine was found to accumulate in the vessel rich group of organs -- heart, lung, liver, brain, kidney, spleen and bowel. This group of organs showed a rapid decay rate approximately paralleling
the decay rate of lidocaine from the plasma, so that by 30 minutes the limit of detection for parent lidocaine had been reached for most of these rapidly equilibrating tissues. The perfusion model simulation determined that lidocaine is redistributed from the vessel rich organs to adipose tissue and skeletal muscle, and the slow decline of drug concentrations from these tissues over time accounts for lidocaine's characteristically long half-life of elimination. Distribution of lidocaine to the vessel rich group of organs is analogous to the distribution phase, while redistribution of this drug to fat and muscle is said to equal the elimination phase in relation to the pharmacokinetic disappearance curve.

Clearance mechanisms for lidocaine play an important role in the elimination phase, and in the overall disposition of this antiarrhythmic drug. Lidocaine is extensively metabolized by liver microsomal enzymes, with negligible amounts being metabolized extrahepatically. It has been determined that the extraction ratio is between 0.7 and 0.8 using isolated perfused liver systems, indicating that the hepatic clearance ($C_{lH}$) of lidocaine may be dependent primarily upon liver blood flow, and probably only marginally on the activity of microsomal drug metabolizing enzymes (Branch et al., 1972; Rane, Wilkinson and Shand, 1977). However, some evidence suggests that lidocaine is not wholly
dependent upon the rate of hepatic blood flow for its metabolism, and that the activity of the microsomal drug metabolizing enzymes may play a more important role in the disposition of this drug than was previously known (Lautt and Skelton, 1977). Also, the dual circuit nature of blood delivery to the liver makes measurement of blood flow changes difficult. Usually the portal vein is used to measure hepatic blood flow, which only takes into account 70% of the splanchnic blood flow (Strunin, 1977).

Lidocaine steady-state volume of distribution ($V_{d_{ss}}$) was significantly reduced by pretreatment with cimetidine and also by exposure to halothane anesthesia, while this parameter was unaltered in subjects treated with ranitidine. Reduction of $V_{d_{ss}}$ caused by cimetidine in this study is consistent with data reported by Feeley et al. (1982 a), while the unaltered $V_{d_{ss}}$ found after ranitidine treatment similarly agrees with data reported by Feeley and Guy (1983). In addition, findings reported by White et al. (1976), that halothane anesthesia alters the distribution and redistribution of ketamine, parallels our findings that exposure to halothane anesthesia reduces lidocaine $V_{d_{ss}}$.

Decreased $V_{d_{ss}}$ caused by cimetidine treatment may be explained by increases in lidocaine protein binding sites resulting in decreases in the fraction of lidocaine free in the blood. That is to say, increased blood protein binding
would tend to limit drug distribution. However, Feeley et al. (1982a) recently reported that cimetidine decreases, rather than increases, lidocaine protein binding, which would tend to cause increases in $V_{dss}$ if the fraction of drug free in the tissue and the volume of the tissue compartment remain constant. This will be discussed in more detail subsequently. A more plausible reason for the reduction in $V_{dss}$ is a cimetidine associated decrease in muscle blood flow. By blocking $H_2$ receptors in the vasculature, cimetidine was found to cause significant reductions in histamine-induced increases in blood flow to gastric, mesenteric, renal, and hepatic arteries of animals (Harvey, Owen and Shaw, 1980; Charbon, Browers and Sala, 1980).

Introduction of histamine through intravenous infusion is known to produce a multiplicity of responses, including changes in blood pressure, pulse rate, gastric acid secretions, esophageal sphincter tone, as well as to induce a cutaneous vascular flush and headache. A selective $H_2$ receptor agonist, 4-methylhistamine, has been reported to cause dose dependent vasodilation in skeletal muscle (Johnston and Owen, 1977). If cimetidine can block endogenous histamine-induced vasodilation in skeletal muscle, then this could explain the large decrease in lidocaine $V_{dss}$ found in our study, since lidocaine has extensive distribution to skeletal muscle. Ranitidine treatment did not
The relationship between lidocaine \( V_{dss} \) as measured in the cimetidine-ranitidine study and levels of alpha\(_1\)-acid glycoprotein (AAG), the major binding protein for basic drugs in the blood, would be predicted to be inverse. This occurs because there is a direct relationship between the free fraction of basic drugs and levels of AAG (Evans and Shand, 1973; Fremstad et al., 1979). The volume of distribution-area \( V_d \) depends upon the unbound fraction of drug according to the following relationship:

\[
V_d = V_{\text{blood}} + \frac{\text{unbound drug in blood}}{\text{unbound drug in tissue}} \cdot V_{\text{tissue}}
\]

where \( V_{\text{blood}} \) is the volume of the blood compartment in liters, and \( V_{\text{tissue}} \) is the volume of the tissue compartment in liters. \( V_{dss} \) and \( V_d \) are not equal, but changes in both parameters are usually proportional. Increases in levels of AAG should result in a decrease in the unbound fraction of drug in the blood, and would result in a decreased \( V_{\text{tissue}} \), which in turn will result in a decreased \( V_d \). This is only true if all the other parameters that have an effect on \( V_d \) are held constant, which may not be the case in our study as was seen when \( V_{dss} \) is plotted versus levels of AAG (Figure 10). Feeley et al. (1982 a) state that cimetidine treatment causes decreased lidocaine protein binding as discussed earlier, and this would tend to cause an increase in \( V_d \) because the amount of unbound drug in blood would increase. In reality, the size of \( V_{\text{tissue}} \) and the amount of unbound
drug in the tissue could change drastically with cimetidine's ability to alter skeletal muscle blood flow. A good correlation between $V_{d_{SS}}$ and levels of AAG was not found in our study because of the input of all these variables in the determination of $V_{d_{SS}}$. However, a tendency towards a decrease in lidocaine $V_{d_{SS}}$ was noted when levels of AAG exceed 100 mg/dl, and this tendency does not seem to have been caused by cimetidine treatment (Table 6).

The clinical relevance of decreased lidocaine $V_{d_{SS}}$ found in both studies lies in the fact that a loading dose is necessary when administering this drug as a continuous infusion. That is to say, a single bolus of a drug is given intravenously so that steady-state concentrations of lidocaine are achieved rapidly. The mathematical equation used to calculate a loading dose ($D_1$) is the product of the steady-state concentration ($C_{ss}$) and $V_d$:

$$D_1 = C_{ss} \cdot V_d$$

The relationship of $V_d$ and $C_{ss}$ to $D_1$ shows that a decrease in $V_d$ with $C_{ss}$ remaining constant should warrant a decrease in $D_1$. However, to avoid high blood concentrations and toxicity $D_1$ for lidocaine is often calculated using the volume of the central space ($V_c$), which is much smaller than $V_d$ or $V_{d_{SS}}$. Thus, use of $V_c$ in patients on cimetidine to calculate a lidocaine $D_1$ should prevent toxicity.
Lidocaine clearance ($Cl_g$) was significantly reduced in patients as a result of halothane anesthesia, and in subjects pretreated with cimetidine. Ranitidine treatment did not significantly affect lidocaine $Cl_g$, but showed a nonsignificant increase when compared to the other three treatment groups. The effects that the two $H_2$ blockers studied have on lidocaine $Cl_g$ parallel those reported in the literature (Feeley et al., 1982a; Feeley and Guy, 1983). Decreased lidocaine $Cl_g$ caused by halothane anesthesia has not been reported in the literature, but the magnitude of the decrease is consistent with reports about halothane's ability to cause decreased hepatic blood flow (Gelman, 1976). The probable mechanisms responsible for the decreased $Cl_g$ caused by halothane and cimetidine are decreased microsomal enzyme activity and decreased hepatic blood flow (Gelman, 1976; Somogyi and Gugler, 1982; Wood and Wood, 1982).

Cimetidine treatment alters lidocaine clearance most probably by inhibition of cytochrome P-450 metabolism due to the small changes seen upon examination of the data compared amongst treatment groups (Table 3). Further evidence is presented upon comparison of peak and end of infusion lidocaine concentrations between treatment groups (Table 2). No significant difference is noted in these concentrations with either cimetidine or ranitidine pretreatment, which contradicts a report in the literature that cimetidine causes
increases in both peak and end of infusion lidocaine levels (Feeley et al., 1982a).

On the other hand, altered lidocaine clearance caused by halothane anesthesia may well involve a combination of inhibition of cytochrome P-450 mediated metabolism and decreased hepatic blood flow because the magnitude of the decrease in Cl<sub>S</sub> due to halothane anesthesia is larger than that seen due to cimetidine treatment. In addition, halothane anesthesia has been reported to affect in vitro drug metabolism, as well as cause decreases in hepatic blood flow in vivo (Brown, 1971; Juhl and Einer-Jensen, 1974).

Alterations in lidocaine clearance may be clinically important because this drug is commonly administered as an infusion following a loading dose in order to maintain steady-state concentrations and prevent ventricular arrhythmias in patients suffering from myocardial infarction. The infusion rate (k) is dependent upon steady-state concentration of the drug (C<sub>ss</sub>) and Cl<sub>S</sub> according to the following relationship:

\[ k = Cl_S \cdot C_{ss} \]

A reduced Cl<sub>S</sub> could cause C<sub>ss</sub> to rise to toxic levels. However, cimetidine treatment did not decrease lidocaine Cl<sub>S</sub> to a large extent, and there was large inter and intra-subject variability in lidocaine pharmacokinetics, so that no downward adjustment in k may be necessary in patients treated
with these two drugs concomitantly. That is clinically, cimetidine associated changes in lidocaine pharmacokinetics may be difficult to detect. On the other hand, patients receiving halothane anesthesia and lidocaine infusions should have their infusion rate adjusted accordingly.

Measurements of the half-life for elimination ($t_{\frac{1}{2}} \beta$) of lidocaine were unchanged as a result of treatment with either of the $H_2$ receptor blockers or with halothane anesthesia because of the following relationship:

$$t_{\frac{1}{2}} = \frac{0.693 \cdot V_d}{C_l_s}$$

where an equal decrease in the magnitude of $C_l_s$ and $V_d$ should leave $t_{\frac{1}{2}}$ unaltered. Figure 5 shows this phenomena graphically, where the line describing the terminal elimination phase is shifted upwards without a change in slope ($\beta$). Since $t_{\frac{1}{2}}$ is inversely related to $\beta$, then no change in $\beta$ as a result of treatment with $H_2$ receptor antagonists or halothane anesthesia means that there should be no change in $t_{\frac{1}{2}}$. This result stresses the need in pharmacokinetic studies to examine all three parameters ($V_d_{ss}$, $C_l_s$, and $t_{\frac{1}{2}}$) when testing for potential drug interactions, and trying to elucidate mechanisms of action.

Half-life for elimination is an important pharmacokinetic parameter because it is a measure of the time required for a drug to reach steady-state concentrations.
during multiple dosing, and the time required for a drug to be completely cleared from the body during single dose therapy. It takes approximately 4 half-lives to remove 94% of a drug that depends upon first order kinetics from the body; therefore, the period of sample collection during a pharmacokinetic study should be equal to at least 3-4 half-lives in order to obtain accurate results. Gibaldi and Perrier (1975) recommend that the sampling period be equal to the limit of detection for the study drug during a pharmacokinetic study, thus signaling that the drug is completely cleared from the body.

A nice illustration relating $t_{1/2}$ to the length of sample collection is the data obtained from the MEGX concentration-time curve during the halothane study. The patients receiving nitrous-narcotic anesthesia demonstrated MEGX half-lives that were approximately equal to the sample collection period, indicating that a longer collection period is required in order to make valid conclusions about halothane's effects on the metabolism of lidocaine (Table 10).

Pharmacokinetic data were obtained for the disposition of lidocaine during the cimetidine-ranitidine study using a computer modeling program that attempts to fit concentration-time data to compartments, as well as a model independent method, which does not require that the data
fit compartments. A comparison of the kinetic data obtained from the two methods of analysis shows larger standard deviations for most of the values obtained using the computer model fitted to a two or two/three compartment combination (Tables 3, 4 and 5). Using either method, the inter and intrasubject variability demonstrated upon investigation of the data is large, but the variability in the data is much less when the model independent method is used. These large variations in lidocaine pharmacokinetics seen in our study using both methods of analysis have been reported previously (Bennett et al., 1982), and may reflect the difference in each individual's ability to metabolize lidocaine.

The difficulty experienced in choosing whether the concentration-time data fits a two or three compartment model provides a good explanation for the large difference between the final pharmacokinetic data obtained from the computer modeling program and the model independent method. An F-test performed on the sums of squares obtained from the computer modeling program for each individual's data showed that a three compartment model fit the lidocaine pharmacokinetic disappearance curve better than the two compartment model in some cases. The slope and intercept of lidocaine's distributional phase (\( \alpha \) and \( A \) respectively) were the initial estimates most affected by the computer's
difficulty in fitting the data to a two or three compartment model, and an examination of data calculated for the two/three compartment model combination shows that the addition of another compartment does not fit the data any better than the two compartment model alone (Tables 4 and 5). The model independent method overcomes this problem inherent with virtually any computer modeling program by analyzing the whole pharmacokinetic disappearance curve as noncompartmental.

The finding that both cimetidine and halothane decrease lidocaine clearance may suggest that these drugs decrease hepatic blood flow because it has been established that lidocaine has a high hepatic extraction ratio and intrinsic clearance using isolated perfused liver systems (Shand, Kornhauser and Wilkinson, 1975). Lidocaine metabolism is dependent mostly upon the rate of liver blood flow and only marginally on the activity of drug metabolizing enzymes in the liver because of the drug's large extraction ratio and intrinsic clearance (Wilkinson and Shand, 1975). Reduction of lidocaine clearance by dl-propranolol, a drug which affects the cardiovascular system by causing decreased cardiac output and liver blood flow was found, indicating that lidocaine clearance and liver blood flow are directly related (Branch et al., 1973). Lidocaine clearance may also be reduced during low cardiac output states such as congestive heart failure or hemorrhage, indicating that
reduced blood flow and clearance of this drug are directly related (Benowitz et al., 1974). There is some controversy in the literature as to the true effects of cimetidine and halothane on hepatic blood flow; however, the problems arise with the methodology used to measure hepatic blood flow.

Measurement of hepatic blood flow has been accomplished using a variety of techniques, a few of which are clearance of the cardiac dye indocyanine green, distribution of radiolabelled microspheres, and direct attachment of an electromagnetic flowmeter. Indocyanine green clearance has been widely used to measure the rate of liver blood flow, but the accuracy of the method has been criticized recently because of large intrasubject variability in the clearance of this compound due to the differential ability of the liver to extract this compound in each individual (Jackson, 1981b). Radiolabelled microspheres have been used to determine the distribution of cardiac output in experimental animals (Amory, Steffenson and Forsyth, 1971; Wyler and Weisser, 1972). The single greatest problem with this technique lies in the inflexibility of the microsphere, and its inability to pass through capillaries that causes the radiolabel to become entrapped in the first capillary bed downstream from the injection site. Direct attachment of an electromagnetic flowmeter has been shown to be the most accurate method;
however, invasion of the abdominal cavity triggers a sympa­
thetic discharge, which is sufficient to cause a 40% reduc­tion in hepatic blood flow (Gelman, 1976).

Measurement of hepatic blood flow becomes an even more difficult process because of the dual circuit nature of blood flow to the liver, as well as effects that extraneous factors such as age, posture, presence of food in the gut, or exercise state have on liver blood flow (George, 1978). The use of lidocaine clearance as an initial indicator of changes in hepatic blood flow is war­ranted as the best method so far discussed because it is noninvasive, and therefore may provide the most accurate reflection of drug interactions involving liver blood flow. However, cimetidine and halothane have been re­ported to affect both liver blood flow and the activity of microsomal drug metabolizing enzymes, both of which will affect the clearance of lidocaine. Unless the po­tential effects of cimetidine or halothane on liver blood flow and the activity of microsomal drug metabolizing enzymes can be separated, then no concrete statements can be made concerning effects on liver blood flow. Halothane anesthesia causes a more profound reduction in lidocaine clearance than does cimetidine treatment. It may be specu­lated from this that halothane anesthesia causes both re­duced hepatic blood flow and hepatic microsomal drug
metabolizing activity, while cimetidine treatment causes only reduced microsomal drug metabolizing activity.

In conclusion, cimetidine treatment and halothane anesthesia, but not ranitidine treatment lead to significant reductions in lidocaine Cl_s and Vd_ss indicating the need to adjust the loading dose and infusion rates in patients receiving these drugs in combination. Large inter and intra-subject variability in lidocaine kinetics demonstrated during the cimetidine-ranitidine study may make the small changes reported clinically irrelevant. On the other hand, the effects that halothane anesthesia has on lidocaine pharmacokinetics may be extended to other high clearance drugs such as propranolol, meperidine and morphine. It would also be interesting to investigate the effects of other volatile anesthetics such as ethrane or isoflurane on lidocaine pharmacokinetics. Also with the administration of prophylactic cimetidine to decrease gastric pH prior to surgery could lead to the use of all three drugs at the same time. The possible combinations become endless.

The relationship between Vd_ss and levels of AAG is interesting because the levels of this protein respond to stress, and heart patients, who are the most likely candidate to receive lidocaine, are under a great deal of stress. This means that the loading dose of lidocaine would need to be adjusted with accord to the decreased Vd_ss in patients with increased levels of AAG. Lidocaine dose would have to
be adjusted in patients receiving cimetidine treatment, but not for those receiving ranitidine treatment, indicating that ranitidine may be the drug of choice in patients receiving lidocaine. Lidocaine is not so much a problem in patients receiving anesthesia, but preoperative drugs that depend upon liver blood flow for their clearance may present a problem because of halothane's ability to alter both drug distribution and drug clearance.
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