Introduction

Several studies have shown that halothane may influence drug disposition. However, the mechanism remains unclear and may be related to halothane-induced changes in hepatic blood flow and/or inhibition of drug metabolizing activity. The effects of altered hepatic blood flow and intrinsic drug metabolizing activity vary according to the hepatic extraction ratio of the drug studied. Liver blood flow is the primary determinant of systemic clearance (Cl_s) after IV administration of a hydrophilic drug such as propranolol, while the systemic or intravenous clearance of a drug with a low extraction ratio is dependent on intrinsic drug metabolizing capacity. Following oral administration, oral clearance (Cl_o) reflects only the intrinsic drug metabolizing activity of the liver (Cl_int) and is independent of hepatic blood flow. Liver blood flow and hepatic drug metabolizing capacity (intrinsic clearance) can be calculated from a knowledge of pharmacokinetics after simultaneous oral and IV administration of a drug which is completely absorbed from the gut and completely metabolized by the liver. The purpose of the present study, therefore, was to define the relative contributions of changes in hepatic blood flow (HBF) and intrinsic metabolizing ability to altered drug disposition during halothane anesthesia, using the simultaneous administration of the model compound, propranolol, into the portal and systemic venous systems (I).

Methods

Six dogs (22.9 ± 1.8 kg) were anesthetized with thiopental, tracheal intubation performed, ventilation controlled to maintain normal blood gases and anesthetized with halothane (2.0 MAC) in oxygen. Intra-arterial pressure was monitored and end-tidal halothane concentrations were measured by gas chromatography. The studies were performed on each dog on three consecutive days: firstly, the day before anesthesia in conscious dogs (Day 1), secondly during halothane anesthesia (Day 2) and thirdly, 24 hours after anesthesia (Day 3). Each dog simultaneously received 40 mg of unlabelled propranolol directly into the portal vein, thus bypassing variable drug absorption following oral administration, and 200 mcg of 3H-propranolol (specific activity 45 mcg/mg) intravenously into the femoral vein, via chronically implanted catheters. Blood samples were taken every 5 minutes for the first hour and then every 15 minutes for a further 3 hours. Unlabelled propranolol concentrations were assayed by HPLC and 3H-propranolol concentrations by liquid scintillation counting of the HPLC effluent that corresponded to the propranolol peak. From this data, Cl_s, Cl_o, Cl_int, extraction ratio (E), bioavailability (I=E), intravenous elimination half-life (t1/2iv), volume of distribution (Vd) and HBF were calculated. As propranolol is only metabolized by the liver and was injected into the portal vein (i.e., 100% absorption), propranolol oral clearance (Cl_o) equals total intrinsic clearance (Cl_int).

Intravenous Clearance (Cl_int) = Cl_0 = D0 / AUC_0

where D0 = intraportal dose and AUC_0 = area under the concentration/time curve for intraportal drug.

Systemic (Intravenous) Clearance (Cl_s = DTV / AUC_V)

where DTV = IV dose and AUC_V = area under the concentration/time curve for IV drug.

HBF = D0AUC_V / AUC_0 - DTVAUC_V

The results were analyzed using Student's t test for paired data, p<0.05 being taken as the minimal level of significance.

Results

The results are shown in the table. During halothane anesthesia, intravenous clearance fell by 62% (p<0.05) from 2110.41 ± 297.60 on Day 1 to 799.27 ± 233.06 ml/min on Day 2, reflecting marked inhibition of liver drug metabolism. Cl_s was decreased (p<0.05) from 469.88 ± 32.87 on Day 1 to 279.79 ± 38.18 ml/min on Day 2 while t1/2_V was increased (p<0.05) from 87.03 ± 11.74 to 154.67 ± 23.12 min during halothane anesthesia. These changes, though less marked, were still evident 24 hour post anesthesia. Bioavailability (I=E) increased (p<0.05) from 0.24 ± 0.04 on Day 1 to 0.41 ± 0.05 on Day 2 and was still increased (p<0.05) on Day 3. Although halothane lowered HBF by 26% from 641.85 ± 79.63 to 473.17 ± 47.11 on Day 2, this change was not significant.

Conclusions

The large increase in intrinsic clearance indicates that halothane markedly inhibits drug metabolism, causing a fall in clearance and an increase in t1/2, which has important kinetic and toxic implications. The decrease in Cl_int produced by halothane changed propranolol from a high extraction drug to one of medium extraction, so that its clearance is now dependent on both HBF and metabolizing ability. We conclude that inhibition of hepatic drug metabolism appears to be a major mechanism for the alterations in drug disposition observed during halothane anesthesia.

Table: EFFECT OF HALOTHANE ON DRUG DISPOSITION

<table>
<thead>
<tr>
<th>Cl_int</th>
<th>t1/2_V</th>
<th>Cl_s</th>
<th>Vd</th>
<th>I-E</th>
<th>HBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>2110.41</td>
<td>87.03</td>
<td>469.88</td>
<td>59.92</td>
<td>0.41* 473.17</td>
</tr>
<tr>
<td>Day 2</td>
<td>799.27*</td>
<td>114.74</td>
<td>327.87</td>
<td>42.44</td>
<td>0.24* 279.79</td>
</tr>
<tr>
<td>Day 3</td>
<td>1095.53</td>
<td>128.32</td>
<td>357.10</td>
<td>50.69</td>
<td>0.07* 473.17</td>
</tr>
</tbody>
</table>

* Significant different (p<0.05) from Day 1.

References

1. CiIn Pharmacokinetics 1:15-155, 1976

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