The Effect of Halothane on Drug Disposition: Contribution of Changes in Intrinsic Drug Metabolizing Capacity and Hepatic Blood Flow


Several studies have shown that halothane may influence drug disposition in animals and humans, but the mechanism remains unclear. The relative contributions of changes in metabolizing capacity and hepatic blood flow to altered drug disposition were investigated during halothane anesthesia, using propranolol as a model compound. The studies were performed on six dogs on three separate days: first, the day before anesthesia, second, during halothane (2.0 MAC) anesthesia, and third, 24 h after anesthesia. Each dog simultaneously received 40 mg unlabeled propranolol directly into the portal vein and 200 mgCi of $^3$H-propranolol intravenously via chronically implanted catheters. Blood samples were taken every 5 min for the first hour and then every 15 min for a further 3 h for the measurement of unlabeled and $^3$H-propranolol concentrations. During halothane anesthesia, intraportal–intrinsic clearance was decreased by 62% ($P < 0.05$) from 2,110 ± 298 to 799 ± 233 ml/min, while systemic clearance was decreased ($P < 0.05$) from 470 ± 33 ml/min preanesthesia to 280 ± 38 ml/min during halothane anesthesia. The intravenous elimination half-life was increased ($P < 0.05$) from 87 ± 12 to 155 ± 23 min during anesthesia. Although halothane anesthesia tended to lower liver plasma flow from 642 ± 80 to 473 ± 47 ml/min, this change was not significant. The large change in portal or intrinsic clearance indicates that halothane anesthesia markedly inhibits drug-metabolizing ability. The authors therefore conclude that the alterations in drug disposition observed during halothane anesthesia are mainly due to inhibition of drug-metabolizing capacity in the liver. (Key words: Anesthetics, volatile halothane. Liver: blood flow; metabolism. Metabolism: inhibition. Pharmacokinetics: propranolol. Sympathetic nervous system: sympatholytic agents, propranolol.)

Although it is well recognized that drug pharmacokinetics may be modified by pathophysiologic processes associated with certain disease states, concern has been focused only recently on the changes in drug disposition that have been noted in the perioperative period. During this period, a number of changes occur that might be expected to alter drug disposition; these include the "stress" of surgery and surgery itself, changes in regional blood flow due to altered pathophysiology and surgery, and the effects of both intravenous and inhalational anesthetics.

Several studies have shown that halothane may influence drug disposition in animals and humans. However, the mechanism remains unclear. Inhalational anesthetics may influence drug pharmacokinetics by three mechanisms: first, by acute alteration in drug distribution, as may be seen when changes in drug binding or volume of distribution occur; second, by changes in hepatic blood flow; and third, by changes in intrinsic drug-metabolizing ability of the liver. Although many factors may be responsible for variations in hepatic blood flow during surgery, inhalational anesthetics such as halothane have been shown to decrease hepatic blood flow. In addition, halothane may inhibit drug-metabolizing activity. In rats, using the aminopyrine "breath test" as a sensitive noninvasive index of in vivo drug metabolism, halothane has been shown to inhibit the rate of aminopyrine elimination in a dose-dependent manner for at least 24 h after anesthesia. Thus, there is evidence that inhalational anesthetics might have important effects on hepatic drug clearance. Hepatic clearance, the clearance of drug from the body by the liver, depends on both liver blood flow and the liver's ability to remove a drug from blood as it passes through the liver, which in turn depends on the drug-metabolizing enzyme systems of the liver. Thus, intrinsic clearance ($CL_{int}$) reflects the intrinsic ability of the hepatic drug-metabolizing enzyme systems and is independent of hepatic blood flow.

The effects of altered hepatic blood flow and intrinsic hepatic metabolizing activity vary according to the hepatic extraction ratio of the drug studied. Following intravenous administration, for drugs that are avidly cleared by the liver and therefore have a high extraction ratio, the rate of drug delivery to the liver, i.e., hepatic blood flow, is the primary determinant of hepatic drug clearance. In contrast, the systemic or intravenous clearance of drugs with a low extraction ratio is dependent not on liver blood flow but on intrinsic drug-metabolizing activity. However, when drug metabolizing ability is

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markedly decreased, the extraction ratio of a highly
extracted drug will decrease, resulting in its intravenous
clearance now dependent on both hepatic
blood flow and drug-metabolizing ability. In addition,
after oral administration of both high and low extraction
drugs, clearance reflects only the liver's intrinsic drug-
metabolizing capacity and is not influenced by changes
in hepatic blood flow. Thus, it is possible to measure
intrinsic clearance and liver blood flow from a knowledge
of the disposition characteristics of a drug following
simultaneous oral and intravenous administration, if the
drug is completely absorbed from the gut and completely
metabolized by the liver. Simultaneous administration
of radiolabeled drug intravenously and unlabeled drug
orally—dual route administration—allows the calculation
of intrinsic clearance and hepatic blood flow under
identical conditions during the same time period.

The purpose of the present study was to define the
relative contributions of changes in hepatic blood flow
and intrinsic metabolizing ability to altered drug dispo-
sition during halothane anesthesia, independent of other
factors such as surgery, which are usually associated
with anesthetic administration. We therefore studied
the effects of halothane anesthesia on the pharmacoki-
netics of the model compound propranolol, using the
dual route technique, which permits the calculation of
all the determinants of drug disposition.

Methods

Six male mongrel dogs (22.9 ± 1.8 kg ± SEM) were
studied. Each dog was studied on three consecutive
days; first, on the day before anesthesia while conscious
day 1), second, during halothane anesthesia (day 2),
and third, 24 h after anesthesia (day 3).

Anesthetic Technique

The dogs were induced with thiopental (5 mg/kg)
followed by tracheal intubation. Anesthesia was main-
tained with halothane (2.0 MAC, 1.74%) in oxygen.
Ventilation was controlled to maintain normal blood
gases (PaCO₂ 35–41 mmHg). Intraarterial pressure was
monitored continuously, and end-tidal halothane con-
centrations were measured by gas chromatography at
approximately hourly intervals throughout the study.
Two hours after the commencement of anesthesia when
hemodynamic conditions were stable and halothane end-
tidal concentration was constant at 2.0 MAC, propranolol
was administered as described below. Anesthesia was
maintained at 2.0 MAC halothane throughout the study
period, and the total MAC hours of halothane admin-
istered was calculated. After completion of the study,
the dog was allowed to recover consciousness and was
extubated.

Pharmacokinetic Techniques

All the dogs had chronically implanted femoral vein,
femoral artery, and portal vein cannulae inserted 5 days
before preanesthesia day 1 under pentobarbital anes-
thesia (50 mg/kg). The dogs were studied on 3 consecu-
tive days; on all 3 days the pharmacokinetic study
technique was identical. Each dog received 40 mg un-
labeled propranolol directly into the portal vein by a
constant infusion pump over 10 min (thus bypassing
the effect of variable drug absorption following oral admin-
istration), and simultaneously a trace dose of 200 mCi
of ³H-propranolol (specific activity 67 mCi/mg, Ameri-
sham Searle Corporation, Arlington Heights, Illinois)
was given intravenously into the femoral vein.

Blood samples were obtained every 5 min for the
first hour after drug administration, and then every 15
min for a further 3 h for the measurement of both
unlabeled and ³H-propranolol concentrations. Unlabeled
propranolol concentration in plasma was measured by
high-performance liquid chromatography and the ³H-
propranolol plasma concentration by liquid scintillation
counting of the high-performance liquid chromatogram
effluent corresponding to the propranolol peak, as we
have previously described. Plasma samples were ob-
tained prior to propranolol administration for the mea-
surement of propranolol binding in plasma by equilib-
rium dialysis as previously described.

From these data, systemic clearance (Clₛ), portal clear-
ance (Clₚ), hepatic extraction ratio (E), bioavailability
(F) or (1 – E), intravenous elimination half-life (t₁/₂v),
volume of distribution (Vd), and liver plasma flow were
calculated as described below.

As propranolol is only metabolized by the liver and
was injected into the portal vein (equivalent of 100% oral
absorption), the apparent clearance of portally
administered propranolol (Clₚ) is numerically equal to
total intrinsic clearance, (Clₘᵢₙᵢᵦ).\(^{14}\)

Theoretic Calculations

Propranolol clearance following intravenous or sys-
temic administration (Clₛ) was calculated as follows:

\[
Clₛ = \frac{Dₚ}{AUCₚ}
\]

where Dₚ is the dose of labeled propranolol administered
intravenously and AUCₚ the area under the concentra-
tion–time curve calculated by the trapezoidal rule for
labeled drug administered intravenously.

The clearance of drug administered into the portal
vein (Clₚ) was calculated as
Liver plasma flow (Q) was calculated as follows:

By definition, following administration of intraportal dose (D₀), the amount of drug entering the systemic circulation = D₀F, where F is the fractional systemic availability. Thus

\[ Cl_s = \frac{D_0 F}{AUC_o} \]  

But as \( D_0 / AUC_o = Cl_o \) (equation [2]), and by definition \( F = 1 - E \), where E is the hepatic extraction ratio:

\[ Cl_l = (1 - E) Cl_o. \]  

Also by Fick’s principle

\[ Cl_l = QE \]

where Q = apparent liver plasma flow.

Thus substituting for \( E \) into equation (4)

\[ Q = \frac{Cl_l Cl_o}{Cl_u - Cl_l}. \]

Hence

\[ \text{liver plasma flow} = \frac{D_0 D_0}{AUC_o D_0 - AUC_o D_0}. \]

**STATISTICAL ANALYSIS**

Statistical comparisons were performed using analysis of variance, followed by Students’ t test for paired data where appropriate. The minimal accepted level of significance was taken as \( P < 0.05 \).

**Results**

Figure 1 shows mean plasma propranolol concentrations following intraportal administration plotted against time for the three study days, indicating that there was a marked increase in propranolol concentration during halothane anesthesia. The plasma concentrations of \(^3\)H-propranolol following intravenous administration are displayed in figure 2. The concentrations following intravenous administration also decreased more slowly during halothane anesthesia.

During halothane anesthesia, the clearance following portal administration (that is the intrinsic clearance of propranolol), decreased by 62% from 2,110 ± 298 ml/min on day 1 to 799 ± 233 ml/min on day 2 (\( P < 0.05 \)) (table 1; fig. 3), reflecting the marked inhibition of liver drug metabolism. Twenty-four hours after anesthesia, some recovery had occurred in the intrinsic clearance, but it was still depressed by almost 50% (1,095 ± 331 ml/min), compared with the preanesthesia day. Less marked changes were seen in the systemic clearance (\( Cl \)) of intravenously administered \(^3\)H-propranolol, which decreased from 470 ± 33 ml/min preanesthesia to
280 ± 38 ml/min during halothane anesthesia (P < 0.05) (table 1; fig. 4); this represented a decrease of 40%.

There was no significant change in the volume of distribution (Vdhl) throughout the study period. However, plasma binding of propranolol was reduced during halothane anesthesia, resulting in an increase in the free fraction of propranolol from 7.1 ± 1.0% on the preanesthesia day to 9.6 ± 1.4% during halothane anesthesia (P < 0.05). This returned toward normal 24 h after anesthesia when the mean free fraction was 8.1 ± 0.9%.

The half-life of elimination following intravenous administration (t₁/₂α) was increased (P < 0.05) from 87 ± 11 min preanesthesia to 155 ± 23 min during halothane anesthesia, reflecting the observed changes in both portal and systemic propranolol clearance.

The amount of drug entering the systemic circulation, bioavailability (F) or (1 − E), increased (P < 0.05) from 0.25 ± 0.04 on the preanesthesia day (day 1) to 0.41 ± 0.05 during halothane anesthesia. Twenty-four hours postanesthesia on day 3, the bioavailability was still increased (P < 0.05) to 0.40 ± 0.07, as compared with 0.24 ± 0.04 on day 1 (fig. 5; table 1). Thus, on day 1, 24 h before anesthesia, the hepatic extraction ratio (E) of propranolol was 0.75 (moderately high extraction), but on day 2, during anesthesia, the hepatic extraction was 0.59 (intermediate extraction), indicating that the change in hepatic intrinsic clearance had caused a reduction in hepatic extraction ratio.

Although halothane anesthesia appeared to decrease mean liver plasma flow by 26% (473 ± 47 ml/min during halothane compared with 642 ± 80 ml/min on the preanesthesia day), this change was not statistically significant (P = 0.16). Twenty-four hours after anesthesia (day 3), liver plasma flow was 583 ± 83 ml/min.

The mean duration of halothane anesthesia on day 2 was 11.7 ± 0.4 (SEM) MAC hours.

Discussion

Because of the central role performed by the liver in the elimination of drugs, it is important to separate the effects on drug clearance of the following: 1) alteration in the intrinsic ability of the liver to metabolize drugs (CLint), and 2) the rate at which drugs are delivered to the liver through alterations in hepatic blood flow. Intrinsic clearance reflects the maximal ability of the liver to remove drug and is independent of liver blood flow. For a drug like propranolol, which is completely absorbed from the gut and is completely metabolized only by the liver, it has previously been shown that the

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**Table 1. Effect of Halothane on Drug Disposition in Six Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Intrinsic Clearance (ml/min) (CLint)</th>
<th>Intravenous Half-life (min) (t₁/₂α)</th>
<th>Systemic Clearance (ml/min) (CL)</th>
<th>Volume of Distribution (L) (Vdhl)</th>
<th>Bioavailability (1 − E)</th>
<th>Liver Plasma Flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preanesthesia</td>
<td>2.110 ± 298</td>
<td>87 ± 12</td>
<td>470 ± 33</td>
<td>56.9 ± 4.2</td>
<td>0.25 ± 0.04</td>
<td>642 ± 80</td>
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<tr>
<td>Day 1</td>
<td></td>
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<td></td>
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<tr>
<td>Anesthesia Day 2</td>
<td>799 ± 233†</td>
<td>155 ± 23</td>
<td>280 ± 38</td>
<td>59.9 ± 7.9</td>
<td>0.41 ± 0.05†</td>
<td>473 ± 47</td>
</tr>
<tr>
<td>Postanesthesia</td>
<td>1,095 ± 331</td>
<td>94 ± 12</td>
<td>333 ± 57</td>
<td>42.8 ± 5.7</td>
<td>0.40 ± 0.07†</td>
<td>583 ± 83</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
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</table>

* Values are expressed as mean ± SEM.
† Significantly different (P < 0.05) from Control Day 1.
Fig. 3. Change in propranolol clearance following portal administration (ml/min) on day 1, 24 h prior to anesthesia, on day 2 during halothane (2.0 MAC) anesthesia, and on day 3, 24 h after anesthesia.

Fig. 4. Change in systemic propranolol clearance (ml/min) on day 1, 24 h prior to anesthesia, on day 2 during halothane (2.0 MAC) anesthesia, and on day 3, 24 h after anesthesia.

Fig. 5. Change in hepatic extraction ratio (E) on day 1, 24 h prior to anesthesia, on day 2 halothane (2.0 MAC) anesthesia, and on day 3, 24 h after anesthesia.

clearance following oral administration ($Cl_{in}$) is numerically equal to intrinsic hepatic clearance ($Cl_{inh}$). It is possible that inhalational anesthetics such as halothane might inhibit the absorption of propranolol from the gut, and we therefore injected propranolol directly into the portal vein. We have thus shown in this study that halothane anesthesia reduced portal and therefore intrinsic clearance by over 60%, indicating that halothane anesthesia markedly inhibits drug-metabolizing ability in vivo.

It is interesting that halothane anesthesia reduced the hepatic extraction ratio from 0.75 to 0.59 during anesthesia, resulting in an increase in the bioavailability from 0.25 to 0.41. An increase in intrinsic clearance, produced, for example, by enzyme induction, will result in an increase in the extraction ratio, while conversely a decrease in intrinsic clearance will reduce the hepatic extraction ratio. Thus, the marked decrease in intrinsic clearance, produced by halothane anesthesia, has effectively changed propranolol from a high-extraction drug with low bioavailability to one of medium extraction. This has important therapeutic and pharmacokinetic implications, since low-extraction drugs can be visualized as having enzyme-dependent kinetics, while the kinetics of high-extraction drugs administered intravenously are blood flow dependent. The changes in hepatic drug clearance shown during this study resulted in an increased systemic elimination half-life and a reduced systemic clearance.

Halothane anesthesia (2.0 MAC) in the dog tended to reduce hepatic plasma flow (26%), but this was not
statistically significant. Halothane anesthesia has been shown by other workers to decrease hepatic blood flow by 20–30%. A more recent study, using electromagnetic flow probes to measure hepatic artery and portal vein blood flow demonstrated that increasing inspired halothane concentrations caused incremental decreases in hepatic blood flow in parallel with the decrease in blood pressure, so that at 2.0 MAC there was almost a 50% decrease in blood flow. Gelman et al using a microsphere technique in dogs, have shown that hepatic arterial blood flow remained unchanged during 1.0 MAC halothane anesthesia and decreased by almost 50% during 2.0 MAC halothane anesthesia. Our study only suggested a decrease in hepatic plasma flow during halothane anesthesia. The dual route approach used in our study, employing simultaneous intraportal and intravenous administration of propranolol, has been shown by us in other situations to give estimates of hepatic plasma flow almost identical to those obtained with more conventional methods employing the Fick principle upon which it is based. This method also has the advantage of averaging the functional hepatic plasma flow over the 4-h study period. Any decrease in hepatic plasma flow due to halothane anesthesia may to some extent have been masked by the beta-blockade caused by propranolol, which in itself can cause a decrease in hepatic blood flow of up to 20%. However, the trend toward lower hepatic plasma flow observed during anesthesia is unlikely to be due to higher plasma propranolol levels resulting from increased bioavailability, as the dose given would cause near maximal beta-blockade on all 3 days. It is well recognized that hypocarbia, hypercarbia, hypoxemia, and changes in acid–base balance influence hepatic blood flow. These parameters were carefully maintained at normal values throughout the study. Hypoxemia has been shown to have minimal effects on hepatic blood flow.

We observed a small, but significant, reduction in plasma propranolol binding during halothane anesthesia. This would be unlikely to affect the clearance of propranolol, since, for highly extracted drugs elimination is not restricted by protein binding. It is interesting that in a recent in vitro study halothane did not affect propranolol binding in serum. Alpha,-acid glycoprotein (AAG) is a plasma protein that has been shown to increase in response to surgery and trauma and is the principal binding protein for propranolol. Plasma propranolol binding has been shown to increase on the day after surgery in humans, probably because of an increase in AAG concentration. It is possible that surgery for the placement of chronic cannula might affect AAG concentration and propranolol binding. Alterations in serum binding of propranolol have been shown to be elicited by the presence of an indwelling venous catheter in the rat. The effect of inhalational anesthetics on drug binding deserves further investigation.

We therefore conclude from this study that halothane anesthesia markedly inhibits drug-metabolizing capacity in the liver and that this appears to be a major mechanism for the alterations in drug disposition observed during halothane anesthesia. These changes were still evident 24 h later. A reduction in intrinsic hepatic clearance that leads to a substantial increase in drug concentrations in blood during anesthesia has pharmacokinetic and toxic implications for other drugs, such as lidocaine, beta-adrenergic blockers, and some benzodiazepines, which may be administered during the perioperative period. The individualization of drug therapy not only during anesthesia and surgery in the operating room but also in the postoperative intensive care unit, should be considered. In addition, the effects of other volatile anesthetics and intravenous anesthetic techniques on the various affecting drug disposition remain to be investigated.

References


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