Leonid Roytblat MD, Simon Gelman MD PhD,
Todd Henderson BS, Dale Parks PhD

H₁ and H₂ receptor antagonists and hepatic oxygen supply-demand relationship in pigs

The hypothesis that histamine receptor (H₁ and H₂) blockade beneficially affects the hepatic oxygen supply-demand relationship was tested during experiments performed on 13 miniature pigs. Hepatic arterial and portal blood flows were measured with electromagnetic flowmeters. Cardiac output was determined by thermodilution. H₁ and H₂ receptor blockade was achieved with promethazine, 5 mg · kg⁻¹ and cimetidine 30 mg · kg⁻¹ IV, respectively. The study demonstrated no significant effect of H₁ and H₂ receptor blockade on hepatic oxygen uptake and no noticeable effects of cimetidine on hepatic circulation. However, promethazine decreased total hepatic blood flow, primarily by decreasing portal blood flow; this resulted in an increase in oxygen extraction as reflected in a decreased oxygen content in hepatic venous blood. The results reject the posed hypothesis: H₁ receptor antagonist promethazine decreased, while H₂ receptor antagonist cimetidine did not affect hepatic blood flow and oxygen supply; hepatic oxygen demand remained unaffected during H₁ and H₂ receptor blockade.

Nous avons testé l'hypothèse voulant que le blocage des récepteurs histaminiques H₁ et H₂ augmente le ratio apport/demande de l'oxygène au foie. Chez 13 cochons miniatures, nous avons mesuré le débit cardiaque par thermodilution et les débits artériel hépatique et veineux porte avec un débitmètre électromagnétique. Nous utilisons 5 mg · kg⁻¹ IV de prométhazine pour le blocage H₁ et 30 mg · kg⁻¹ IV de cimétidine pour le

blocage H₂. Nous n'avons observé aucun effet des bloquants H₁ et H₂ sur le métabolisme oxydatif hépatique, non plus que d'effet notable de la cimétidine sur la circulation hépatique. Toutefois, la prométhazine diminuait le débit sanguin hépatique surtout en provenance de la veine porte de telle sorte que l'extraction de l'oxygène par le foie en était augmentée, avec réduction du contenu en oxygène du sang veineux hépatique.

There are wide indications for the use of H₁ and H₂ receptor antagonists in anaesthesia practice. According to some authorities, H₁ antagonists are indicated in all forms of anaphylaxis.¹ H₂ antagonists are routinely used to increase pH and decrease volume of gastric contents before anaesthesia induction to prevent aspiration and subsequent pulmonary complications.² Also, it has been suggested that both H₁ and H₂ receptor antagonists be used to prevent cardiovascular changes occurring during the administration of drugs which release histamine, e.g., muscle relaxants.^{3,4}

Histamine plays an important role in the regulation of the splanchnic and hepatic circulations.⁵⁻⁷ Intestinal and gastric vasodilatation associated with the administration of histamine is mediated by both H₁ and H₂ receptors.^{5,8-10} The vasodilating effect of histamine in the preportal circulatory bed leads to an increase in portal blood flow.^{8,11,12} On the other hand, histamine may substantially increase portal vascular resistance¹³⁻¹⁵ by constricting hepatic veins.^{7,16,17} Thus, the net effect of histamine on portal flow may depend on the effect of histamine on preportal vasculature and on the hepatic vascular bed *per se*. Hepatic arterial blood flow after histamine administration was found to increase in dogs¹⁸ and decrease in cats.¹² Some older studies, as reviewed by Greenway and Stark,⁷ demonstrated an increase in hepatic arterial blood flow by histamine in dogs as well as in cats.

The effect of H₁ and H₂ receptor antagonists on the hepatic circulation have not attracted much attention. Studies by Feely *et al.* demonstrated a decrease in total hepatic blood flow after cimetidine administration.^{19,20} However, the methodology of these studies was severely criticized,^{21,22} and, therefore, the results have not been

Key words

HISTAMINE: receptor antagonists, cimetidine, promethazine;
LIVER: blood flow, oxygen supply.

From The Department of Anesthesiology, The University of Alabama at Birmingham, 619 South 19th Street, Birmingham, Alabama 35233.

Address correspondence to: Dr. S. Gelman, Department of Anesthesiology, The University of Alabama at Birmingham, 619 South 19th Street, Birmingham, Alabama 35233.

Supported by NIH Grant #5R01GM37611.

Accepted for publication 10th September, 1990.

generally accepted.²³ A recent study in humans did not reveal any substantial changes in total hepatic blood flow nor in portal blood flow under the influence of famotidine, another H₂ receptor antagonist.²⁴

Although H₁ and H₂ receptor blockade is associated with a substantial decrease in intestinal oxygen demand,²⁵ possibly resulting from a reduction in secretion and motility,²⁶ the effects of H₁ and H₂ antagonists on hepatic oxygen supply and uptake have received relatively little attention. In addition, H₂-receptor antagonists decrease mixed function oxidase activity in the rat liver.²⁷ Such an effect might be associated with a decrease in hepatic oxygen requirement. Histamine receptor blockade can improve survival of animals in the haemorrhagic shock model.^{28,29} The beneficial effect of histamine receptor antagonists in those experiments could be related to their favourable effect on oxygen supply–demand relationship in various tissues and organs, including the liver. Thus, the effect of histamine receptor blockade may beneficially affect the hepatic oxygen supply–demand relationship by the following mechanisms: (1) decreased oxygen requirement in the preportal tissues with a subsequent increase in oxygen content in portal blood, and (2) decreased hepatic oxygen requirement. The present study was designed to test the hypothesis that histamine receptor blockade beneficially affects the hepatic oxygen supply–demand relationship.

Methods

Anaesthesia and surgical preparation

The study was approved by the University of Alabama Animal Use Committee. Experiments were performed on 13 miniature pigs (eight experimental and five control) of either sex weighing 18–27 kg. The animals fasted for 18–20 hr. Anaesthesia was achieved with sodium pentobarbitone, 35 mg·kg⁻¹ IM, followed by 1–2 mg·kg⁻¹ IV throughout the experiment. Muscle relaxation was achieved with pancuronium bromide, 0.1 mg·kg⁻¹ IV. Controlled ventilation at a PaCO₂ of 35–40 mmHg was provided through a tracheal tube with oxygen using an air-shield ventilator. Body temperature was monitored rectally and maintained at 38°C with an electrical heating pad. Throughout the experiment, lactated Ringer's solution was infused at a rate of 5 ml·kg⁻¹·hr⁻¹.

The surgical preparation consisted of exploration and isolation of both carotid arteries and jugular veins. Both carotid arteries were cannulated, one for blood pressure recording and blood sampling, and the other for blood supply to the hepatic artery. The left jugular vein was cannulated for fluid infusion and drug administration. A triple lumen thermistor-tipped catheter was introduced into the pulmonary artery via the right jugular vein for

cardiac output determinations with thermodilution. Laparotomy was performed. The hepatic artery and portal vein were isolated and transected. All visible small branches of the hepatic artery as well as the gastroduodenal artery were ligated. Special care was taken to preserve adventitia of the vessels. Heparin 300 units·kg⁻¹ was administered IV. A cannulating electromagnetic probe of appropriate size with a port for measuring portal venous pressure was inserted into the portal vein so that portal blood would flow to the liver through the probe. The hepatic artery was transected. Tubing with a cannulating electromagnetic probe of appropriate size was used to connect the proximal end of a carotid artery with the hepatic end of the hepatic artery. The proximal end of the hepatic artery was then ligated. Thus, hepatic arterial and portal venous blood flows were measured with an electromagnetic flowmeter (700 series Cliniflow II, Carolina Medical Electronics, Inc.) using cannulating probes. The probes were factory calibrated and electronically zeroed by the instrument. The accuracy of the measurements was verified by passing pigs' blood at different rates through the probes between the experiments. The rates were then compared with the flowmeter output; the differences did not exceed five per cent. An hepatic vein was cannulated subdiaphragmatically through the inferior (posterior) caval vein with a balloon-tipped catheter for monitoring of pressure and blood sampling. The catheter was advanced into the hepatic vein until occlusion and then withdrawn 2–3 cm to ensure free positioning of the catheter tip in the hepatic vein. Blood samples were withdrawn slowly and the balloon was slightly inflated to ensure that blood from the caval vein did not mingle with hepatic venous blood. The position of the catheter was verified after each experiment.

Experimental protocol

The preparation was allowed to stabilize for 30 min, then baseline measurements were performed and blood samples were obtained (time 0). Blockade of H₁ and H₂ receptors was achieved by an IV injection of promethazine, 5 mg·kg⁻¹, and cimetidine, 30 mg·kg⁻¹, respectively. The selected doses were considered to be sufficient for H₁ and H₂ receptor blockade.^{29,30} In subgroup PC (four animals), promethazine was injected IV and all measurements were obtained after 30 min (time 30). Then cimetidine was added, and all measurements were again obtained every 30 min for two hours (times 60, 90, 120, and 150). In another four animals (subgroup CP), the experiments began with an injection of cimetidine, and all measurements were obtained after 30 min (time 30); then, promethazine was administered and the results obtained every 30 min for another two hours (times 60, 90, 120, and 150). In the control group (five animals),

TABLE I Variables characterizing hepatic circulation before H₁ and H₂ receptor antagonists administration (mean $\pm$ SE)

Variables	Experimental group (n = 8)	Control group (n = 5)
MAP (mmHg)	130 $\pm$ 15	125 $\pm$ 7
PP (mmHg)	13.9 $\pm$ 0.7	11.5 $\pm$ 0.5
HVP (mmHg)	9.1 $\pm$ 2.4	7.9 $\pm$ 1.4
CI (ml $\cdot$ min ⁻¹ $\cdot$ kg ⁻¹)	97.2 $\pm$ 9.0	86.4 $\pm$ 16.7
PBF (ml $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	69.1 $\pm$ 13.1	70.4 $\pm$ 14.4
HABF (ml $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	19.2 $\pm$ 7.3	19.4 $\pm$ 12.2
HAR (mmHg $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	7.12 $\pm$ 2.19	7.86 $\pm$ 3.46
PVR (mmHg $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	0.07 $\pm$ 0.03	0.06 $\pm$ 0.03
PPR (mmHg $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	1.79 $\pm$ 0.54	1.66 $\pm$ 0.32
SpIR (mmHg $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	1.42 $\pm$ 0.31	1.38 $\pm$ 0.35

Mean arterial pressure (MAP), portal pressure (PP), hepatic venous pressure (HVP), cardiac index (CI), portal venous blood flow (PBF), hepatic arterial blood flow (HABF), hepatic arterial resistance (HAR), portal venular resistance (PVR), preportal vascular resistance (PPR), total splanchnic vascular resistance (SpIR).

saline rather than H₁ and H₂ receptor antagonists was administered; all measurements were obtained at the same time intervals as in the experimental groups. Experiments with haemoglobin concentrations lower than 10 g $\cdot$ dl⁻¹ at any stage of observation were excluded from the study and not reported.

Measurement and calculations

The measurements included heart rate, systolic, diastolic, and mean systemic arterial pressure, portal venous pressure, hepatic venous pressure, and cardiac index—cardiac output determined with thermodilution in triplicate and divided by body weight. Arterial, portal, and hepatic venous blood samples were obtained for pH/gas tensions and oxygen content analyses, which were performed using an Instrumentation Laboratories model 1301 pH/blood gas analyzer and model 282 Co-oximeter. Total body oxygen delivery was calculated as a product of cardiac index and arterial oxygen content. Hepatic oxygen delivery was calculated as the sum of two multiplications: hepatic arterial blood flow multiplied by arterial oxygen content and portal blood flow multiplied by oxygen content in portal venous blood. Hepatic oxygen uptake was calculated as the difference between hepatic oxygen delivery and the multiplication of total hepatic blood flow and oxygen content in hepatic venous blood. Both hepatic oxygen delivery and hepatic oxygen uptake were expressed in mlO₂ $\cdot$ min⁻¹ $\cdot$ 100 g⁻¹ of liver tissue. Preportal oxygen delivery was also calculated as a product of portal venous blood flow and arterial oxygen content. Preportal oxygen uptake was calculated as the difference between preportal oxygen delivery and the multiplication of portal blood flow and portal venous oxygen content.

TABLE II Variables characterizing hepatic oxygen supply uptake relationship before H₁ and H₂ receptor antagonists administration (mean $\pm$ SE)

Variables	Experimental group (n = 8)	Control group (n = 5)
CaO ₂ (mlO ₂ $\cdot$ dl ⁻¹)	16.0 $\pm$ 1.6	16.8 $\pm$ 1.9
SpvO ₂ (%)	80.2 $\pm$ 6.7	79.8 $\pm$ 4.0
ShvO ₂ (%)	53.4 $\pm$ 16.9	48.5 $\pm$ 17.1
TDO ₂ (mlO ₂ $\cdot$ min ⁻¹ $\cdot$ kg ⁻¹)	15.6 $\pm$ 1.4	15.0 $\pm$ 4.1
PPDO ₂ (mlO ₂ $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	11.0 $\pm$ 2.0	11.7 $\pm$ 2.5
PPVO ₂ (mlO ₂ $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	2.0 $\pm$ 0.6	2.1 $\pm$ 0.3
HDO ₂ (mlO ₂ $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	12.1 $\pm$ 2.2	12.9 $\pm$ 3.8
HVO ₂ (mlO ₂ $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	4.4 $\pm$ 2.0	5.4 $\pm$ 1.5
HDO ₂ –HVO ₂ (mlO ₂ $\cdot$ min ⁻¹ $\cdot$ 100 g ⁻¹)	7.7 $\pm$ 2.7	7.4 $\pm$ 0.4
Extr O ₂ (%)	36 $\pm$ 7	39 $\pm$ 8

Oxygen content in arterial blood (CaO₂), oxygen saturation in portal venous blood (SpvO₂), oxygen saturation in hepatic venous blood (ShvO₂), total body oxygen delivery (TDO₂), preportal oxygen delivery (PPDO₂), preportal oxygen uptake (PPVO₂), hepatic oxygen delivery (HDO₂), hepatic oxygen uptake (HVO₂), hepatic oxygen delivery-uptake gradient (HDO₂–HVO₂), hepatic oxygen extraction (Extr O₂).

Preportal and hepatic oxygen extraction ratios and supply-uptake gradients were also calculated. Total splanchnic, hepatic arterial, preportal, and portal venous vascular resistances were also calculated as ratios of appropriate pressure gradients by flows.

Data were analyzed using repeated measures analysis of variance. Multiple range Fisher's protected least significant difference test was used to make pair-wise comparisons. The differences were considered significant if $P < 0.05$. All computations were performed with the aid of the Statistical Analysis System.

Results

The baseline values of the variables characterizing hepatic circulation and hepatic oxygen supply-uptake relationship observed before H₁ and H₂ receptor antagonists administration are presented in Tables I and II, respectively. There were no statistically significant changes in any of the determined variables in the control group during the 150 minutes of observation. These variables included: arterial blood gases (PaO₂, PaCO₂, pH), haemoglobin and haematocrit values as well as systemic arterial blood pressure, cardiac output, total body oxygen delivery, and all variables characterizing hepatic circulation and oxygen supply-uptake relationship. There were no significant differences in any variable at baseline between the experimental and control groups prior to administration of H₁ and H₂ receptor antagonists. Also, there were no significant differences in the baseline values between the two subgroups, CP and PC, nor were there significant

FIGURE 1 Changes (mean $\pm$ SE) in portal blood flow (PBF) after cimetidine (C) and promethazine (P) administration. 0, 30, 60, 90, 120, 150: minutes of observation after administration of cimetidine at time "0" and promethazine at time "30" (subgroup CP, identified with circles and solid line) or after administration of promethazine at time "0" and cimetidine at time "30" (subgroup PC, identified with squares and dashed line). * $P < 0.05$ vs baseline values. † $P < 0.05$ vs corresponding value in subgroup CP. The data from the control group are not depicted, for clarity, since there were no significant differences in any variable over time (150 min), nor were there significant differences among the groups at time "0."

FIGURE 2 Changes (mean $\pm$ SE) in hepatic arterial blood flow (HABF) after cimetidine (C) and promethazine (P) administration. See Figure 1 for abbreviations and symbols.

differences between these subgroups at any stage of observation except at 30 min after administration of H_1 and H_2 antagonist; the observed differences in this regard are identified in Figures 1–8.

Cimetidine or promethazine alone or their combination caused no changes in cardiac output or total body oxygen delivery. Cimetidine alone did not decrease portal blood flow (Figure 1, 30 minutes of observation). Promethazine alone, as well as the combination of promethazine and

FIGURE 3 Changes (mean $\pm$ SE) in oxygen saturation in portal venous blood (SpvO₂) after cimetidine (C) and promethazine (P) administration. See Figure 1 for abbreviations and symbols.

FIGURE 4 Changes (mean $\pm$ SE) in oxygen saturation in hepatic venous blood (ShvO₂) after cimetidine (C) and promethazine (P) administration. See Figure 1 for abbreviations and symbols.

cimetidine, led to a substantial (30 per cent) decrease in portal blood flow (Figure 1); portal pressure did not change and calculated portal venular resistance increased by 30 per cent. There was a decrease (30 per cent) in hepatic arterial blood flow following promethazine administration (Figure 2). The H_1 and H_2 receptor blockade was associated with a decrease in oxygen tension, content and saturation in the portal vein; however, no change was observed when cimetidine was administered alone (Figure 3). Oxygen saturation in the hepatic venous blood was substantially (almost halved) decreased ($P < 0.05$) when promethazine or a combination of promethazine and cimetidine was used; however, it was not affected when cimetidine alone was administered (Figure 4). The observed changes resulted in a significant decrease (39 per

FIGURE 5 Changes (mean $\pm$ SE) in hepatic oxygen delivery (HDO₂) after cimetidine (C) and promethazine (P) administration. See Figure 1 for abbreviations and symbols.

FIGURE 6 Changes (mean $\pm$ SE) in hepatic oxygen uptake (HVO₂) after cimetidine (C) and promethazine (P) administration. See Figure 1 for abbreviations and symbols.

cent) in hepatic oxygen delivery after injection of promethazine or after combined administration of promethazine and cimetidine; however, hepatic oxygen delivery did not decrease when cimetidine alone was used (Figure 5). Preportal oxygen delivery decreased 25 per cent after administration of promethazine or the combination of promethazine and cimetidine, but did not change after injection of cimetidine alone. Oxygen delivery-uptake gradient in the preportal tissues did not change after cimetidine injection but decreased 45–50 per cent after promethazine or promethazine-cimetidine combination. Hepatic oxygen uptake apparently was not affected by cimetidine or by promethazine or by their combination (Figure 6). Subsequently, hepatic oxygen extraction was not affected by cimetidine alone but was increased by a

FIGURE 7 Changes (mean $\pm$ SE) in hepatic oxygen delivery-uptake gradient (HDO₂-HVO₂) after cimetidine (C) and promethazine (P) administration. See Figure 1 for abbreviations and symbols.

FIGURE 8 Changes (mean $\pm$ SE) in hepatic oxygen extraction (Extr O₂) after cimetidine (C) and promethazine (P) administration. See Figure 1 for abbreviations and symbols.

third during the administration of promethazine or combination of promethazine and cimetidine (Figure 7). The arterial fraction of hepatic oxygen delivery doubled after promethazine and did not change significantly after cimetidine administration. Hepatic oxygen delivery-uptake gradient was not affected by cimetidine alone but was substantially decreased (by 30–53 per cent) by promethazine and combination of promethazine and cimetidine (Figure 8).

Discussion

Innervation of the hepatic vasculature is rich and complex, and mainly achieved through the two plexuses which freely mingle in the region where the hepatic artery and portal vein run in close position.³¹ Therefore, the fact

that the hepatic artery and portal vein were transected probably did not affect the innervation of the liver because only the muscle layer and intima were transected while the adventitia was preserved. Also, if some degree of denervation occurred in our preparation, the degree of denervation was similar in all groups and equal through all stages of experiments; therefore, the differences among the groups and stages were likely to be related to the histamine receptor antagonists rather than to the degree of denervation.

The results of the study reject the posed hypothesis: neither H_1 nor H_2 antagonist nor their combination improved the hepatic oxygen supply-demand relationship. It is worthwhile noting that H_1 and H_2 receptor blockade with promethazine and cimetidine, respectively, was not associated with changes in systemic blood pressure or cardiac output, although promethazine administration resulted in substantial decreases in portal and hepatic arterial blood flows. A promethazine-induced decrease in portal blood flow may result partially from a reduction in intestinal secretion and motility.²⁶ However, the degree of decrease in blood flow through preportal tissues exceeded the degree of decrease in oxygen requirement since oxygen content and saturation in portal blood significantly decreased after promethazine administration.

A promethazine-induced decrease in hepatic arterial and portal blood flows, in addition to decreased oxygen content and saturation in portal blood, resulted in a decrease in hepatic oxygen delivery with an associated increase in oxygen extraction by the liver, reflected in a decrease in oxygen content and saturation in hepatic venous blood. Apparently, hepatic oxygen demand was not affected by promethazine since hepatic oxygen uptake did not change. The hepatic oxygen delivery-uptake gradient was decreased by promethazine illustrating a decrease in margin of safety for hepatic oxygenation. This part of the study suggests a potential danger of promethazine when hepatic oxygen supply might be in question. Such a situation might include different surgical procedures, particularly laparotomy.^{32,33} General anaesthesia with many drugs, especially volatile anaesthetics (e.g., halothane or enflurane) may also decrease hepatic blood and oxygen supply³³ which in turn might be dangerous when used in combination with promethazine. It is important to realize, however, that the present study demonstrated such an effect of promethazine only in conditions of pentobarbitone anaesthesia, surgical preparation, and possibly some degree of denervation. Obviously, the possibility that the effect of promethazine in conditions of general anaesthesia with other anaesthetics or in other experimental models might be different and cannot be ruled out. The intimate mechanism by which

promethazine decreased portal blood flow in excess of a decrease in oxygen requirement in the preportal tissues remains to be elucidated.

The study did not demonstrate any beneficial effect of H_2 receptor blockade with cimetidine on hepatic oxygen supply-demand relationship nor did it show any decrease in hepatic blood and oxygen supply. Contrary to the observations by Feely *et al.*^{19,20} the present study did not demonstrate any deterioration in hepatic blood flow or hepatic oxygen supply. Feely *et al.* determined indocyanine green (ICG) clearance but did not measure hepatic ICG extraction. The decrease in ICG clearance during H_2 antagonist administration could have resulted from altered metabolism and a reduced intrinsic hepatic clearance rather than from a decreased blood flow. These studies^{19,20} were criticized^{21,22} and have not been generally accepted.²⁴ Other studies failed to demonstrate a decrease in hepatic blood flow after H_2 receptor antagonist administration.³⁴⁻³⁶ The known effects of cimetidine on the pharmacokinetics of many compounds such as propranolol,¹⁹ antipyrine,³⁷ warfarin,³⁷ diazepam,³⁸ chlordiazepoxide,³⁹ are probably related to factors other than hepatic blood flow. These factors may include certain changes in binding of the drug as well as the inhibition of hepatic drug metabolizing enzymes by cimetidine.³⁷⁻⁴⁰

In conclusion, the results reject the hypothesis that H_1 and H_2 receptor blockade improves hepatic oxygen delivery-uptake relationship. The study demonstrated an absence of significant effects of H_1 and H_2 receptor blockade on hepatic oxygen demand and uptake. The study also demonstrated a lack of effect of cimetidine, an H_2 receptor antagonist, on the hepatic circulation. On the other hand, promethazine, an H_1 receptor antagonist, decreased total hepatic blood flow mainly by a decrease in both portal venous and hepatic arterial blood flows. Since this decrease in hepatic blood flow was not associated with a decrease in hepatic oxygen requirement and uptake, it resulted in an increase in hepatic oxygen extraction and a decrease in oxygen content and saturation in hepatic venous blood.

References

- 1 Levy J. Anaphylactic Reactions in Anesthesia and Intensive Care. Boston, Butterworths, 1986.
- 2 Stoelting RK. Gastric fluid pH in patients receiving cimetidine. *Anesth Analg* 1978; 57: 675-7.
- 3 Scott RPF, Savarese JJ, Ali HH *et al.* Atracurium: clinical strategies for preventing histamine release and attenuating the hemodynamic response. *Anesthesiology* 1984; 61:A287.
- 4 Domenech JS, Garcia RC, Sasiain JMR *et al.* Pancu-

- ronium bromide: an indirect sympathomimetic agent. *Br J Anaesth* 1976; 48: 1143–8.
- 5 Banks RO, Gallavan RH, Zinner MJ. Vasoactive agents in control of the mesenteric circulation. *Fed Proc* 1985; 44: 2743–9.
 - 6 Richardson PDI, Withrington PG. Liver blood flow. II. Effects of drugs and hormones on liver blood flow. *Gastroenterology* 1981; 81: 356–75.
 - 7 Greenway CV, Stark RD. Hepatic vascular bed. *Physiol Rev* 1971; 51: 23–65.
 - 8 Pawlick W, Taue LL, Tepperman BL, Miller TA, Jacobson ED. Histamine H₁ and H₂ receptor vasodilation of canine intestinal circulation. *Am J Physiol* 1977; 233: E219–E224.
 - 9 Harvey CA, Owen DAA, Shaw KD. Evidence for both histamine H₁- and H₂-receptors in the gastric vasculature of the cat. *Br J Pharmacol* 1980; 69: 21–7.
 - 10 Charbon GA, Brouwers HAA, Sala A. Histamine H₁- and H₂-receptors in the gastrointestinal circulation. *Naunyn Schmiedebergs Arch Pharmacol* 1980; 312: 123–9.
 - 11 Pawlik W, Shepherd AP, Jacobson ED. Effect of vasoactive agents on intestinal oxygen consumption and blood flow in dogs. *J Clin Invest* 1975; 56: 484–90.
 - 12 Krarup N. Effects of histamine, vasopressin, and angiotensin II on hepatosplanchnic haemodynamics, liver function, and hepatic metabolism in cats. *Acta Physiol Scand* 1975; 75: 311–7.
 - 13 Richardson PDI, Withrington PG. A comparison of the effects of bradykinin, 5-hydroxytryptamine and histamine on the hepatic arterial and portal venous vascular beds of the dog: histamine H₁ and H₂-receptor populations. *Br J Pharmacol* 1977; 60: 123–33.
 - 14 Richardson PDI, Withrington PG. Responses of the simultaneously perfused hepatic arterial and portal venous vascular beds of the dog to histamine and 5-hydroxytryptamine. *Br J Pharmacol* 1978; 64: 581–8.
 - 15 Bauer W, Dale HH, Poulsson LT, Richards DW. The control of circulation through the liver. *J Physiol* 1932; 74: 343–75.
 - 16 Andrews WHH, Hecker R, Maegraith BG, Ritchie HD. The action of adrenalin, 1-noradrenalin, acetylcholine, and other substances on the blood vessels of the perfused canine liver. *J Physiol* 1955; 128: 413–34.
 - 17 Greenway CV, Oshiro G. Effects of histamine on hepatic volume (outflow block) in anaesthetized dogs. *Br J Pharmacol* 1973; 47: 282–90.
 - 18 Schwartz SI. Influence of vasoactive drugs on portal circulation. *Ann NY Acad Sci* 1970; 170: 296–314.
 - 19 Feely J, Wood AJJ. Reduction of liver blood flow and propranolol metabolism by cimetidine. *N Engl J Med* 1981; 304: 692–5.
 - 20 Feely J, Wood AJJ. Effect on apparent liver blood flow of histamine-receptor blockers and inhibition of prostaglandin synthesis. *Clin Pharmacol Ther* 1983; 33: 91–4.
 - 21 Jackson JE. Reduction of liver blood flow by cimetidine. *N Engl J Med* 1981; 305: 99–100.
 - 22 Lebrech D, Goldfard G, Benhamou JP. Reduction of liver blood flow by cimetidine. *N Engl J Med* 1981; 305: 100.
 - 23 Campra JL, Reynolds TB. The hepatic circulation. In: Arias IM, Jakoby WB *et al.* (Eds.). *The Liver: Biology and Pathobiology*, New York: Raven Press, 1981; 911–30.
 - 24 Ohnishi K, Saito M, Nomura F *et al.* Effect of famotidine on hepatic haemodynamics and peptic ulcer. *Am J Gastroenterol* 1987; 82: 415–8.
 - 25 Tverskoy M, Gelman S, Fowler KC, Bradley EL. Influence of fentanyl and morphine on intestinal circulation. *Anesth Analg* 1985; 64: 577–84.
 - 26 Kock NG, Darle N, Dotevall G. Inhibition of intestinal motility in man by glucagon given intraportally. *Gastroenterology* 1967; 53: 88–92.
 - 27 Yee NS, Shargel L. Effect of cimetidine or ranitidine pretreatment on hepatic mixed function oxidase activity in the rat. *Drug Metab Dispos* 1986; 14: 580–4.
 - 28 Altura BM, Halevy S. Beneficial and detrimental actions of histamine H₁ and H₂ receptor antagonists in circulatory shock. *Proc Natl Acad Sci USA* 1978; 75: 2941–4.
 - 29 Goetsch DD, Wilson RC, Huber TL. Effects of promethazine on hemorrhagic shock in the dog. *Am J Vet Res* 1982; 43: 2193–5.
 - 30 Zeng JZ, Bircher J. Lack of inhibition of clomethiazole metabolism by cimetidine: model experiments in the dog. *Eur J Clin Invest* 1983; 13: 475–9.
 - 31 Lautt WW. Afferent and efferent neural roles in liver function. *Prog Neurobiol* 1983; 21: 323–48.
 - 32 Gelman S. Disturbances in hepatic blood flow during anaesthesia and surgery. *Arch Surg* 1976; 111: 881–3.
 - 33 Gelman S. General anaesthesia and hepatic circulation. *Can J Physiol Pharmacol* 1987; 65: 1762–79.
 - 34 Henderson JM, Ibrahim SZ, Millikan WJ Jr, Santi M, Warren WD. Cimetidine does not reduce liver blood flow in cirrhosis. *Hepatology* 1983; 3: 919–22.
 - 35 Ohnishi K, Nakayama T, Saito M *et al.* Effects of cimetidine and ranitidine on splanchnic haemodynamics in patients with chronic liver disease. *Am J Gastroenterol* 1985; 80: 290–3.
 - 36 Dunk AA, Jenkins WJ, Burroughs AK *et al.* The effect of ranitidine on the plasma clearance and hepatic extraction of indocyanine green in patients with

- chronic liver disease. *Br J Clin Pharmacol* 1983; 16: 117-20.
- 37 *Serlin MJ, Sibeon RG, Mossman S et al.* Cimetidine: interaction with oral anticoagulants in man. *Lancet* 1979; 2: 317-9.
- 38 *Klotz U, Reimann I.* Delayed clearance of diazepam due to cimetidine. *N Engl J Med* 1980; 302: 1012-4.
- 39 *Desmond PV, Patwardhan RV, Schenker S, Speeg KV Jr.* Cimetidine impairs the elimination of chlordiazepoxide (Librium) in man. *Ann Intern Med* 1980; 93: 266-8.
- 40 *Rendic S, Sunjic V, Toso R, Kajfez F, Ruff HH.* Interaction of cimetidine with liver microsomes. *Zenobiotica* 1979; 9: 555-64.