Effect of propranolol on hepatic blood flow in normal and portal hypertensive rats

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Summary

1. The effects of propranolol on heart rate, arterial pressure, portal venous pressure and fractional hepatic blood flow were studied in rats with hepatic artery ligature or with portal vein stenosis, and in sham-operated rats. The effect of propranolol on cardiac output was also studied in normal rats.

2. In rats with hepatic artery ligature or with portal vein stenosis, and in sham-operated rats, propranolol decreased heart rate and portal venous pressure significantly and did not alter arterial pressure. Propranolol decreased fractional hepatic blood flow significantly in rats with hepatic artery ligature, but did not change hepatic blood flow in rats with portal vein stenosis or in sham-operated rats.

3. We conclude therefore that: (a) propranolol decreases portal venous pressure in rats; (b) this decrease in portal venous pressure results in a reduction in portal blood flow which is related, in part, to a reduction in cardiac output; (c) propranolol does not alter hepatic blood flow in normal rats or in rats with portal hypertension.

Key words: blood flow, liver, portal hypertension, propranolol.

Introduction

Propranolol induces a decrease in portal venous pressure in patients with cirrhosis and might therefore be useful in the prevention of recurrent gastrointestinal bleeding due to portal hypertension [1, 2]. This effect is likely to result from a decrease in portal venous blood flow, due, in part, to a decrease in cardiac output; however, propranolol might also decrease hepatic blood flow and alter hepatic function in these patients. The purpose of this study was to estimate the effect of propranolol on hepatic blood flow in normal rats and rats with portal hypertension.

Methods

Animals

Eighty-four adult male rats (Charles River, Saint-Aubin-lès-Elbeuf, France) weighing 220–320 g were divided into four groups (one group of 12 normal rats and three groups of 24 rats each): one of each three groups was composed of rats with hepatic artery ligature, one of rats with portal vein stenosis and one of sham-operated rats. Each of these three groups was divided into two subgroups: one subgroup received propranolol intravenously (10 mg/kg body wt.) and the other received sodium chloride solution (154 mmol/l: saline).

Cardiac output and heart rate were measured in 12 normal rats of the first group. In the three other groups, heart rate and arterial pressure were measured in all 24 rats. In order to ensure that there was a normal haemodynamic state, portal venous pressure was measured in six rats from each subgroup and fractional hepatic blood flow in the other six rats. All haemodynamic measurements were performed under pentobarbital anaesthesia (5 mg/100 g body wt. intraperitoneally), before and 15 min after injection of propranolol or saline. Rectal temperature was maintained at 38°C. The anaesthetized rats were fixed in a supine position. After tracheal intubation, two catheters were inserted, one into the
left common carotid artery, and one into the right jugular vein. Heparin (50 i.u.) was injected into the jugular vein catheter.

**Hepatic artery ligature**

Under ether anaesthesia, the proper hepatic artery was exposed after median laparotomy. The proper hepatic artery was separated from the portal vein and was doubly ligated and divided above the origin of the gastroduodenal artery. The abdominal incision was then sutured. Sham-operated rats underwent laparotomy and mesentery exposition. Hepatic artery ligature and sham-operation were performed 1 day before haemodynamic measurements.

**Portal vein stenosis**

Rats underwent partial portal vein ligation to induce portal hypertension and portacaval anastomoses [3, 4]. Stenosis of the portal vein was performed by the method previously reported [3]. Under ether anaesthesia, the portal vein was exposed after median laparotomy. A polyethylene catheter of 0.96 mm outside diameter (Biotrol Pharma, Paris, France) was placed alongside the length of the portal vein. A ligature placed proximal to the bifurcation of the splenic vein was tied around both the catheter and the portal vein; the catheter was then removed and the abdominal incision sutured. Portal vein stenosis was performed 20 days before the haemodynamic measurements.

**Arterial pressure, heart rate and cardiac output measurements**

Arterial pressure was measured with the catheter inserted into the carotid artery, which was connected to a square-wave electromagnetic manometer. Heart rate was measured on the arterial pressure tracing.

To calculate cardiac output, the indicator dilution technique was used. After a rapid injection of approximately 1 µCi of $^{125}$I-labelled albumin into the jugular vein, arterial blood samples (approximately 50 µl) were manually collected each second with the ticking of a metronome, up to 8 s, in pre-weighted tubes. The tubes were weighed and the radioactivity was counted in a well-type scintillation counter (Nuclear–Chicago, IL, U.S.A.); the results were expressed in c.p.m./ml. The injected radioactivity of $^{125}$I, expressed in c.p.m., was calculated from the difference between the syringe radioactivity before the injection, and the residual radioactivity in the syringe and in the catheter which was inserted into the jugular vein. From the quantity of radioactivity injected, and the radioactivity in the various samples, together with the time occupied by the first circulation, the cardiac output per minute was determined from the Stewart–Hamilton formula [5]. Saline was re-infused after each measurement in order to maintain constant blood volume.

**Portal vein pressure measurement**

After a short abdominal midline incision was made, the mesentery of the ileum was exposed. A polyethylene catheter of 0.7 mm outside diameter (William Cook Europe, ApS, Søborg, Denmark), flushed with saline, was inserted into the junction of two small ileal veins and gently advanced into the portal vein. The correct position of the catheter was visually checked through the portal vein wall. The catheter was fixed to the ileal vein with a silk ligature and the abdominal incision was sutured. Portal venous pressure was measured with the catheter and recorded on a square-wave electromagnetic manometer. To ensure that correct portal venous pressure was obtained, the following criteria were established: (a) the pressure tracing had to show a rapid rise followed by a stable plateau with slight respiratory variations; (b) blood could be easily aspirated.

**Hepatic blood flow measurement**

For assessing hepatic blood flow, fractional hepatic blood flow (percentage of the whole blood volume passing through the liver per minute) was measured as previously described with colloidal radiogold ($^{198}$Au) [6]. A radiopaque catheter of 0.70 mm outside diameter (William Cook Europe), flushed with saline, was inserted into the right jugular vein and gently advanced by fluoroscopic control through the right auricle into the posterior vena cava. The posterior half of the body was bent to the left to form a 45° angle with the axis of the anterior half of the body. The catheter was then pulled into the supra-hepatic segment of the posterior vena cava and advanced into a right hepatic vein. Fractional hepatic blood flow was estimated with colloidal $^{198}$Au (Commissariat à l’Energie Atomique, Saclay, France) (20 µCi) injected into the left jugular vein. Arterial and hepatic venous blood samples, 0.10 ml each, were collected every minute for 5 min after the injection. The same volume of saline was re-infused in order to maintain constant blood
volume. Radioactivity, expressed in c.p.m./g of blood, was counted by gamma scintillation (Nuclear-Chicago). Fractional hepatic blood flow is equal to \( K/E \), where \( K \) is the fractional clearance calculated by the least squares method and \( E \) is the colloidal radiogold extraction calculated according to the formula: (\( C_a - C_h \))/\( C_a \), with \( C_a \) being the arterial concentration of colloidal \(^{198}\text{Au} \), and \( C_h \) its hepatic venous concentration.

**Statistical analysis**

The values are expressed as means ± sd. The Student's \( t \)-test for paired data was used for statistical comparisons.

**Results**

In the first group of normal rats, cardiac output decreased significantly after propranolol injection from 78.9 ± 10.1 to 52.7 ± 10.9 ml/min (\( P < 0.01 \)); heart rate decreased from 415 ± 21 to 305 ± 21/min (\( P < 0.001 \)). After saline injection, cardiac output and heart rate did not change significantly: 79.0 ± 12.8 to 78.3 ± 13.3 ml/min, and 425 ± 32 to 415 ± 32/min respectively.

The results of heart rate, arterial pressure, portal venous pressure, and fractional hepatic blood flow are set out in Table 1. After propranolol injection, heart rate, portal venous pressure and fractional hepatic blood flow decreased significantly in rats with hepatic artery ligature (\( P < 0.001 \), \( P < 0.001 \), \( P < 0.01 \) respectively). In rats with portal vein stenosis and in sham-operated rats, heart rate and portal venous pressure decreased significantly after propranolol injection (\( P < 0.001 \)), but fractional hepatic blood flow did not change significantly (\( P > 0.2 \)). In rats with hepatic artery ligature, in rats with portal vein stenosis, and in sham-operated rats, arterial pressure did not change significantly after propranolol injection (\( P > 0.1 \)). No significant variation was observed after saline injection (Table 2).

**Discussion**

This study shows that propranolol decreased portal venous pressure in normal and portal hypertensive rats as well as in rats with hepatic artery ligature. This decrease in portal venous pressure seems to be due to a reduction in portal blood flow. This was demonstrated by the

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**Table 1. Effect of propranolol injection (10 mg/kg body wt.) on haemodynamic measurements in rats**

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (min(^{-1})) (n = 12)</th>
<th>Arterial pressure (mmHg) (n = 12)</th>
<th>Portal venous pressure (mmHg) (n = 6)</th>
<th>Fractional hepatic blood flow (min(^{-1})) (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before   After</td>
<td>Before    After</td>
<td>Before     After</td>
<td>Before     After</td>
</tr>
<tr>
<td>Rats with hepatic artery ligature</td>
<td>452 ± 38  312 ± 43*</td>
<td>109 ± 11   102 ± 16†</td>
<td>6-6 ± 0-5   4-7 ± 0-2*</td>
<td>0-972 ± 0-136  0-585 ± 0-124‡</td>
</tr>
<tr>
<td>Rats with portal vein stenosis</td>
<td>440 ± 41  312 ± 41*</td>
<td>107 ± 14   99 ± 10†</td>
<td>13-8 ± 2-0  9-9 ± 2-5*</td>
<td>0-619 ± 0-072  0-687 ± 0-103†</td>
</tr>
<tr>
<td>Sham-operated rats</td>
<td>445 ± 27  316 ± 28*</td>
<td>110 ± 8    103 ± 11†</td>
<td>7-2 ± 0-7   5-7 ± 0-8*</td>
<td>1-046 ± 0-152  1-109 ± 0-152†</td>
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* Significantly different from the basal value (\( P < 0.001 \)).
† Not significantly different from the basal value.
‡ Significantly different from the basal value (\( P < 0.01 \)).

**Table 2. Effect of saline injection (0.5 ml) on haemodynamic measurements in rats**

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (min(^{-1})) (n = 12)</th>
<th>Arterial pressure (mmHg) (n = 12)</th>
<th>Portal venous pressure (mmHg) (n = 6)</th>
<th>Fractional hepatic blood flow (min(^{-1})) (n = 6)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before   After</td>
<td>Before    After</td>
<td>Before     After</td>
<td>Before     After</td>
</tr>
<tr>
<td>Rats with hepatic artery ligature</td>
<td>442 ± 30  425 ± 27</td>
<td>113 ± 8    112 ± 9</td>
<td>6-8 ± 1-1   6-8 ± 1-0</td>
<td>1-016 ± 0-120  0-590 ± 0-116</td>
</tr>
<tr>
<td>Rats with portal vein stenosis</td>
<td>428 ± 29  425 ± 31</td>
<td>103 ± 12   101 ± 13</td>
<td>12-8 ± 2-6  13-0 ± 2-7</td>
<td>0-619 ± 0-086  0-640 ± 0-083</td>
</tr>
<tr>
<td>Sham-operated rats</td>
<td>442 ± 43  440 ± 45</td>
<td>106 ± 8    105 ± 7</td>
<td>7-2 ± 1-1   7-0 ± 1-0</td>
<td>1-004 ± 0-123  0-932 ± 0-165</td>
</tr>
</tbody>
</table>
reduction in hepatic blood flow in rats with hepatic artery ligature, since, in these rats, hepatic blood flow is equivalent to portal blood flow. The reduction in portal blood flow induced by propranolol might result from (a) a reduction in cardiac output (this decrease was observed in the normal rats and accordingly in the other groups of rats, since heart rate decreases after propranolol injection), and/or (b) a vasoconstriction in the splanchnic area and an ensuing increase in splanchnic vascular resistance [7]. In normal and in portal hypertensive rats, the reduction in portal blood flow measured with the colloidal radiogold clearance method, despite the decrease in portal venous pressure. In these rats, hepatic blood flow is the sum of portal blood flow and hepatic artery blood flow. The absence of effect of propranolol on hepatic blood flow in spite of a decrease in cardiac output was previously demonstrated in 20 weeks old hypertensive rats by the microsphere technique [8]. This absence of change in hepatic blood flow after propranolol injection might result in a reactional increase in hepatic artery blood flow to compensate the reduction in portal blood flow. The interaction between hepatic artery and portal vein blood flows suggested by our results in normal and portal hypertensive rats has already been observed in dogs [9] and in man [10, 11] after portacaval shunt or acute portal vein derivation. However, the mechanism for this arterio-portal interaction is still unclear.

The mild reduction in hepatic blood flow observed in patients with cirrhosis during oral administration of propranolol [2] and the results of this experimental study suggest that propranolol should not alter hepatic functions through a major reduction in hepatic blood flow.

Acknowledgment
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References