EFFECT OF DROPERIDOL ON DOPAMINE-INDUCED INCREASE IN EFFECTIVE RENAL PLASMA FLOW IN DOGS

E. G. BRADSHAW, B. J. PLEUVRY AND H. L. SHARMA

SUMMARY

The interaction between small doses of dopamine and droperidol on effective renal plasma flow was studied in dogs. Small doses of dopamine are known to produce renal vasodilatation by a dopaminergic mechanism and droperidol, a selective dopamine antagonist used in neuroleptanaesthesia, may attenuate this response. Effective renal plasma flow was measured non-invasively using $^{125}$I-hippuran. A 20-min infusion of dopamine $2 \mu g \ kg^{-1} \ min^{-1}$ significantly enhanced effective renal plasma flow (mean increase of 16%; $P<0.05$) in anaesthetized dogs. This effect was abolished (mean decrease 6.6%) by droperidol $0.2 \ mg \ kg^{-1}$ administered at the commencement of anaesthesia. It is concluded that droperidol reduces the renal vasodilatation induced by dopamine in anaesthetized dogs.

The haemodynamic effects of dopamine are crucially dependent on dose (Goldberg, 1972). In low doses it has a unique action, increasing renal blood flow via an action on specific dopamine receptors (Yeh, McNay and Goldberg, 1969). Dopamine is used increasingly for the prophylaxis and treatment of cardiogenic shock following open-heart surgery (Holtzer et al., 1973; Daenen, de Leval and Stark, 1977; Hess et al., 1979).

The butyrophenone, droperidol, is frequently used in anaesthesia, including that for open-heart surgery (Whitwam and Russell, 1971) and drugs in this class are known to be selective dopamine antagonists (Anden et al., 1970). This study was undertaken to determine whether the response of the renal vasculature to a small dose of dopamine could be affected by a clinically acceptable dose of droperidol administered some hours before the dopamine.

A variety of factors affect renal blood flow other than those which were the subject of the study (Papper and Papper, 1964). In order to minimize these effects, it was considered necessary to use each subject as its own control. As this involved four separate experiments, dogs rather than humans were used in the investigation.

METHODS

Six beagle dogs (8–16 kg) were studied. Anaesthesia was induced with pentobarbitone sodium $30 \ mg \ kg^{-1}$ i.v., the trachea was intubated and the lungs ventilated artificially to normocarbia. Anaesthesia was maintained with 60% nitrous oxide in oxygen and incremental doses of fentanyl $25 \ \mu g$ i.v. as needed.

The bladder was catheterized and the dog placed prone on a warming blanket. Rectal temperature and e.c.g. were monitored throughout the experiment and arterial pressure was measured regularly using a sphygmomanometer. An isotonic solution (Compound Sodium Lactate Injection B.P.) was infused via a cannula placed in a hind limb vein and the rate adjusted to deliver $100 \ ml \ h^{-1}$. Samples for blood-gas analysis and gamma counting were removed via a cannula inserted in a forelimb vein. Before measurement of effective renal plasma flow (ERPF), the bladder was completely emptied and the catheter occluded.

A gamma camera was positioned over the kidneys and $100 \ \mu g$ of $^{125}$I-labelled hippuran was injected via the infusion cannula. Radioactivity over the kidneys was monitored continuously and renograms plotted by a computer (Nuclear Data). These plots were used as a qualitative assessment of renal perfusion and no dog was included in the study if its renal perfusion was inadequate. A quantitative estimate of renal blood flow was started concurrently and continued if the renogram was normal. Five-millilitre blood samples were collected at 1, 5, 10, 20, 30, 45, 60, 75 and 90 min after injection of $^{125}$I-hippuran. All the urine was collected at the end of the 90-min period and the volume measured. The bladder was washed repeatedly with isotonic solution until no radioactivity remained. Urine and washings were added together and made up to a standard volume. Effective renal plasma flow was calculated using the single injection method with...
urine collection. The advantages of this method for estimating ERPF have been reviewed by O'Reilly, Shields and Testa (1979). In each experiment two consecutive measurements of ERPF were obtained.

Each dog was assigned to one of the following plans of study on a random basis so arranged that each received the four treatments on four consecutive occasions:

(1) Twenty minutes infusion of dopamine 2 \( \mu \text{g kg}^{-1} \text{min}^{-1} \) beginning 5 min before a second renogram and measurement of ERPF.
(2) Control infusion of isotonic solution in equivalent volumes.
(3) Droperidol 0.2 mg kg\(^{-1}\) injected i.v. just after induction of anaesthesia followed by a 20-min infusion of dopamine as in (1).
(4) Droperidol injected as above with a control infusion as in (2).

The effects of dopamine or control infusion on ERPF were expressed as percentage change from the first ERPF measured during the same experiment. Significance of differences between treatments was calculated using a nested analysis of variance, otherwise a paired \( t \) test was used. Results are expressed as means ± SD.

Each dog was allowed 2–4 weeks for recovery between experiments.

The total dose of fentanyl administered did not differ significantly in the four treatments (table I).

**RESULTS**

Only one dog was rejected because of inadequate renal perfusion. This was demonstrated by widening of the renogram curve and slow build up of radioactivity in the bladder (fig. 1).

The addition of droperidol to the anaesthetic regimen did not significantly alter ERPF measured in this study (table I). Dopamine 2 \( \mu \text{g kg}^{-1} \text{min}^{-1} \) produced significantly greater ERPF than the control infusion, but this was abolished when droperidol was present (table II). (The nested analysis of variance showed that the ERPF was significantly altered by the nature of the infusion rather than by the anaesthetic used.)

Heart rate, arterial pressure and rectal temperature were not significantly different in the groups of dogs receiving anaesthesia with or without droperidol (table I). We confirmed in this study that the dose of dopamine used had no effect on the heart rate and arterial pressure. The maximum change in systolic arterial pressure which occurred during the dopamine infusion was \(-1.13 ± 2.08\) kPa and the maximum heart rate change was \(-6.8 ± 5.1\) beat \( \text{min}^{-1} \). These changes were not significantly different from those measured during the control infusion.

The change in urine volume from the first and second estimation suggests that droperidol did not inhibit the effects of dopamine in this respect (table II). However, the urine output was extremely variable, sometimes only small quantities being collected over a 90-min period. All the dogs which received a standard anaesthetic and dopamine showed an increase in urine volume (range +1.0 to +192.5 ml). Two dogs in the droperidol-treated group showed a decrease in urine output (range for all six dogs -30 to 118 ml).

**DISCUSSION**

We have confirmed that a 20-min infusion of dopamine 2 \( \mu \text{g kg}^{-1} \text{min}^{-1} \) improves ERPF in the dog. Furthermore, we have demonstrated that droperidol 0.2 mg kg\(^{-1}\) abolishes this effect. There was no evidence that droperidol alone had any effect on ERPF at this dose.

Whilst it was not possible to demonstrate that droperidol significantly reduced the increase in urine volume produced by dopamine, the addition of droperidol to the anaesthetic made the response to dopamine less predictable.

### Table 1. Initial values (mean ± SD). *Group I v. group II paired t test. n.s. = not significant*

<table>
<thead>
<tr>
<th></th>
<th>Group I (control)</th>
<th>Group II (droperidol 0.2 mg kg(^{-1}))</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective renal plasma flow (ml min(^{-1}))</td>
<td>65.3 ± 25.5</td>
<td>63.7 ± 30.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systolic arterial pressure (kPa)</td>
<td>13.5 ± 2.5</td>
<td>12.5 ± 2.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Heart rate (beat min(^{-1}))</td>
<td>94.2 ± 16.6</td>
<td>102.3 ± 11.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rectal temperature (°C)</td>
<td>36.5 ± 1.0</td>
<td>36.8 ± 0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total dose of fentanyl (( \mu \text{g} ))</td>
<td>102.1 ± 44.5</td>
<td>103.8 ± 37.6</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
DROPERIDOL AND DOPAMINE ON RENAL PLASMA FLOW

Fig. 1. Renograms obtained from anaesthetized dogs injected with $^{131}$I-hippuran 100 μCi. The left-hand curves were obtained from a normal dog and the right-hand curves were obtained from a dog rejected because of inadequate renal function.

Table II. Change* in effective renal plasma flow (ERPF) and urine production induced by a 20-min infusion of dopamine 2 μg kg$^{-1}$ min$^{-1}$ or a control infusion of isotonic solution in anaesthetized dogs with and without droperidol 0.2 mg kg$^{-1}$. n.s. = Not significant; d.f. = degrees of freedom. *Change was calculated from the immediately preceding measurement of ERPF or urine production where no infusions were administered (table I). †Significantly different from control infusions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>ERPF (mean % change)</th>
<th>Urine volume (ml) (mean change over 90 min)</th>
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</thead>
<tbody>
<tr>
<td>Standard anaesthetic</td>
<td></td>
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</tr>
<tr>
<td>Dopamine infusion</td>
<td>+15.98†</td>
<td>+44.9†</td>
</tr>
<tr>
<td>Control infusion</td>
<td>−12.60</td>
<td>+10.5</td>
</tr>
<tr>
<td>Droperidol anaesthetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine infusion</td>
<td>−6.64</td>
<td>+30.9†</td>
</tr>
<tr>
<td>Control infusion</td>
<td>−13.8</td>
<td>+0.03</td>
</tr>
<tr>
<td>Nested analysis of variance:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contribution to change in values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>from anaesthetics</td>
<td>$F = 0.065$ (n.s.)</td>
<td>$F = 0.419$ (n.s.) (1, 2 d.f.)</td>
</tr>
<tr>
<td>from infusions</td>
<td>$F = 4.63$ ($P &lt; 0.05$)</td>
<td>$F = 3.64$ ($P &lt; 0.05$) (2, 20 d.f.)</td>
</tr>
</tbody>
</table>

In man, Birch and Boyce (1977) found that droperidol did not attenuate the effect of an infusion of dopamine 20 μg kg$^{-1}$ min$^{-1}$. However, as pointed out by Zimmerman (1978), this dose of dopamine was too great to produce renal vasodilatation by a specific dopaminergic mechanism. A more selective dose of dopamine was used in man and dogs by Goto, Fujita and Fuse (1979). These authors found that droperidol
apparently increased the effects of dopamine on urine flow and the excretion of sodium and inorganic phosphate. The findings in the present study suggest that droperidol may attenuate the effect of dopamine on urine volume. There was no suggestion that droperidol increased urine volume. These differences may be explained by the timing of the droperidol administration. Goto, Fujita and Fuse (1979) administered droperidol at the time of the dopamine infusion in dogs. In the present study, in order to simulate clinical practice, droperidol was administered at induction of anaesthesia, a minimum of 2 h before the administration of dopamine.

The accepted clinical dose of droperidol is 0.07–0.3 mg kg\(^{-1}\) (Morgan, Lumley and Gillies, 1974). Thus, the dose of droperidol used in this study which attenuated the effects of dopamine was well within the clinical range.

Our investigation in dogs indicates that the use of small-dose dopamine infusions to increase renal blood flow may be ineffective in patients given droperidol some hours previously. A carefully controlled study in man is needed to confirm this.

ACKNOWLEDGMENTS

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REFERENCES


EFFET DU DROPERIDOL SUR UNE AUGMENTATION DU DEBIT EFFECTIF DE PLASMA RENAL PROVOQUEE PAR LA DOPAMINE CHEZ LES CHIENS

RESUME

On a procedé sur des chiens à une étude de l’interaction qui se produit entre petites doses de dopamine et de droperidol sur le débit effectif de plasma rénal. Les petites doses de dopamine produisent, on le sait, une vasodilatation rénale par un mécanisme dopaminergique et le droperidol, qui est un antagoniste sélectif de la dopamine, que l’on utilise dans le domaine de la neuroleptanesthésie, peut atténuer cette réaction. On a mesuré d’une manière non envahissante le débit effectif de plasma rénal en utilisant \( ^{125}\text{I}-\text{hippuran} \). Une infusion de dopamine d’une durée de 20 min à raison de \( 2 \mu \text{g kg}^{-1} \text{min}^{-1} \) a stimulé le débit effectif de plasma rénal (augmentation moyenne de 16%) \( (P<0.05) \) sur des chiens anesthésiés. Cet effet a été aboli (baisse moyenne de 6,6%) à l’aide de droperidol administré à raison de 0,2 mg kg\(^{-1}\) au commencement de l’anesthésie. On en a conclu que le droperidol diminue la vasodilatation rénale provoquée par la dopamine sur des chiens anesthésiés.

WIRKUNG VON DROPERIDOL AUF DURCH DOPAMIN BEWIRKTE, ERHÖHTEN NIERENPLASMADURCHFLUSS BEI HUNDEN

ZUSAMMENFASSUNG

Die Wechselwirkung zwischen kleinen Dosen von Droperidol und Dopamin auf den effektiven Nierenplasmadurchfluss wurde in Hunden untersucht. Kleine Dopaminosen bewirken bekanntlich Nierengefäßweiterung durch einen dopaminergischen Mechanismus, und Droperidol, ein selektives Dopamin-Gegenmittel, das bei neuroleptischer Narkose verwendet wird, kann diese Reaktion verstärken. Der effektive Nierenplasmadurchfluss wurde nicht-invasiv mittels \( ^{125}\text{I}-\text{Hippurin} \) gemessen. Eine 20 Minuten dauernde Infusion von \( 2 \mu \text{g kg}^{-1} \text{min}^{-1} \) Dopamin verbesserte den Nierendurchfluss wesentlich (mittlerer Anstieg 16%) \( (P<0.05) \), bei narkotisierten Hunden. Beendet wurde diese Wirkung (mittlerer Abstieg 6,6%) durch Droperidol 0,2 mg kg\(^{-1}\), verabreicht zu Narkosebeginn. Es wird gefolgtet, dass Droperidol bei Hunden die durch Dopamin eingeleitete Nierengefäßweiterung reduziert.
EL EFECTO DEL DROPERIDOL EN LA DOPAMINA INDUJO UN INCREMENTO DEL FLUJO EFECTIVO DEL PLASMA RENAL EN PERROS

SUMARIO
Se estudió la interacción entre pequeñas dosis de Dopamina y de Droperidol sobre el flujo efectivo del plasma renal. Se sabe que pequeñas dosis de dopamina producen dilatación de los vasos renales mediante un mecanismo dopaminérgico, y el droperidol que es una dopamina antagonica de tipo selectivo usada en neuroleptanestesia, puede atenuar esta respuesta. El flujo efectivo de plasma renal se midió de forma no invasora, usando ¹²⁵I-hipurán. Una infusión de 2 μg kg⁻¹ min⁻¹ de dopamina durante 20 minutos incrementó el flujo efectivo de plasma renal (incremento medio del 16%) (P<0,05), en perros anestesiados. Este efecto se anuló (disminución media del 6,6%), mediante el uso de 0,2 mg kg⁻¹ de droperidol, administrado al principio de la anestesia. La conclusión es que el droperidol reduce la dilatación de los vasos renales, que indujo la dopamina en los perros anestesiados.