ATTENUATION OF THE DIURETIC EFFECT OF DOPAMINE BY DROPERIDOL IN MAN AND DOGS

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SUMMARY

The effects of dopamine 0.5–6.0 μg kg⁻¹ min⁻¹ on urine flow and the excretion of sodium and inorganic phosphate were studied in patients and dogs. In both the patients and the animals the diuretic effect of dopamine was augmented by the i.v. administration of droperidol 0.25 mg kg⁻¹. Similarly, the excretion of sodium and inorganic phosphate was increased by droperidol.

Dopamine has, in addition to its alpha- and beta-adrenergic effects, a unique action in that it has been shown to increase renal and mesenteric blood flow (Goldberg, 1972). Indeed, it has been suggested that dopamine acts on a specific receptor in the renal vascular beds (Yeh, McNay and Goldberg, 1969). However, the renal vasodilatation produced by dopamine may be attenuated by haloperidol (Van Rossum, 1966; Yeh, McNay and Goldberg, 1969) whereas that induced by bradykinin and isoprenaline is unaffected.

We have examined the effect of dehydrobenzperidol (droperidol), a derivative of haloperidol, on the activity of dopamine and, in particular, on its effects on the excretion of sodium and inorganic phosphate. Cuche and colleagues (1976) have reported that, in dogs, dopamine caused an increase, not only in the rate of sodium excretion, but also in that of phosphate, and they have shown that this was unrelated to parathyroid hormone activity.

METHODS

Clinical study

Thirty adult patients (ASA class 1 or 2) without evidence of renal impairment were selected. They were undergoing elective surgery (thyroidectomy or mastectomy) and the expected duration of surgery was between 2 and 4 h. All patients were informed of the nature of the experiment in detail and written consent was obtained before the initiation of the study. Atropine 0.5 mg and hydroxyzine hydrochloride 100 mg were administered 1 h before the induction of anaesthesia.

Following the administration of oxygen for 1–2 min, anaesthesia was induced with thiopentone 5 mg per kg of body weight. Endotracheal intubation was performed after the administration of suxamethonium 1 mg kg⁻¹. Halothane 0.5–1.5% in 66% nitrous oxide in oxygen (group 1) and droperidol 0.25 mg kg⁻¹, fentanyl 10–20 μg kg⁻¹ and 66% nitrous oxide in oxygen (group 2) were administered randomly. In this latter group, droperidol 0.25 mg kg⁻¹ was given before the induction of anaesthesia. Following the induction of anaesthesia the bladder was catheterized with an indwelling balloon catheter and the long saphenous vein was cannulated. In this way urine could be collected readily and its volume measured, and blood could be withdrawn for the determination of the concentrations of the serum electrolytes and of haemoglobin.

In a further group (group 3), anaesthesia was maintained as in group 1, and droperidol 0.25 mg kg⁻¹ was administered i.v. during the infusion of dopamine. Lactated Ringer’s solution 500 ml was infused during the 30 min following the induction of anaesthesia. Subsequently, lactated Ringer’s solution 500 ml h⁻¹ was given. The total mean volume of fluid infused during each study was 1650 ml.

Approximately 1 h after the start of surgery, urine was collected for 30 min (control). Following this, dopamine diluted with saline to 200 μg ml⁻¹ was infused at 4–6 μg kg⁻¹ min⁻¹ for 30 min in groups 1 and 2. Fifteen minutes after the beginning of the dopamine infusion, urine was collected and this was repeated every 15 min thereafter with each collection being terminated by a “washout” with air. A blood sample was obtained at the halfway point and concentrations of the serum electrolytes, the osmotic pressure and the creatinine clearance (glomerular filtration rate) (GFR) were obtained. In group 3, after the infusion of small doses of dopamine (0.5–1.0 μg kg⁻¹ min⁻¹) for 30 min, droperidol 0.25 mg kg⁻¹ was
given i.v. and then dopamine was administered for an additional 30 min.
In each patient systolic arterial pressure was measured by sphygmomanometry and care was taken to ensure that there was no alteration in systemic arterial pressure during the infusion of dopamine.

Animal experiments
Twenty-four mongrel dogs of either sex, weighing 6–8 kg, were fasted for 24 h, but allowed free access to water.

The dogs were anaesthetized with pentobarbitone 20 mg kg\(^{-1}\) i.v. and following endotracheal intubation the lungs were ventilated with a Harvard Respirator with a mixture of air, oxygen and halothane 0.7–0.9%. The ventilation and inspired gas concentrations were adjusted to maintain \(P_a CO_2\) at 3.99–5.32 kPa and \(P_a O_2\) at 12.63–17.29 kPa. Oesophageal temperature was maintained at 37 ± 0.5 °C.

Cannulae were inserted into the right femoral vein and into the right femoral artery to permit the infusion of drugs and for blood sampling and arterial pressure recording respectively. A polyethylene cannula was passed into the left ureter via a subcostal incision to enable urine to be collected. The left renal artery was exposed and 0.9% saline 0.25 ml min\(^{-1}\) was infused via a 27-gauge curved needle. When required, dopamine was infused into the left renal artery also. Four hour before the start of the dopamine the thyroid and parathyroid glands were removed to prevent alterations in the secretion of parathyroid hormone (PTH) (Fischer, Blum and Binswanger, 1973), since this controls the excretion of phosphate.

In eight dogs following 15 control clearance periods and without altering the volume of saline infused (0.25 ml min\(^{-1}\)), dopamine 0.5 μg kg\(^{-1}\) min\(^{-1}\) was infused into the left renal artery. After allowing 15 min for equilibration, 15-min dopamine clearance periods were obtained. Thereafter, droperidol 0.25 mg kg\(^{-1}\) was administered i.v., while the infusion of dopamine was continued for a further 30 min.

In one dog (fig. 4), haloperidol 0.2 mg kg\(^{-1}\) was administered during the infusion of dopamine 1.0 μg kg\(^{-1}\) min\(^{-1}\) and then 1 h later dopamine 0.5 μg kg\(^{-1}\) min\(^{-1}\) was infused concurrently with an infusion of haloperidol 0.02 mg kg\(^{-1}\) min\(^{-1}\). A 0.9% saline solution was infused 100 ml h\(^{-1}\) during every experiment.

The concentrations of creatinine (Steinitz and Turkand, 1940) and phosphate (Fiske and SubbaRow, 1925) in urine and plasma were determined colourimetrically.

Results

Clinical study
The changes in systolic arterial pressure, heart rate and renal function associated with the i.v. infusion of dopamine are presented in table I. In groups 1 and 2, urine flow, osmotic clearance and the excretion of sodium and potassium increased markedly with increases in GFR. The increase in urine volume and sodium excretion was more marked in group 1 than in group 2, but the difference between the two groups was not statistically significant.

In group 3 (table I and fig. 1) in which small doses of dopamine were administered, GFR remained unchanged, but urine flow, osmotic clearance and the excretion of sodium and potassium all increased. This increase was augmented to reach values similar to those obtained in group 1 when droperidol had been administered concurrently with the infusion of dopamine. In addition, in group 3, there were significant increases in the excretion of organic phosphate which were of similar magnitude to the osmotic clearance and the sodium excretion.

Arterial pressure and heart rate were unchanged in all groups. Cardiac arrhythmia was noted in one
### Table I. Effects of dopamine infusion on surgical patients (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Urine flow (ml min⁻¹)</th>
<th>GFR (ml min⁻¹)</th>
<th>Osmotic clearance (ml min⁻¹)</th>
<th>Sodium excretion (µmol min⁻¹)</th>
<th>Potassium excretion (µmol min⁻¹)</th>
<th>Phosphate excretion (µg min⁻¹)</th>
<th>Systolic pressure (mm Hg)</th>
<th>Heart rate (beat min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1: dopamine 4.0–6.0 µg kg⁻¹ min⁻¹ (n = 8)</strong></td>
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<tr>
<td>Control</td>
<td>0.69 ± 0.21</td>
<td>63.8 ± 9.2</td>
<td>1.26 ± 0.24</td>
<td>128.6 ± 48.3</td>
<td>47.1 ± 9.8</td>
<td>—</td>
<td>123 ± 4</td>
<td>84 ± 4</td>
</tr>
<tr>
<td>Dopamine</td>
<td>5.15 ± 1.25</td>
<td>89.2 ± 8.8*</td>
<td>7.13 ± 1.78**</td>
<td>710.5 ± 182.1**</td>
<td>90.4 ± 16.9*</td>
<td>—</td>
<td>111 ± 6</td>
<td>84 ± 2</td>
</tr>
<tr>
<td><strong>Group 2: dopamine 4.0–6.0 µg kg⁻¹ min⁻¹ (n = 8)</strong></td>
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<tr>
<td>Control</td>
<td>0.70 ± 0.14</td>
<td>62.0 ± 8.7</td>
<td>2.04 ± 0.33</td>
<td>135.6 ± 42.0</td>
<td>43.6 ± 7.6</td>
<td>—</td>
<td>123 ± 4</td>
<td>80 ± 2</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2.97 ± 0.81</td>
<td>92.9 ± 13.9*</td>
<td>6.27 ± 1.96*</td>
<td>496.0 ± 149.3*</td>
<td>56.3 ± 6.4</td>
<td>—</td>
<td>122 ± 4</td>
<td>89 ± 7</td>
</tr>
<tr>
<td><strong>Group 3: dopamine 0.5–1.0 µg kg⁻¹ min⁻¹ (n = 8)</strong></td>
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<tr>
<td>Control</td>
<td>0.84 ± 0.19</td>
<td>73.2 ± 9.8</td>
<td>1.00 ± 0.28</td>
<td>145.6 ± 39.0</td>
<td>19.2 ± 3.8</td>
<td>254.0 ± 68.0</td>
<td>121 ± 9</td>
<td>88 ± 5</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2.48 ± 0.35*</td>
<td>76.7 ± 6.4</td>
<td>4.00 ± 1.00*</td>
<td>545.0 ± 108.1*</td>
<td>51.9 ± 12.5*</td>
<td>593.6 ± 96.3*</td>
<td>105 ± 12</td>
<td>75 ± 10</td>
</tr>
<tr>
<td>Dopamine + droperidol</td>
<td>4.66 ± 0.77*</td>
<td>80.1 ± 11.5</td>
<td>7.06 ± 1.81**</td>
<td>789.6 ± 178.4**</td>
<td>80.5 ± 21.6*</td>
<td>830.9 ± 107.2**</td>
<td>109 ± 10</td>
<td>90 ± 7</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.02, ***P < 0.01; compared with control period.

### Table II. Effect of dopamine on phosphate and sodium excretions in thyroparathyroidectomized dogs (n = 8, mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Urine volume (ml min⁻¹)</th>
<th>GFR (ml min⁻¹)</th>
<th>Plasma PO⁴ (µg ml⁻¹)</th>
<th>UPO⁴V (µg min⁻¹)</th>
<th>FEPO⁴ (%)</th>
<th>Plasma Na⁺ (mmol litre⁻¹)</th>
<th>UNaV (mmol min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.12 ± 0.02</td>
<td>10.5 ± 1.2</td>
<td>43.0 ± 5.7</td>
<td>10.9 ± 2.0</td>
<td>2.3 ± 0.5</td>
<td>143.0 ± 1.5</td>
<td>37.6 ± 4.3</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.23 ± 0.03*</td>
<td>10.9 ± 1.2</td>
<td>42.4 ± 2.7</td>
<td>18.5 ± 5.5</td>
<td>6.2 ± 1.5</td>
<td>147.0 ± 1.4</td>
<td>50.6 ± 12.6</td>
</tr>
<tr>
<td>Dopamine + droperidol</td>
<td>0.37 ± 0.05**</td>
<td>11.9 ± 1.0</td>
<td>45.0 ± 2.3</td>
<td>47.5 ± 7.0***</td>
<td>10.4 ± 2.0***</td>
<td>146.0 ± 1.2</td>
<td>64.4 ± 12.3*</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.02, ***P < 0.01; UPO⁴V, UNaV = phosphate and sodium excretion volumes; FEPO⁴ = fractional excretion of phosphate. Control 4 h after thyroparathyroidectomy; dopamine 0.5 µg kg⁻¹ min⁻¹ infusion into the left renal artery; dopamine + droperidol 0.25 mg kg⁻¹ administered i.v. during dopamine infusion.
patient in each of groups 1 and 2, but this disappeared immediately after the discontinuation of the infusion of dopamine.

Animal study

The fractional excretion of inorganic phosphate decreased from 16.0% to 2.3% and the good correlation between plasma $PO_4$ concentration and the fractional excretion ($y = 2.4x + 5.25$, $r = 0.74$, $P < 0.05$) during normal periods was lost following removal of the thyroid and parathyroid glands (fig. 2).

![Graph](https://example.com/fig2.png)

**Fig. 2.** The correlation between plasma inorganic phosphate concentration and fractional excretion ($FEPO_4$) during normal periods was lost after thyroparathyroidectomy (T-PTX), $y = 2.47x + 5.25$; $r = 0.74$; $P < 0.05$.

During the infusion of dopamine alone, the urine volume and the excretion of phosphate increased significantly (table II), but the increases in the excretion of sodium were small and not significant statistically. The i.v. infusion of droperidol 0.25 mg kg$^{-1}$ augmented the increases in urine volume and the excretion of sodium and phosphate (fig. 3).

Dopamine 1.0 $\mu$g kg$^{-1}$ min$^{-1}$ increased not only the output of urine and the excretion of sodium and phosphate, but also GFR (fig. 4). However, haloperidol did not affect the diuresis produced by dopamine. Dopamine 0.5 $\mu$g kg$^{-1}$ min$^{-1}$ also increased the output of urine and the excretion of sodium during the infusion of haloperidol.

**DISCUSSION**

The infusion of dopamine 4.0–6.0 $\mu$g kg$^{-1}$ min$^{-1}$ to patients produced increases in the volume of urine, GFR, osmotic clearance and the excretion of sodium and phosphate. Similar results have been reported by Goldberg (1972).

When compared with the halothane group (group 1), the diuretic effect was less in group 2, but there was no statistically significant difference between the two groups. In group 3, in which the dose of droperidol was less, a significant diuretic effect was observed although GFR remained unchanged. The diuretic effect of dopamine was clearly greater when droperidol was administered during the infusion of dopamine. Similar results were observed in the animal studies. Thus it has been shown that the use of droperidol during surgery does not interfere with the diuretic effect of dopamine.

In the central nervous system (Corrodi, Fuxe and Hökfelt, 1967), haloperidol blocks the dopamine receptor in the nigrostriatal tract, and droperidol (Gotoh and Fujita, 1975) exhibits a similar although much weaker action.

Haloperidol (Yeh, McNay and Goldberg, 1969), like other derivatives of butyrophenones, is known to block the effect of dopamine on renal vasodilatation for short periods. However, the present findings indicated that the increases in GFR and the excretion of sodium and phosphate produced by dopamine were not blocked by clinical doses of haloperidol. Moreover, droperidol did not only not block the diuretic action of dopamine, but increased it. Birch and Boyce (1977) reported that droperidol did not attenuate the response of the renal artery to dopamine in man. The results of the present study indicate that the infusion of dopamine will probably be effective in the presence of butyrophenones in man.

Increases in the excretion of sodium induced by doses of dopamine which are of themselves too small to cause significant changes in systemic and renal haemodynamics have been thought to be a result of changes in intrarenal blood distribution as occurs with
acetylcholine and papaverine (Meyer, McNay and Goldberg, 1967; Carriere, Friborg and Guay, 1971). However, May and Carter (1970) proved that cholinergic agents, like acetylcholine, inhibit sodium reabsorption in the proximal renal tubule even when administered in doses so small as to induce no change in the intrarenal haemodynamics. Using a microperfusion technique, Seely and Dirks (1967) reported that dopamine decreased sodium reabsorption on the proximal convoluted tubule. According to our studies (unpublished observations), dopamine used in combination with phenoxybenzamine produced a marked increase in action and induced excretion of sodium and phosphate even in small doses (0.002–0.05 μg kg⁻¹ min⁻¹, infused into the renal artery) which produced no significant changes in GFR or para-aminohypuric acid excretion in the dog.

Slick and colleagues (1975) and DiBona (1977) reported that the renal sympathetic nerves directly influence renal tubular sodium transport in the absence of alteration in renal haemodynamics. Cuche and others (1976) reported that noradrenaline inhibits the excretion of phosphate. Phosphate is almost completely reabsorbed by proximal renal tubule (Agus et al., 1973; Bank, Aymedijian and Weinstein, 1974). From these findings it is suggested that dopamine acts directly on the proximal renal tubule to inhibit the reabsorption of sodium and phosphate, and the increase in the diuresis produced by dopamine by droperidol is considered to be an effect of the alpha-adrenergic blocking action of the droperidol (Janssen et al., 1963; Muldoon et al., 1977).

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REFERENCES


ATTENUATION DE L'EFFET DIURETIQUE DE LA DOPAMINE PAR LE DROPERIDOL CHEZ L'HOMME COMME CHEZ LE CHIEN

RESUME
Les effets de la dopamine, administrée à raison de 0,5–6,0 µg kg⁻¹ min⁻¹, sur le débit d'urine et l'excrétion de sodium et de phosphates inorganiques ont été étudiés sur des malades et sur des chiens. Chez les malades comme chez les chiens l'effet diurétique de la dopamine a été accru par l'administration intraveineuse de droperidol à raison de 0,25 mg kg⁻¹. D'une manière similaire, on a augmenté, par le droperidol, l'excrétion de sodium et de phosphates inorganiques.

SCHWÄCHUNG DER DIURETISCHEN WIRKUNG VON DOPAMIN DURCH DROPERIDOL IN MENSCH UND HUND

ZUSAMMENFASSUNG
Die Wirkungen von Dopamin 0,5–6,0 mg kg⁻¹ auf den Harnfluss und die Ausscheidung von Sodium und anorganischen Phosphaten wurden in Patienten und Hunden untersucht. In Patienten und Hunden wurde die diuretische Wirkung von Dopamin durch eine intravenöse Verabreichung von Droperidol 0,25 mg kg⁻¹ verstärkt. Ähnlich wurde auch die Ausscheidung von Sodium und anorganischen Phosphaten durch Droperidol verstärkt.

ATENUACION DEL EFECTO DIURETICO DE DOPAMINA MEDIANTE DROPERIDOL EN EL HOMBRE Y EN PERROS

SUMARIO
Se estudiaron los efectos ejercidos por dopamina 0,5–6,0 µg kg⁻¹ sobre la circulación de orina y la excreción de sodio y fosfato inorgánico en pacientes y en perros. Tanto en los pacientes como en los animales el efecto diurético de la dopamina fue aumentado por la administración intravenosa de droperidol 0,25 mg kg⁻¹. De forma semejante, la excreción de sodio y de fosfato inorgánico fue aumentada por droperidol.