Treatment of intra-operative hypertension with enflurane, nicardipine, or human atrial natriuretic peptide: haemodynamic and renal effects

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The purpose of this study was to assess the effects of the calcium entry blocker nicardipine and alpha human atrial natriuretic peptide (hANP) on antihypertensive and diuretic activity in hypertensive surgical patients. The site of the diuretic actions of these drugs along the nephron were also investigated by measuring the excretion rate of inorganic phosphate (PO_4). Hypertension during gastrectomy was treated by increasing the concentration of enflurane, by nicardipine infusion ($0.5-2.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), or by hANP infusion ($0.05-0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) under general anaesthesia. Enflurane, nicardipine and hANP all decreased arterial pressure to the same extent. Urine flow, Na and PO_4 excretion increased following the administration of nicardipine or hANP. Fractional distal reabsorption of sodium was suppressed from $89.7 \pm 2.8\%$ to $82.1 \pm 5.0\%$ by the hANP, but not by the nicardipine infusion. Creatinine clearance was increased by hANP infusion, but did not change in the nicardipine group. It is concluded that nicardipine and hANP can be used safely for the treatment of hypertension during surgery. Both drugs induced phosphaturic

diuresis, but the site of action of the two drugs on the nephron may be different. Phosphate reabsorption is considered to occur largely in the renal proximal tubule, so that its appearance in the urine in increased quantities without the change of renal circulation in the nicardipine group suggests a proximal tubular action of this drug. However, the site of action of hANP in the kidney was not determined because GFR increased and distal sodium reabsorption was suppressed due to the drug infusion.

Cette étude évalue les effets de l'inhibiteur calcique nicardipine et du peptide atrial alpha natriurique humain (hANP) sur l'activité antihypertensive et diurétique chez le patient hypertendu. Sur le néphron, on a aussi recherché le site de l'activité diurétique de ces produits par la mesure de la vitesse d'excrétion du phosphate inorganique (PO_4). L'hypertension survenant pendant la gastrectomie a été traitée par l'augmentation de la concentration d'enflurane, par une perfusion de nicardipine, ($0,5-0,2 \mu\text{g} \cdot \text{kg}^{-1}$) ou par une perfusion de hANP sous anesthésie générale. L'enflurane, la nicardipine et l'hANP ont tous abaissé au même degré la pression artérielle. Le débit urinaire, le sodium et l'excrétion de PO_4 ont augmenté à la suite de l'administration de nicardipine ou de hANP. La réabsorption fractionnée distale du sodium est diminuée de $89,7 \pm 2,8\%$ à $82,1 \pm 5,0\%$ par l'hANP contrairement à la perfusion de nicardipine. La clearance de la créatinine est augmentée par la perfusion d'hANP, mais ne change pas pour le groupe nicardipine. On conclut que l'hANP et la nicardipine peuvent être utilisés en toute sécurité pour le traitement de l'hypertension pendant la chirurgie. Les deux médicaments provoquent une diurèse phosphaturique, mais le site d'action des deux médicaments pourrait être différent. On croit que la réabsorption du phosphate survient principalement au niveau du tube proximal, alors que son apparition dans l'urine en plus grande quantité sans changement de circulation rénale, dans le groupe nicardipine, suggère une action tubulaire proximale. Cepen-

Key words

ANAESTHETICS, VOLATILE: enflurane;
BLOOD PRESSURE: hypertension;
HORMONES: atrial natriuretic peptide;
KIDNEY: function;
PHARMACOLOGY: nicardipine.

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dant, le site rénal de l'action de l'hANP n'a pu être déterminé parce que la filtration glomérulaire augmente et la réabsorption distale du sodium est supprimée par sa perfusion.

Many calcium (Ca) entry blocking drugs are currently undergoing clinical investigation for hypertensive surgical patients. These drugs may be more effective than high concentration of inhalation anaesthetics for maintaining the renal circulation and diuresis during the control of blood pressure, because an increase in glomerular filtration rate (GFR) and sodium diuresis often accompanies their administration to hypertensive subjects.¹ However, only a few of these drugs have been studied sufficiently well to permit clinical characterization of their renal effects.² Differences have also been observed in the response of normotensive and hypertensive patients to Ca antagonists in clinical studies.³⁻⁴ A change of renal perfusion has been suggested as one of the important mechanisms involved in sodium diuresis due to Ca antagonists. However, in animal studies^{5,6} in which blood pressure was decreased, Ca antagonists accelerated the natriuretic effect without altering renal blood flow (RBF) or GFR. These findings suggest that the mechanism of the diuresis is not solely alteration of the renal circulation, but also inhibition of sodium reabsorption in the renal tubules. These unresolved problems have encouraged further research to examine the effect of the popular Ca antagonist, nicardipine, on renal perfusion and renal tubular electrolyte reabsorption in hypertensive surgical patients under general anaesthesia.

We also investigated the renal effects of alpha human atrial natriuretic peptide (hANP), because the effect of hANP on RBF has been found to be variable in animal studies, although an increase in GFR has usually been observed following ANP infusion.⁷⁻⁸ These renal haemodynamic effects of ANP are unique when compared with the actions of previously studied vasodilatory agents. However, Richards *et al.*⁹ reported that the effects of intravenous hANP on blood pressure in conscious humans are variable because reflex sympathetic stimulation may counter the decrease in blood pressure caused by hANP-induced vasodilatation.⁹⁻¹⁰

The antihypertensive effects of nicardipine and hANP were compared, and the sites of the diuretic actions of these drugs along the nephron were also investigated by measuring the excretion of inorganic phosphate (PO_4) in this study. Since PO_4 reabsorption is considered to occur mainly in the early proximal renal tubule, its appearance in the urine in increased quantities suggests a proximal tubular effect of diuretic agents.¹¹ The distal tubular reabsorption of sodium can be determined from the difference in the fractional excretion of PO_4 (FEPO_4) and

the fractional excretion of sodium (FENa). These two analyses of the reabsorption of electrolytes can then be used to postulate the site of action of a drug on the renal tubule in clinical study.

Methods

Thirty-two patients (20 men and 12 women aged 30–69 yr) undergoing gastrectomy for gastric cancer or gastric ulcer were included in the study. The studies were carried out according to the principles of the Declaration of Helsinki. No drugs were administered to the patients simply for the purpose of data acquisition. Informed written consent to the protocol, which was approved by the University Hospital Review Board, was obtained from each of the subjects. The criterion of hypertension in this study was a systolic BP over 160 mmHg during surgery. The patients had no history of renal disease and the plasma creatinine concentration before surgery was less than $1.5 \text{ mg} \cdot \text{dl}^{-1}$ in all patients.

All operations were begun between 9:00 and 10:00 am. The patients did not receive antihypertensive agents on the morning of surgery. Before the induction of anaesthesia, a 16-gauge teflon catheter was inserted into an antecubital vein for fluid and drug administration. Anaesthesia was induced with intravenous thiopentone ($5 \text{ mg} \cdot \text{kg}^{-1}$) and vecuronium bromide ($0.15 \text{ mg} \cdot \text{kg}^{-1}$) was given to facilitate tracheal intubation. Ventilation was controlled with a mechanical ventilator and the arterial carbon dioxide pressure (PaCO_2) was maintained at 35–44 mmHg. Anaesthesia was maintained with N_2O ($4 \text{ L} \cdot \text{min}^{-1}$), O_2 ($2 \text{ L} \cdot \text{min}^{-1}$) and enflurane (1.0–2.0% of inspired concentration). Immediately after the induction of anaesthesia, a 22-gauge teflon catheter was inserted percutaneously into the radial artery to measure the blood pressure, as well as for arterial blood gas analysis and the collection of blood samples. Urine samples were collected every 20 min via an indwelling bladder catheter inserted after the induction of anaesthesia. Suprapubic pressure and bladder washout with air were used to ensure emptying of the bladder. Ringer's lactate solution was administered at a rate of $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ *iv* to all patients during the study. No blood transfusions were given because the blood loss was <200 ml during the study in all cases. The blood pressure was treated after collecting a urine sample for 20 min.

The 32 patients were randomly allocated to three groups. In Group 1 ($n = 11$) hypertension was treated by increasing the inspired concentration of enflurane. In Group 2 ($n = 11$), BP was maintained within 110–150 mmHg by controlling the rate of infusion of nicardipine (0.5 – $2.0 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). In Group 3 ($n = 10$), BP was maintained at 110–150 mmHg by varying the rate of hANP infusion (0.05 – $0.2 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). The concen-

trations of N₂O and enflurane were not changed during the infusion of nicardipine and hANP in Groups 2 and 3 during hypertension and following the treatment.

An initial 20 min urine sample was obtained during hypertension but before treatment. Two further 20 min samples were obtained after BP was controlled to 110–150 mmHg.

The sodium concentrations of plasma and urine were determined by flame photometry. Plasma osmolality was measured using a Knauer osmometer. Urine and plasma concentrations of PO₄ and creatinine were determined colorimetrically.

Osmotic clearance (Cosm), FENa, FEPO₄, the fractional distal reabsorption of sodium (FDRNa), and the distal tubular rejection fraction of sodium (DTRFNa) were calculated from the following formulae:

$$\text{Cosm (ml} \cdot \text{min}^{-1}) = V_u \times U_{\text{osm}} / P_{\text{osm}}$$

$$\text{FENa (\%)} = (V_u \times U_{\text{Na}}) / (C_{\text{cr}} \times P_{\text{Na}})$$

$$\text{FEPO}_4 (\%) = (V_u \times U_{\text{PO}_4}) / (C_{\text{cr}} \times P_{\text{PO}_4})$$

$$\text{FDRNa (\%)} = 100 \times (\text{FEPO}_4 - \text{FENa}) / \text{FEPO}_4$$

$$\text{DTRFNa (\%)} = 100 - \text{FDRNa}$$

where V_u is the urine output (ml · min⁻¹), U_{osm} and P_{osm} respectively are the urinary and plasma osmolality (mOsm · L⁻¹), U_{Na} and U_{PO_4} are the urinary concentrations of sodium (mEq · L⁻¹), and P_{Na} and P_{PO_4} are the plasma concentrations of sodium (mEq · L⁻¹) and PO₄ (mg · dl⁻¹), and C_{cr} is the creatinine clearance (ml · min⁻¹). The FDRNa has been calculated from the fractional excretion of lithium and FENa in other reports,^{12–13} but, as we could not infuse lithium into our surgical patients, FEPO₄ was used for the calculation of FDRNa instead of lithium clearance.

The parametric data were analyzed by one-way analysis of variance, and non-parametric data were analysed by the Friedman test and the Kruskal-Wallis test for multiple comparisons. Correlations between the increases of FENa (ΔFENa) and FEPO₄ (ΔFEPO_4) were calculated from the difference between, before and during nicardipine infusion and the correlation coefficient was calculated by Pearson's test in Group 2. Simple linear regression analysis was done by the least squares method.

Results are presented as the mean $\pm$ SD, and a value of $P < 0.05$ was taken to indicate a significant difference.

Drugs

The following drugs were used:

1 Nicardipine hydrochloride (2,6-dimethyl-4(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-(2-(N-benzyl-N-methylamino))-ethyl ester 5-methyl ester hydrochloride) was obtained from Yamanouchi Pharmaceutical Company, Japan.

2 Alpha human atrial natriuretic peptide (Ser-Leu-Arg-

TABLE I Clinical data for the three groups of patients (mean $\pm$ SD)

Group	Drug	Sex	Age (yr)	Weight (kg)
1	Enflurane	m:7, f:4	54.3 $\pm$ 6.4	56.9 $\pm$ 14.7
2	Nicardipine	m:7, f:4	53.8 $\pm$ 8.2	57.1 $\pm$ 13.2
3	hANP	m:6, f:4	54.8 $\pm$ 7.2	56.7 $\pm$ 15.3

TABLE II Blood pressure and plasma electrolytes at the midpoint of urine collection

Group	During hypertension	Period of blood pressure control	
		First phase	Second phase
Plasma PO ₄ (mg · dl ⁻¹)			
1	2.74 ± 0.59	2.87 ± 0.63	2.81 ± 0.59
2	3.04 ± 0.61	2.95 ± 0.43	2.95 ± 0.43
3	3.23 ± 0.71	3.43 ± 0.66	3.15 ± 0.68
Plasma Na (mEq · L ⁻¹)			
1	144.2 ± 2.4	144.3 ± 1.3	144.5 ± 1.8
2	141.9 ± 2.8	142.1 ± 2.4	142.5 ± 2.3
3	141.9 ± 2.8	141.9 ± 2.3	140.8 ± 2.5
Systolic blood pressure (mmHg)			
1	169 ± 11	131 ± 13*	128 ± 12*
2	171 ± 12	129 ± 12*	131 ± 11*
3	172 ± 14	141 ± 8*	132 ± 10*
Diastolic blood pressure (mmHg)			
1	96 ± 14	74 ± 5*	79 ± 7*
2	97 ± 18	76 ± 12*	78 ± 11*
3	101 ± 12	86 ± 11*	83 ± 9*

* $P < 0.01$; compared with the values for each group in the hypertensive period. Mean $\pm$ SD.

Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Try) was obtained from Suntory Pharmaceutical Company, Japan.

Results

There were no differences in the sex, age, and body weight among the three groups (Table I). The mean inspired concentrations of enflurane during the hypertensive period were 1.8 $\pm$ 0.2%, 1.9 $\pm$ 0.1%, and 1.8 $\pm$ 0.2% in Groups 1, 2 and 3, respectively. In Group 1, the enflurane concentration was increased to 2.9 $\pm$ 0.3% during the period of blood pressure control.

Systolic and diastolic blood pressure were decreased ($P < 0.01$) 20 min after the start of infusion of nicardipine or hANP in Groups 2 and 3 (Table II). The Ccr increased ($P < 0.05$) in Group 3, but did not change in Groups 1 and 2 (Table III). Urine volume, sodium and PO₄ excretion were increased in Groups 2 and 3 ($P < 0.01$). The increase of

TABLE III Effects of enflurane (Group 1), nicardipine (Group 2) or hANP (Group 3) on urine volume (Vu), creatinine clearance (Ccr), and electrolyte excretion.

<i>During</i>		<i>Period of blood pressure control</i>	
<i>Group</i>	<i>hypertension</i>	<i>First phase</i>	<i>Second phase</i>
<i>Vu (ml · min⁻¹)</i>			
1	0.78 ± 0.50	0.74 ± 0.62	0.65 ± 0.68
2	0.68 ± 0.31	2.76 ± 2.27†§	1.78 ± 1.01†
3	0.70 ± 0.46	6.87 ± 3.41†§¶	8.27 ± 6.17†§¶
<i>Ccr (ml · min⁻¹)</i>			
1	75.3 ± 32.5	76.8 ± 34.5	72.6 ± 39.5
2	69.8 ± 23.0	78.5 ± 22.1	81.9 ± 33.2
3	65.0 ± 20.0	91.0 ± 30.7*	89.2 ± 20.0*
<i>UNaV (μEq · min⁻¹)</i>			
1	82.4 ± 33.0	92.5 ± 51.3	83.9 ± 41.8
2	101.9 ± 59.4	485.0 ± 354.2†§	396.2 ± 359.8†§
3	87.2 ± 75.6	1045.7 ± 749.5†§	1168.0 ± 315.4†§
<i>UPO₄V (μg · min⁻¹)</i>			
1	287 ± 183	360 ± 199	295 ± 216
2	244 ± 210	769 ± 528†‡	655 ± 638†‡
3	215 ± 155	1251 ± 1082†‡	1183 ± 467†§

* $P < 0.05$, † $P < 0.01$; compared with the values in the hypertensive period in each group.

‡ $P < 0.05$, § $P < 0.01$; compared with the values for Group 1 in each period.

¶ $P < 0.05$; compared with the values for Group 2 in each period.

urine volume in Group 3 was greater than in Group 2 ($P < 0.05$). The FENa and FEPO₄ also increased in Groups 2 and 3, but did not change in Group 1 (Table IV). The FDRNa decreased and DTRFNa increased ($P < 0.05$) during hANP infusion in Group 3, but did not change in Groups 1 and 2.

The relationship between the increase of FENa (Δ FENa) and FEPO₄ (Δ FEPO₄) as calculated from the difference in the values obtained before and during nicardipine infusion is shown in the Figure. There was a ($r = 0.885$, $P < 0.01$) relationship between Δ FENa and Δ FEPO₄ in the first phase of nicardipine infusion. Plasma sodium and PO₄ levels did not change in any of the groups (Table II).

Discussion

The main findings of our study were that enflurane, nicardipine and hANP all decreased arterial pressure to the same extent. During infusion of nicardipine a diuresis and phosphaturia were observed in all patients regardless of the GFR and plasma PO₄ levels, whilst the fractional distal reabsorption of sodium did not change. These data suggest that nicardipine induced phosphaturic diuresis by inhibition of electrolyte reabsorption in the proximal renal tubule.

TABLE IV Effects of enflurane (Group 1), nicardipine (Group 2) or hANP (Group 3) on electrolyte excretion rates and osmotic clearances

Group	During hypertension	Period of blood pressure control	
		First phase	Second phase
FENa (%)			
1	1.10 ± 0.53	0.79 ± 0.24	0.81 ± 0.46
2	0.92 ± 0.50	3.97 ± 3.27†‡	3.46 ± 2.25†§
3	1.09 ± 0.82	5.94 ± 4.31†§	6.31 ± 3.94†§
FEPO ₄ (%)			
1	9.1 ± 4.1	11.1 ± 7.0	10.7 ± 7.6
2	9.0 ± 6.4	24.2 ± 15.8†‡	25.7 ± 15.9†§
3	12.8 ± 5.6	37.1 ± 21.0†§	38.6 ± 13.9†§
FDRNa (%)			
1	87.3 ± 5.3	85.8 ± 4.0	88.5 ± 4.8
2	88.1 ± 6.6	86.0 ± 7.3	86.2 ± 6.7
3	89.7 ± 2.8	82.1 ± 5.0*	80.7 ± 5.3*
DTRFNa (%)			
1	12.7 ± 5.3	14.2 ± 4.0	13.9 ± 4.7
2	11.9 ± 6.6	14.0 ± 7.3	13.8 ± 6.7
3	10.3 ± 2.8	17.9 ± 5.0*	19.3 ± 5.3*
Cosm (ml · min ⁻¹)			
1	1.4 ± 0.7	1.5 ± 0.8	1.1 ± 1.0
2	1.5 ± 0.4	3.9 ± 3.2*	3.6 ± 3.2*
3	1.7 ± 1.5	9.8 ± 6.9†§	10.7 ± 4.6†§

* $P < 0.05$, † $P < 0.01$; compared with the values in the hypertensive period in each group.

‡ $P < 0.05$, § $P < 0.01$; compared with the values for Group 1 in each period.

FIGURE The relationship ($Y = 3.83X + 5.18$, $r = 0.885$) between the increase of FENa (Δ FENa) and that of FEPO₄ (Δ FEPO₄) as calculated from the differences in values before and during the first 20 min of nicardipine infusion (Group 2).

In clinical studies analyzing the mechanism of the diuretic action of Ca antagonists, sodium excretion rate has been the variable most frequently investigated, although sodium is not a good indicator of the site of action of a drug in the renal tubule, because sodium is reabsorbed or excreted at many sites. Therefore, we investigated the renal handling of PO_4 , because PO_4 reabsorption occurs mainly in the proximal tubule.^{11,14} Thus, an increased quantity of PO_4 in the urine without a change of the plasma PO_4 level suggests a proximal tubular site of diuretic activity of a drug. We found that nicardipine infusion produced a dramatic increase in PO_4 excretion, even in patients with unchanged or decreased Ccr and plasma PO_4 concentrations (Tables II and III).

In animal studies,^{5,6} calcium antagonists increased natriuresis without altering renal blood flow (RBF) or GFR. Abe *et al.*^{15,16} also reported that redistribution of RBF due to the administration of nicardipine was not such an important factor in sodium diuresis. They suggested that nicardipine had a diuretic effect via an increase of GFR, a decrease in the fractional reabsorption of sodium in the proximal renal tubules, and intrarenal haemodynamic alterations. However, they did not determine which of these three factors provided the main contribution to sodium diuresis due to nicardipine infusion.

Because the systemic administration of a drug alters several variables that influence phosphorus excretion, we have previously evaluated the changes in tubular sodium and PO_4 reabsorption caused in anaesthetized dogs by infusion of nicardipine into the renal artery without any alterations to the systemic and renal circulations.¹⁷ In dogs receiving a low dose of nicardipine ($5 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) into the renal artery, the blood pressure, RBF, and GFR did not change, but urine volume and urinary sodium and PO_4 excretion increased. In the current clinical study, RBF was not determined, but GFR has a stronger influence on PO_4 excretion than RBF.¹⁸ However, Ccr did not change, and there was no relationship between the increase of Ccr and the change of PO_4 excretion during nicardipine infusion. These findings suggest that renal circulatory changes are not an important factor in phosphaturia due to nicardipine infusion.

The relationship between the increase of FENa and FEPO_4 during nicardipine infusion (Figure) suggests that the movement of PO_4 may be associated with that of sodium in the renal tubules. Some investigators have reported that PO_4 reabsorption was highly dependent on the presence of sodium transport.^{19,20} Elimination of net sodium transport by inhibiting sodium-potassium ATPase activity with ouabain or by the removal of potassium from the perfusate has been shown to eliminate PO_4 reabsorption. These results suggest that proximal PO_4 reabsorption may be explained by simple chemical coupling with sodium transport. However, phlorizin blocks

glucose reabsorption and decreases sodium transport²¹ but increases PO_4 reabsorption.²⁰ Thus, the movement of phosphate may be dissociated from the movement of sodium, and the precise cellular mechanisms whereby sodium and PO_4 interact remain unclear.

Excretion volumes of PO_4 and FEPO_4 and FDRNa were all increased by hANP infusion, and the Ccr was also raised. These findings suggest that this peptide has an influence on the renal circulation and direct effects on the tubular reabsorption of electrolytes. It has been proposed that increments in GFR can fully account for the natriuresis evoked by atrial natriuretic factor (ANF).²² However, solute and fluid delivery to the last accessible portion of the distal tubule were noted to increase only 2- to 3-fold with ANF, which is far less than the 10- to 50-fold increase in the final urinary solute excretion that commonly occurs.²³ It is therefore reasonable to conclude that ANF-induced natriuresis does not result solely from increments in GFR, or from a decrease in proximal tubular Na reabsorption, but must be due largely to the actions of this peptide at other sites in the kidney. Hammond *et al.*²⁴ also reported that hANP infusion produced a brisk phosphaturic response in the absence of any changes in the GFR. Sonnenberg *et al.*²⁵ reported that administration of atrial extract failed to increase Na delivery to the end-proximal or distal convoluted tubule, whereas Na delivery to the outer medullary collecting duct was increased 3-fold and to the papillary collecting duct nearly 20-fold. Thus, the bulk of the increase in Na excretion that followed ANF administration may be due to reduced collecting duct reabsorption of Na.

Atrial peptide opposes the vascular smooth muscle contraction induced by norepinephrine, angiotensin II, and other vasoconstrictors,^{26,27} but the clinical effect of intravenous hANP on the blood pressure is variable because reflex sympathetic stimulation may counter the decrease in blood pressure caused by hANP-induced vasodilation.⁹ On the other hand, some studies employing infusion of ANP have suggested that the decrease in blood pressure is due mainly to a decrease in cardiac output and that regional or total peripheral resistance increases.^{28,29} There are large species differences in the vascular actions of ANF, and it elicits both direct and reflexly mediated vasoconstriction.²⁹ These reports suggest that the effect of hANP on renal function may be influenced by endogenous stress hormones during surgery, although the primary cause of the diuresis due to this peptide may be a direct action on the renal tubule.

In summary, nicardipine and hANP decreased and maintained blood pressure to within the normal range in hypertensive surgical patients, and both drugs induced diuresis. Measurement of PO_4 excretion was useful for assessing drug effects on the renal tubule in a clinical study. Nicardipine may induce phosphaturia due to the

inhibition of PO_4 reabsorption in the proximal renal tubule, but the site of action of hANP on the renal tubule could not be determined in this study.

References

- 1 Van Schaik BAM, Van Nistelrooy AEJ, Geyskes GG. Antihypertensive and renal effects of nicardipine. *Br J Clin Pharmacol* 1984; 18: 57–63.
- 2 Bauer JH, Reams G. Short- and long-term effects of calcium entry blockers on the kidney. *Am J Cardiol* 1987; 59: 66A–71A.
- 3 Smith SA, Rafiqi EI, Gardener EG, Young MA, Littler WA. Renal effects of nicardipine in essential hypertension: differences between acute and chronic therapy. *J Hypertens* 1987; 5: 693–7.
- 4 Leonetti G, Cuspidi C, Sampieri L, Terzoli L, Zanchetti A. Comparison of cardiovascular, renal and humoral effects of acute administration of two calcium channel blockers in normotensive and hypertensive subjects. *J Cardiovasc Pharmacol* 1982; 4: 319–24.
- 5 Dietz JR, Davis JO, Freeman RH, Villarreal D, Echtenkamp SF. Effects of intrarenal infusion of calcium entry blockers in anesthetized dogs. *Hypertension* 1983; 5: 482–8.
- 6 DiBona GF, Sawin LL. Renal tubular site of action of felopidine. *J Pharmacol Exp Ther* 1984; 228: 420–4.
- 7 Beasley D, Malvin RL. Atrial extracts increase glomerular filtration rate in vivo. *Am J Physiol* 1984; 248: F24–F30.
- 8 Dunn BR, Ichikawa I, Pfeffer JM, Troy JL, Brenner BM. Renal and systemic hemodynamic effects of synthetic atrial natriuretic peptide in the anesthetized rat. *Circ Res* 1986; 59: 237–46.
- 9 Richards AM, Nicholls MG, Espiner EA, *et al.* Effects of alpha-human atrial natriuretic peptide in essential hypertension. *Hypertension* 1985; 7: 812–7.
- 10 Bolli P, Mueller FB, Linder L, *et al.* The vasodilator potency of atrial natriuretic peptide in man. *Circulation* 1987; 75: 221–8.
- 11 Strickler JC, Thompson DD, Klose RM, Giebisch G. Micropuncture study of inorganic phosphate excretion in the rat. *J Clin Invest* 1964; 43: 1596–607.
- 12 Thomsen K. Lithium clearance: a new method for determining proximal and distal reabsorption of sodium and water. *Nephron* 1984; 37: 217–23.
- 13 Dennis VW, Brazy PC. Sodium, phosphate, glucose, bicarbonate and alanine interactions in the isolated proximal convoluted tubule of the rabbit kidney. *J Clin Invest* 1978; 62: 387–97.
- 14 Dennis VW, Stead WW, Myers JL. Renal handling of phosphate and calcium. *Ann Rev Physiol* 1979; 41: 257–71.
- 15 Abe Y, Okahara T, Yamamoto K. Effect of D-3-acetoxy-2, 3-dihydro-5-2-(dimethylamino) ethyl-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one-hydrochloride (CRD) on renal function in the dog. *Jpn Circ J* 1972; 36: 1002–3.
- 16 Abe Y, Komori T, Miura K, *et al.* Effects of the calcium antagonist nicardipine on renal function and renin release in dogs. *J Cardiovasc Pharmacol* 1983; 5: 254–9.
- 17 Goto F, Watanabe I. Calcium entry blocker nicardipine inhibits sodium and inorganic phosphate reabsorption independent of renal circulation in dogs. *Journal of Anesthesia* 1992; 6: 153–60.
- 18 Mudge GH, Berndt WO, Valtin H. Tubular transport of urea, glucose, phosphate, uric acid, sulphate, and thiosulphate. In: Orloff J, Berliner RW (Eds.). *Handbook of Physiology. Section 8: Renal Physiology*. Washington DC: American Physiological Society 1973; 587–652.
- 19 Baumann K, de Rouffignac C, Roinel N, Rumrich G, Ullrich KJ. Renal phosphate transport: inhomogeneity of local proximal transport rates and sodium dependence. *Pflügers Arch* 1975; 356: 287–97.
- 20 Dennis VW, Brazy PC. Sodium, phosphate, glucose, bicarbonate, and alanine interactions in the isolated proximal convoluted tubule of the rabbit kidney. *J Clin Invest* 1978; 62: 387–97.
- 21 Brazy PC, Dennis VW. Characteristics of glucose-phlorizin interactions in isolated proximal tubules. *Am J Physiol* 1978; 234: F279–F286.
- 22 Huang CL, Lewicki J, Johnson LK, Cogan MG. Renal mechanism of action of rat atrial natriuretic factor. *J Clin Invest* 1985; 75: 769–73.
- 23 Briggs JP, Steipe B, Schubert G, Schnermann J. Micropuncture studies of the renal effects of atrial natriuretic substance. *Pflügers Arch* 1982; 395: 271–6.
- 24 Hammond TG, Haramati A, Knox FG. Synthetic atrial natriuretic factor decreases renal tubular phosphate reabsorption in rats. *Am J Physiol* 1985; 249: F315–F318.
- 25 Sonnenberg H, Cupples WA, DeBold AJ, Veress AT. Intrarenal localization of the natriuretic effect of cardiac atrial extract. *Can J Physiol Pharmacol* 1982; 60: 1149–52.
- 26 Ballermann BJ, Brenner BM. Role of atrial peptides in body fluid homeostasis. *Circ Res* 1986; 58: 619–30.
- 27 Palluk R, Gaida W, Hoefke W. Minireview: atrial natriuretic factor. *Life Sciences* 1985; 36: 1415–25.
- 28 Zimmerman RS, Schirger JA, Edwards BS, Schwab TR, Heublein DM, Burnett JC Jr. Cardio-renal-endocrine dynamics during stepwise infusion of physiologic and pharmacologic concentrations of atrial natriuretic factor in the dog. *Circ Res* 1987; 61: 63–9.
- 29 Shen YT, Young MA, Ohanian J, Graham RM, Vatner SF. Atrial natriuretic factor-induced systemic vasoconstriction in conscious dogs, rats, and monkeys. *Circ Res* 1990; 66: 647–61.