CHANGES IN PLASMA AND URINE CALCIUM CONCENTRATIONS INDUCED BY DOPAMINE

by

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CHAPTER I

INTRODUCTION

Introduction to the Problem

Dopamine is a catecholamine commonly used as a drug in the clinical intensive care setting in the management of conditions such as congestive heart failure and shock (Hurst & Logue, 1978). In 1962, Horowitz, Fox, and Goldberg infused dopamine into normal human subjects and found an increase in cardiac output, stroke volume, and arterial pressure accompanied by a decrease or no significant change in peripheral vascular resistance. These authors suggested that dopamine might be useful for patients in whom an increase in cardiac output was desired without an increase in peripheral resistance. Subsequently, dopamine infusion has been found to be beneficial for patients with congestive heart failure (Goldberg, McDonald, & Zimmerman, 1963; Rosenblum, Tai, & Lawson, 1972; and Beregovich, Bianchi, Rubler, Lomnitz, Cagin, & Levitt, 1974). For example, Durairaj and Haywood (1978) found that dopamine infusion was associated with increased cardiac output, decreased systemic resistance, natriuresis, and diuresis in patients with severe congestive heart failure who were unresponsive to the usual therapeutic treatment with digoxin and diuretics.

Dopamine has also been found to be beneficial for patients with certain types of shock when vasopressor action is needed without threat of further reduction of renal blood flow (Hurst & Logue, 1978). Several investigators found that dopamine produced a higher cardiac output than norepinephrine and was more effective in elevating and maintaining arterial pressure than Isuprel (isoproterenol) in patients with bacteremic shock (Loeb, Winslow, Rahimtoola, Rosen, & Gunnar, 1971; and Winslow,

Loeb, Rahimtoola, Rosen & Gunnar, 1973). Controversy exists regarding the use of dopamine in patients with cardiogenic shock. However, Theroux, Mizgala, and Bourassa (1977) found that dopamine administered to patients with cardiogenic shock produced increased systolic arterial pressure, decreased ventricular filling pressure, increased urinary output, and no significant change in heart rate. Further studies are needed to determine the efficacy of the use of dopamine in acute and chronic renal failure (Tally, Forlund, & Beller, 1970; and Vlachoyannis, Weismuller, & Schoeppe, 1976).

While many of the effects of dopamine on hemodynamic and renal function in both man and dog have been extensively studied, other unresolved problems remain. One notable deficit is the paucity of published research on the effect of dopamine on plasma and urine calcium and phosphate concentrations. In one report, Massry and Kleeman (1972) studied calcium excretion during an acute rise in glomerular filtration rate (GFR) and utilized dopamine as one of four means of achieving the increased GFR. These authors found a four-fold increase in calcium excretion but changes in plasma calcium concentration were not reported. Catecholamines in general have been associated with increased excretion of calcium, bone resorption, hypercalcemia, and hypercalciuria (Skrabanek, 1977).

Cuche, Marchand, Gregor, Lang, and Knox (1976) studied the phosphaturic effects of dopamine in the dog but did not report any effect on calcium excretion. No significant change was reported in plasma phosphate concentration. A change in plasma and urine calcium concentrations would be expected if plasma phosphate changes. This expectation

is based on the reciprocal relationship between the concentrations of phosphate and calcium relative to their solubility products (Massry, Friedler, & Coburn, 1973). For example, an increase in phosphate concentration causes a fall in calcium concentration due, in part, to the deposition of calcium-phosphate salts into bone. Conversely, a decrease in plasma phosphate concentration may be associated with an increase in plasma calcium concentration.

Since dopamine may increase phosphate excretion, it is possible that prolonged therapy with dopamine (several days or more) may cause phosphate depletion. It has been demonstrated that severe phosphate depletion is associated with hypercalciuria, increased gastrointestinal absorption of calcium and increased bone resorption (Lotz, Ney, & Bartter, 1964). There are conflicting results regarding changes in plasma calcium concentration. Plasma calcium concentrations were found to rise slightly or not change significantly during some studies while a significant hypercalcemia was noted in other studies (Freeman & McLean, 1941; Massry & Coburn, 1970; and Baylink, Wergedal, & Stauffer, 1971). Any change in extracellular calcium concentration may become clinically significant since calcium is involved in processes such as contraction of cardiac, skeletal, and smooth muscle, nervous tissue excitability, and cerebral function. Increased bone resorption causes increased risk of fractures and hypercalciuria increases the risk of renal calculi (Robbins, 1974, and Beeson, McDermott, & Wyndaarden, 1979).

Except for the report of Massry and Kleeman (1972), no specific work has been done on the effect of dopamine on plasma or urinary calcium concentrations. There is evidence that dopamine may induce changes in phosphate concentration in plasma and urine. Changes in plasma

phosphate concentrations are often accompanied by changes in plasma calcium concentrations. Limited research in this area has yielded conflicting results. Alterations in extracellular calcium concentration can have serious clinical effects. Thus, studies to evaluate the effects of dopamine on calcium concentration in plasma and urine are needed.

In this investigation I have attempted to identify the effects of dopamine on changes in calcium concentrations in plasma and urine.

Review of the Literature

The literature related to dopamine and calcium is extensive. For clarity, the relevant topics will be presented according to the following outline:

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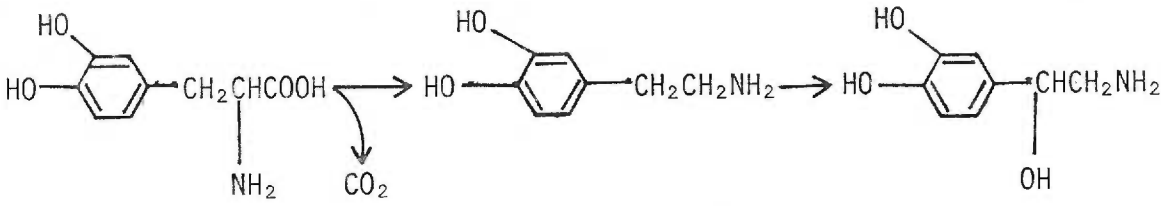
I. ACTIONS OF DOPAMINE

A. Chemistry of dopamine

Dopamine (3,4-dihydroxyphenylethylamine) is an intermediate compound in the synthesis of norepinephrine from phenylalanine (Aviado, 1970). L-aromatic amine acid decarboxylase acts upon dihydroxyphenylalanine (DOPA) to form dopamine. Dopamine-B-hydroxylase then converts dopamine to norepinephrine. The half-life of dopamine is approximately 105 seconds (Arnar-Stone Laboratories, 1975).



DIHYDROXYPHENYLALANINE (DOPA) DOPAMINE NOREPINEPHRINE

(Lehninger, 1975)

B. Alpha-adrenergic effects

Alpha-receptor stimulation in smooth muscle causes contraction (Goodman & Gillman, 1970). Dopamine predominantly causes vasoconstriction in most arterial vascular beds as a result of action on alpha-adrenergic receptors (McDonald & Goldberg, 1963; Eble, 1964; and McNay, McDonald, & Goldberg, 1965). This vasoconstrictor effect will predominate over vasodilating effects if the dopamine dose is adequately large. Eble (1964) found an adequate dose for vasoconstriction to be close to 20 to 40 µg./Kg. · minute in the dog. Black, Rolett, and Hill (1968) demonstrated the ability of dopamine in low doses (5, 8, and 10 µg./Kg.· minute to increase arterial resistance when beta-receptors were blocked with

propranolol. They postulated that under these conditions the action of dopamine is mediated through alpha-adrenergic stimulation.

C. Beta-adrenergic effects

Stimulation of beta-adrenergic receptors causes smooth muscle relaxation and cardiac stimulation. The beta-adrenergic action of dopamine is weak in the peripheral vasculature in experimental animals. McNay and Goldberg (1966 a) studied the relationship between femoral blood flow in the dog and a range of doses of dopamine, norepinephrine, and isoproterenol (administered arterially) when alpha-adrenergic receptors were blocked with phenoxybenzamine. Blood flow in the femoral artery was measured continuously with an electromagnetic flowmeter. The dose of dopamine required to produce a blood flow of 100 ml./minute from a baseline flow of approximately 5 to 10 ml./minute was approximately thirty times greater than the norepinephrine dose and six hundred times greater than the isoproterenol dose. Studies have not been definitive in man. Wheeler, Marquardt, Ayers, and Wood (1967) studied calf blood flow and venous capacitance during intravenous dopamine infusion of 2, 4, and 6 µg./Kg. ·minute. They found that dopamine caused peripheral venoconstriction and arteriolar constriction. Allwood and Ginsberg (1964) studied forearm and hand blood flow prior to and during intraarterial dopamine infusion of 50 µg./Kg. · minute. Phenoxybenzamine, an alpha-adrenergic blocking drug, was then administered. Forearm and hand blood flow initially decreased when dopamine was infused. Flow increased significantly after phenoxybenzamine which suggests stimulation of beta-adrenergic receptors. However, effects of beta-adrenergic blocking agents were not studied.

The cardiac effects of dopamine are produced both by direct action on beta-adrenergic receptors and indirect stimulation of norepinephrine release from storage sites in the sympathetic nerves (Goldberg, 1972). Positive inotropic effects of dopamine have been demonstrated in dogs. There was little chronotropic effect (McDonald & Goldberg, 1963, and Black et al., 1968). Similar results were found in man (Beregovich et al., 1974; Theroux et al., 1977; and Durairaj & Haywood, 1978). In all but one of these studies (McDonald & Goldberg, 1963) the range of doses of dopamine varied from 1 to 10 µg./Kg. · minute. Positive chronotropic effects may occur at significantly higher rates (greater than 16 µg./Kg. · minute) of dopamine infusion (McDonald & Goldberg, 1963).

D. Hemodynamic effects

Dopamine produces a dose related spectrum of effects on hemodynamic status. Purely depressor effects occur with low doses (1 to 3 µg./Kg. · minute), purely pressor effects with high doses (40 to 200 µg./Kg. · minute) and balancing effects with intermediate doses (10 to 20 µg./Kg. · minute). The blood pressure effect produced by dopamine infusion (Eble, 1964) was shown to be a balance between vasoconstriction in some vascular beds (carotid and femoral) and vasodilation in others (superior mesenteric, renal, and celiac). McDonald and Goldberg (1963) identified a similar dose response scale in the dog. Harrison, Pirages, Robison, and Wintroub (1969) found a significant fall in systemic vascular resistance at doses of 8 and 15 µg./Kg. · minute but a significant rise at 30 µg./Kg. · minute. In addition, Harrison et al. found a significant stroke volume increase only at 25 and 30 µg./Kg. · minute but the trend was toward increased stroke volume at all doses.

The hemodynamic effects of dopamine (dosage range 2.1 to 11.6 µg./Kg. · minute) have been studied in normal human subjects, subjects with chronic congestive heart failure (CHF), and coronary artery disease (Horowitz, Fox, & Goldberg, 1962; McDonald, Goldberg, McNay, & Tuttle, 1964; Rosenblum et al., 1972; Theroux et al., 1977; and Durairaj & Haywood, 1978). All of these investigators concluded dopamine increases cardiac output (or specifically cardiac index), and decreases peripheral (systemic) vascular resistance with no significant change in heart rate.

Brooks, Stein, Matson, and Hyland (1969) studied coronary blood flow in the dog during intravenous dopamine infusion of doses ranging from 5 to 100 µg./Kg. · minute. Increasing dose up to 80 µg./Kg. · minute was accompanied by a linear increase in coronary blood flow. Coronary blood flow increased proportionately more than coronary perfusion pressure. Brooks et al. concluded that coronary vasodilation was an effect of dopamine. However, the increased coronary flow was proportional to increases in myocardial oxygen consumption. Therefore, they concluded that coronary vasodilation was secondary to increased myocardial oxygen demands.

In summary, the hemodynamic effects of dopamine are dose related. The blood pressure effect produced by a given dose of dopamine results from a balance between vasoconstriction in some vascular beds and vasodilation in others. Dopamine (dose range 2.1 to 11.6 µg./Kg. · minute) increases cardiac output, decreases peripheral vascular resistance and causes no significant chronotropic change. Dopamine is associated with coronary vasodilation secondary to increased myocardial oxygen demands.

E. Dopamine receptors

Evidence suggesting that dopamine acts on unique vascular receptors began accumulating in 1963. Dopamine was infused in normal human subjects in doses that did not produce a change in mean arterial pressure. Significant reduction in renal artery resistance occurred after dopamine infusion in these normal human subjects (McDonald et al., 1963). The renal vasodilation produced by dopamine was not altered by alpha, beta, or ganglionic blocking agents which are known to block the identified alpha and beta vascular receptors (McDonald and Goldberg, 1963). Eble (1964) demonstrated vasodilation that resisted beta-adrenergic blockade in canine mesenteric and celiac vascular beds. Schuelke, Mark, Schmidt, and Eckstein (1971) found similar results in the coronary vascular bed.

Evidence of selective vasodilation was needed to support the hypothesis that dopamine was acting on previously unidentified receptors. McNay, McDonald, and Goldberg (1965) infused dopamine in doses that did not elevate blood pressure into canine renal and femoral arteries. Renal artery infusion of dopamine (dose range 0.75 to 12 µg.) produced vasodilation while the same dose produced femoral arterial vasoconstriction. The rate was not specified. These authors concluded that dopamine probably has a direct renal vasodilating action.

In 1969 Yeh, McNay, and Goldberg constructed dose response curves for dopamine, bradykinin, and isoproterenol before and after haloperidol (a specific blocker for dopamine) infusion into canine renal and mesenteric arteries. Phenoxybenzamine was administered prior to haloperidol infusion to block the alpha-adrenergic effects of dopamine. Haloperidol administration selectively attenuated vasodilation produced by

dopamine in the renal and mesenteric beds. Large doses of dopamine overcame the haloperidol blockade. This reversal of the haloperidol blockade with dopamine administration indicated that the antagonism was competitive. Yeh et al. concluded that these results support the concept of specific dopamine receptors. Other investigators are attempting to define the specific structural characteristics of these dopamine receptors. (Goldberg, Kohli, Kotake, & Volkman, 1978).

F. Renal effects

Dopamine is the only catecholamine that produces both vasoconstriction and vasodilation of the renal vasculature (McNay & Goldberg, 1966 b). The vasodilation effect is dose related. McNay, McDonald, and Goldberg (1965) infused dopamine into the renal arteries of dogs in doses of 0.75 to 192 µg. (rate of infusion was not specified). Blood flow was measured by an electromagnetic flowmeter placed on the renal artery. At doses of 0.75 to 6 µg. an increase in renal blood flow was the only hemodynamic response that occurred. When dopamine was infused in a dose of 12 to 96 µg. transient initial vasoconstriction occurred which increased in amplitude and duration with increasingly larger doses. At doses of 96 to 192 µg. the response was predominantly vasoconstriction. They concluded that dopamine, when given in a dose that does not significantly alter mean arterial blood pressure (0.75 to 12 µg.), increased renal blood flow by decreasing renal vascular resistance.

Additional studies in both dog (Meyer, McNay, & Goldberg, 1967) and man (McDonald et al., 1964) have confirmed that the effects produced by dopamine infusion on renal function are qualitatively comparable between the species. Meyers, et al. (1967) infused dopamine intravenous-

ly into dogs at rates of 3 and 6 μg./Kg. · minute and 1.2 and 0.6 μg./Kg. · minute into the renal artery. McDonald et al. (1964) infused dopamine into normal human subjects intravenously at rates of 2.6 to 7.1 μg./Kg. · minute.

Comparison of the results showed that sodium excretion increased by approximately three times in both man and dog following dopamine infusion. In man, GFR increased an average of 16% (from 109 to 126 ml./minute) and clearance of para-aminohippuric acid (reflecting effective renal plasma flow) increased 58% (from 507 to 798 ml./minute) (McDonald et al., 1964). In the dog, GFR increased an average of 11% and clearance of para-aminohippuric acid increased 25% (Meyer et al., 1967). However, it should be noted that the increase in GFR and ERPF in the dog reported by these authors was not verifiable when calculated from the data in their tables.

McNay, McDonald, and Goldberg (1965) concluded that dopamine causes increased renal blood flow by acting directly on renal blood vessels. These investigators compared the results obtained from infusion of dopamine directly into one renal artery (0.6 and 1.2 μg./Kg. · minute) to those obtained from intravenous infusion of dopamine (7.5 μg./Kg. · minute). The increase in renal blood flow occurred too rapidly after intrarenal arterial infusion to be secondary to systemic hemodynamic changes. Also, both intravenous and intraarterial dopamine produced comparable increments in renal blood flow since the intravenous dose was approximately eight times that of the mean intraarterial dose. This adjustment is necessary because the dose of intravenous dopamine delivered to the kidney would be approximately one-eighth of that delivered by intraarterial infusion since each kidney receives approxi-

mately one-eighth of the cardiac output (Leaf & Cotran, 1977). Intravenous dopamine infusion of 7.5 µg./Kg. · minute produced a 38% increase in renal blood flow. Intraarterial dopamine infusion of 0.6 µg./Kg. · minute produced a 25% increase, while an intraarterial dose of 1.2 µg./Kg. · minute produced a 38% increase in renal blood flow.

Meyer et al. (1967) also infused dopamine directly and unilaterally into the renal arteries of dogs at rates of 1.2 to 6 µg./Kg. · minute. They also infused dopamine intravenously at rates of 3 and 6 µg./Kg. · minute in dogs. They found that increased sodium excretion could be produced by dopamine independently of changes produced in the systemic circulation. This was demonstrated by the fact that the kidney infused with dopamine produced greater increments in sodium excretion than the uninfused kidney. Intravenous infusion of dopamine produced increased sodium excretion in both kidneys.

Davis, Walter, and Murdaugh (1968) supported this finding and, using micropuncture technique, also found that dopamine-induced natriuresis is independent of proximal tubular changes in sodium reabsorption. They hypothesized the probability of a direct or indirect tubular effect at a more distal site. The question of whether dopamine induced the natriuresis by a direct renal tubular effect or by renal vascular changes is unresolved.

Extracellular volume expansion results in natriuresis (Leaf & Cotran, 1977). Expansion of extracellular fluid volume simultaneously increases GFR and decreases fractional reabsorption of sodium. To test the effects of increased GFR without decreasing fractional reabsorption of sodium, Lindheimer, Lalone, and Levinsky (1967) infused dopamine intravenously at various rates (10, 15, and 20 µg./Kg. · minute) to

increase GFR while not depressing sodium reabsorption. To eliminate the variable effects that mineralocorticoids might have produced in their results, they infused high doses of mineralocorticoids in four dogs and blocked the mineralocorticoid activity in three others with spironolactone. Following dopamine infusion, increases in GFR from 7 to 59% (mean 29%) occurred in the dogs given large intramuscular doses of the mineralocorticoid deoxycorticosterone acetate (DOCA). In the dogs (3) given spironolactone the increase in GFR was from 5 to 83% (mean 34%). The mean increase in sodium excretion was 17 μgEq./minute (77%). Glomerular filtration rate was increased in nineteen other dogs by the infusion of approximately 2100 ml. of isotonic saline. The authors report the increment in GFR was less than 30% in thirteen of the nineteen experiments. No additional data was given to determine the mean increase in GFR and range. Sodium excretion increased more than 400 μEq./minute in all but two saline experiments (data for calculating the exact percentage of increase in sodium excretion was not given).

The degree of natriuresis found by Lindheimer et al. (77% mean increase in sodium excretion) was significantly less than that found by McDonald et al. (1964) (322% mean increase) and Davis et al. (1968) (191% mean increase). However, it was not possible to determine how closely the variable of extracellular volume expansion was controlled from the reports of McDonald et al. (1964) and Davis et al. (1968). If extracellular volume expansion was not adequately controlled in these latter studies, then it is possible that the additional degree of natriuresis was induced by expansion of the extracellular fluid volume and not by dopamine.

Massry and Kleeman (1972) replicated the study of Lindheimer et al. in part but extended it to examine calcium and magnesium excretion during acute increments in GFR. Intravenous dopamine infusion of 10, 15, and 20 µg./Kg. · minute in a 2.5% dextrose solution was maintained at a rate equal to urine flow to attain an acute increase in GFR without extracellular volume expansion. With dopamine infusion GFR increased by 38%. The renal excretion rates of sodium, calcium, and magnesium also increased. For example, sodium excretion increased from 29 ± 12 (SE) to 102 ± 13 µEq./minute. Calcium excretion increased from 13 ± 6 to 52 ± 9 µg./minute. These findings indicate that dopamine infusion resulted in a 350% increase in sodium excretion and a 400% increase in calcium excretion. This 350% increase in sodium excretion, obtained with dopamine without extracellular volume expansion, is comparable to the increase found by McDonald et al. (322%) and Davis et al. (191%) with undetermined control of extracellular volume expansion. The results obtained from dopamine infusion were compared to results obtained from saline loading. Approximately two liters (1800 cc.) of isotonic saline was infused over 90 minutes and then maintained at a rate equal to urine flow. A comparable increase in GFR was obtained during both dopamine infusion and saline loading. However, with saline loading the urinary excretion of sodium increased from 33 ± 10 to 918 ± 141 µEq./minute (a nearly 3,000% increase) and calcium excretion increased from 16 ± 5 to 317 ± 47µg./minute (a nearly 2,000% increase). Changes in plasma calcium concentration were not reported in either the dopamine or saline experiments. No other studies involving calcium excretion in relation to dopamine infusion were found in the literature.

Cuche, Marchand, Greger, Lang, and Knox (1976) examined the effects of dopamine on the renal handling of phosphate in dogs. They found that intrarenal artery infusion of dopamine at 1.05 µg./Kg. · minute appeared to have a phosphaturic effect independent of changes in parathyroid hormone, calcitonin, renal blood flow, and sodium excretion. Lenfesty and Keyes (1979) were unable to confirm this finding with intravenous infusion of dopamine.

In summary, dopamine produces renal vasodilation. This effect is dose related and is the only renal hemodynamic effect to occur at intra-arterial doses of 0.75 to 6 µg. At doses greater than 12 µg. transient vasoconstriction occurs. At doses greater than 96 µg. vasoconstriction is the predominant effect. Dopamine increases renal blood flow by decreasing renal vascular resistance. These effects are similar in man and dog when dopamine is infused at rates of 2.6 to 7.1 µg./Kg. · minute intravenously and 0.6 to 1.2 µg./Kg. · minute intraarterially. Other effects from dopamine infusion are increased GFR and increased effective renal plasma flow. The increase in renal blood flow appears to be due to a direct dilation of renal vasculature and is not secondary to systemic hemodynamic changes. Dopamine consistently results in a natriuresis. The question of whether dopamine causes natriuresis by a direct effect on the renal tubule by decreasing fractional reabsorption or by changes in renal vascular resistance is unresolved. The relationship of the degree of natriuresis following dopamine infusion to the expansion of extracellular fluid volume is not clearly identified in the literature. It has, however, been determined that intravenous dopamine infusion results in a 77 to 350% increase in sodium excretion.

A 400% increase in calcium excretion was found in a single study. No other studies were found in the literature that examined calcium excretion in relation to dopamine infusion. A phosphaturic effect of dopamine was reported in a single study.

II. CALCIUM

A. General balance and gastrointestinal absorption

Calcium ion concentration in the extracellular fluids depends on a balancing interaction of the following factors: calcium uptake from the intestine, bone deposition and resorption, and gastrointestinal or urinary excretion. The state of calcium balance (either positive or negative) is reflected in the difference between the quantity of calcium ingested and that excreted in the urine and feces. For example, a positive balance (calcium retention) is seen during growth, pregnancy, or in response to prolonged calcium starvation. A negative balance occurs with infantile rickets, osteomalacia, hyperparathyroidism, and during starvation or calcium deficiency (Best & Taylor, 1966).

In most species calcium is absorbed by an active process in the proximal small bowel (Brobeck, 1973). This process requires the active form of vitamin D which induces the synthesis of a calcium binding protein in the duodenal mucosa (Haussler & Nagode, 1969, and MacGreggor, Hamilton, & Cohn, 1970). Vitamin D (cholecalciferol) is enzymatically hydroxylated in the liver to form 25-dihydroxycholecalciferol. This metabolite has little physiological activity until it is further hydroxylated by a 1, alpha-hydroxylase found in the kidney to produce the active compound 1, 25- dihydroxycholecalciferol (Leaf & Cotran, 1976). Parathyroid hormone (PTH) acts to facilitate calcium absorption by stimulating production of the active metabolite of vitamin D. Both

PTH and vitamin D metabolism are controlled by complex feedback regulation.

Phosphate depletion is another factor that can stimulate production of the active metabolite of vitamin D. A low serum phosphate concentration stimulates the activity of 1, alpha-hydroxylase which increases the production of 1, 25-dihydroxycholecalciferol (Leaf & Cotran, 1976). This increase in production of activated vitamin D (vital to intestinal calcium absorption) that results from low serum phosphate demonstrates the close relationship of the plasma concentrations of phosphate and calcium. A balance is maintained in this relationship that can be quantitatively estimated by determining the product of the total calcium in mg. per 100 ml. and the inorganic phosphate in mg. per 100 ml. This is referred to as the solubility product and it remains approximately constant between 30 and 40 in adults (Best et al., 1966). If this product rises above its normal maximal limit bone deposition is induced and, conversely, if it falls below its normal minimal limit bone resorption is induced (Best et al., 1966).

The average daily dietary intake of calcium in man is 400 to 800 mg. per day. Fifty to 70% of this total will be primarily composed of the unabsorbable calcium of food and will be excreted in the feces. Calcium secretion into the small intestine also occurs (Beeson et al., 1979). Smaller quantities of calcium are excreted in the urine.

B. Normal renal handling of calcium

The filtered load of calcium equals the product of GFR (120 ml./minute in man) and the calcium concentration of the filtrate (3 mEq./liter). This value is 360 μEq./minute or 518 mEq./day (Goldberg, Agus,

& Goldfarb, 1976). Only 0.55 to 1.0% of this filtered calcium is excreted in the urine due to extremely effective tubular reabsorption. This quantity of filtered calcium includes that part of the total plasma calcium concentration which is ionized (approximately 50%), and that part which is complexed with citrate and other organic anions and so is not freely ionized but is ultra-filterable(approximately 5 to 10%). Brenner and Rector (1976) summarized data from the experimental literature and found the fraction of filtered calcium to average 0.63. This excludes that calcium (approximately 40%) which is bound to serum protein and is therefore nonfilterable (Leaf & Cotran, 1976).

There have been extensive micropuncture studies in the mammalian kidney to determine the manner in which calcium reabsorption occurs. Goldberg et al. (1976) list the following approximations: 50 to 55% of the filtered load is reabsorbed in the proximal tubule, 20 to 30% is reabsorbed in the loop of Henle, 10 to 15% is reabsorbed in the distal convoluted tubule, and 2 to 8% is reabsorbed in the collecting ducts. There is no evidence for tubular secretion of calcium. Urinary excretion of calcium is presumed to be controlled by alteration of tubular reabsorption (Sutton & Dirks, 1977). There is support of the hypothesis that some form of active transport mechanism for calcium is present in the proximal tubule, thick ascending limb of the loop of Henle, distal tubule, and collecting system (Sutton & Dirks, 1977; and Agus, 1978). Very little is known about the cellular mechanisms of calcium transport in each nephron segment and a maximal transport capacity for calcium has not been reported.

C. General relationship of sodium and calcium reabsorption

Walser, in 1961, found that free calcium ion and sodium clearance

rose and fell together during diuresis induced by a variety of methods in dogs. This relationship was not altered by reducing calcium or sodium intake, varying urinary flow or urinary ionic strength, or by varying chloride excretion. Data from micropuncture studies show that, under normal circumstances, sodium and calcium are reabsorbed together throughout the nephron although there may be some dissociation of this relationship at the hairpin turn of the loop of Henle (Sutton & Dirks, 1975, 1977). The handling of sodium and calcium beyond the loop of Henle appears to be separate and current data support the idea that the terminal nephron (the late distal tubule and collecting system) is the major site for final regulation of urinary calcium excretion (Agus, 1978).

D. Effects of hemodynamic alterations on urinary calcium excretion

Gonda, Wong, Seely, and Dirks (1969) examined the effects of two vasodilators, acetylcholine and bradykinin, infused into the renal arteries of dogs. The effects upon sodium and divalent cation (calcium) excretion were examined alone and in association with variation in the systemic blood pressure. They found that infusion of the vasodilators consistently produced increases in the fractional excretion of calcium that correlated significantly with sodium excretion. Elevation of perfusion pressure (mean arterial pressure), in addition to renal vasodilation, had a synergistic effect that resulted in much greater fractional excretion rates when compared to the kidney that was non-dilated. These effects on calcium and sodium excretion occurred in the absence of changes in the filtered load. Thompson, Kaufman, and DiScala (1971) infused acetylcholine and prostaglandin E_1 into the renal arteries of dogs and found similar results. They found that increases in urine and

plasma flow without increases in GFR were accompanied by increases in sodium, calcium and phosphorus excretion. There was no alteration in the usual linear relationship between sodium and calcium excretion noted during vasodilation with either chemical.

Kaloyanides (1971) studied the specific effect of perfusion pressure on sodium and calcium excretion in the isolated dog kidney using pitressin and DOCA. He found that increasing renal arterial pressure by approximately 50 mmHg. caused a significant increase in both the absolute and fractional excretion of sodium and calcium in the absence of consistent changes in GFR or renal blood flow. The magnitude of the change in excretion of one cation is significantly correlated with that of the other. The hemodynamically induced alterations in fluid and electrolyte reabsorption described in these studies are generally believed to be a result of changes in Starling's forces operating at the level of the peritubular capillary bed which surrounds the proximal tubules (Goldberg et al., 1976). However, while a significant correlation has been found between calcium and sodium excretion in response to increased renal arterial pressure, direct alteration of tubular calcium transport (independent of changes in sodium excretion) by increased renal arterial pressure has not been shown (Kaloyanides, 1971).

E. Effects of GFR and volume expansion on urinary calcium excretion

In 1961, Walser found that saline infusion into dogs produced an increase in both urinary sodium and calcium excretion. Subsequently, data from a variety of studies (including micropuncture studies) has supported the belief that volume expansion with saline results in decreased tubular reabsorption of sodium (Massry & Coburn, 1973). As described above, Massry and Kleeman (1972) studied calcium excretion in

the dog during an acute rise in GFR which was induced by the following four methods: protein feeding (27% rise in GFR compared with control), intravenous dexamethasone (20% rise), dopamine infusion (38% rise), and saline infusion (33% rise). They observed that marked increases in GFR without extracellular volume expansion that resulted from use of the first three methods increased calcium excretion from 13 ± 6 to 52 ± 9 μg./minute and sodium excretion from 29 ± 12 to 102 ± 13 μEq./minute. Similar acute increments in GFR produced from extracellular volume expansion with saline infusion were associated with a greater increase in the excretory rates of both ions: calcium excretion increased from 16 ± 5 to 317 ± 47 μg./minute and sodium excretion increased from 33 ± 10 to 918 ± 141 μEq./minute.

Massry, Coburn, Chapman and Kleeman (1967), and Blythe, Gitelman, and Welt (1968) studied changes in urinary calcium and sodium excretion following saline volume expansion with a superimposed acute GFR reduction (6 to 45% reduction compared with control values). Reduction in GFR was accomplished by inflation of an intra-aortic balloon placed cephalad to the renal arteries. They found that even though the filtered load of calcium was substantially reduced, calcium excretion increased when sodium excretion was enhanced. These observations indicate that extracellular volume expansion with saline causes a decreased renal tubular reabsorption of calcium as well as sodium.

Duarte and Watson (1967) used a micropuncture technique to study the reabsorption of calcium in proximal renal tubules of dogs. They found that extracellular volume expansion produced by saline infusion decreased the proximal tubular reabsorption of both calcium and sodium. Davis and Murdaugh (1970) used both hyperoncotic albumin and saline infusions in the dog to study the relationship between calcium and sodium

excretion. They found that albumin produced a natriuresis but had no effect on calcium excretion. Saline infusion (dose range 10 to 100 ml./Kg.) significantly increased calcium and sodium excretion. Hyperoncotic solutions such as albumin have previously been shown to decrease sodium reabsorption in the proximal tubule, while saline decreases sodium reabsorption in both proximal and distal parts of the nephron (Massry & Coburn, 1973). From these observations Davis and Murdaugh (1970) suggested that the different effects of saline and albumin on urinary calcium excretion could be due to depression of distal as well as proximal tubular calcium reabsorption by saline volume expansion. The specific distal nephron site of inhibition of calcium reabsorption by saline volume expansion has not been determined.

F. Effect of parathyroid hormone on urinary calcium excretion

Parathyroid hormone (PTH) enhances tubular calcium reabsorption, initially decreases urinary calcium excretion, and increases urinary phosphate excretion. However, continued excessive PTH action on bone results in an elevation of serum calcium that eventually increases calcium excretion despite the stimulus for calcium reabsorption (Leaf & Cotran, 1976). The tubular site where PTH acts has not been totally confirmed but micropuncture studies in the dog indicate that a major site of enhancement of calcium reabsorption is in or beyond the distal convoluted tubule (Sutton, Wong, & Dirks, 1976). There is evidence that the proximal and phosphaturic effects of PTH are mediated by generation of cyclic AMP but there is no definite evidence supporting the enhancement of calcium reabsorption by this mechanism (Agus, Gardner, Beck, & Goldberg, 1973; and Agus, 1978).

G. Effects of phosphate depletion on serum calcium and urinary calcium

A significant increase in urinary calcium excretion has been shown to occur during phosphate depletion in man, dog, and other laboratory animals (Massry & Coburn, 1973). Coburn and Massry (1970) studied changes in serum and urinary calcium concentrations in dogs before and after prolonged phosphate depletion (30 to 160 days), and after phosphate repletion. Phosphate depletion was induced by a low phosphate diet and aluminum hydroxide gel administration. The effect of diurnal variation in urinary excretion was evaluated in relation to the results. During phosphate depletion they found that GFR fell by 14 to 53% compared to control values and hypercalciuria occurred despite the reduced filtered load of calcium. The percentage of filtered calcium excreted increased from control values of 0.35% ± 0.14 (mean ± SE) to 3.61% ± 0.64 when serum phosphorus concentrations were between 1.0 and 2.0 mg./100 ml. When serum phosphorus concentrations were less than 1.0 mg./100 ml., the percentage of filtered calcium excreted decreased to 0.77% ± 0.19% which was equivalent to pre-phosphate depletion or control values. The hypercalciuria occurred in the absence of consistent changes in the renal excretion of sodium and magnesium, or the urinary concentration of complexing ions such as citrate. Phosphate repletion reversed both the decrease in GFR and the increase in calcium excretion demonstrated during phosphate depletion.

Additional experiments were done to evaluate the role of parathyroid hormone in calcium excretion during phosphate depletion. Parathyroid extract was administered to phosphate depleted dogs in seven experiments. Glomerular filtration rate and filtered load of calcium increased. Fractional excretion of calcium was reduced but remained significantly greater (in all but one experiment) than values in control animals which

did not receive parathyroid extract. In five other experiments, thyroparathyroidectomy was performed on phosphate depleted dogs. Fractional excretion of calcium either decreased or did not change. This effect on fractional excretion of calcium is unlike the increase in fractional excretion of calcium reported in normal dogs following thyroparathyroidectomy (Kleeman, Bernstein, Rockney, Dowling, & Maxwell, 1961). In addition, the serum calcium concentration remained normal after thyroparathyroidectomy until serum phosphorous increased slightly. Hypocalcemia then developed.

The observations of Coburn and Massry (1970) indicate, in part, that phosphate depletion is associated with: (1) hypercalciuria resulting from reduced tubular calcium reabsorption which is not produced by changes in tubular reabsorption of other ions, and (2) a state of functional hypoparathyroidism which may contribute to the reduction of tubular reabsorption of calcium. These authors suggest that elevated serum calcium may cause hypoparathyroid function in the phosphate depleted state. Elevated serum calcium has been found during phosphate depletion in the dog and rat (Freeman & McLean, 1941, and Baylink, Wergedal, and Stauffer, 1971) even though this occurred only transiently in certain dogs in this study of Coburn and Massry.

Baylink et al. (1971) studied the effects of a low phosphorus diet in intact and thyroparathyroidectomized rats on certain processes of bone mineralization and turnover. Rats fed a low phosphorus diet became hypophosphatemic and hypercalcemic. Serum phosphorus, total calcium and ionized calcium in rats fed normal or low (0.04%) phosphorus diets for three days were compared. Serum phosphorus concentration in the control group was 9.8 mg./100 ml. ± 0.5 (mean ± SD) and 5.0 mg./100

ml. ± 1.0 in the low phosphorus diet group; serum calcium in the control group was 10.5 mg./100 ml. ± 0.2 and 13.8 mg./100 ml. ± 0.6 in the low phosphate diet group; and serum ionized calcium was 5.3 mg./100 ml. ± 0.2 in the control group and 7.0 mg./100 ml. ± 0.4 in the low phosphate diet group. By the end of 14 days the group that was fed the 0.04% phosphorus diet developed a 50% decrease in serum phosphorus concentration, a 19% increase in serum calcium concentration, significant decreases in parameters used to measure formation and mineralization of bone matrix, and a 342% increase in endosteal bone resorption rate. Hypophosphatemia and hypercalcemia were apparent after one day, although the authors stated endosteal bone resorption was not demonstrably increased for four days. Rats fed a 0.2% phosphorus diet demonstrated a significant increase in bone resorption but no change in matrix formation or mineralization. The magnitude of the increase in bone resorption was similar in intact and thyroparathyroidectomized rats fed similar concentrations of dietary phosphorus which contributed to the conclusion of Baylink et al. that parathyroid hormone and calcitonin were not involved in this response. The reciprocal relationship between serum calcium and phosphorus was also clearly demonstrated in the thyroparathyroidectomized rats. The observations from this study indicate that phosphate depletion in both intact and thyroparathyroidectomized states results in significant, rapid hypophosphaturia, hypercalcemia, and increase in bone resorption, and decreased bone formation in the phosphorus depleted state. An increase in ionized calcium is a result of the increase in the total serum calcium. Ivey, Morey, and Baylink (1977) also studied phosphate depleted rats. They found that an increased rate of bone resorption results in liberation of calcium phos-

phate, while a decreased rate of bone formation reduces the amount of phosphate removed from circulation.

Lotz, Ney, and Bartter (1964) studied phosphorus depletion induced by magnesium-aluminum hydroxide gel ingestion in two normal human volunteers over an eighty-five day period. The authors stated the subjects were given constant dietary and fluid intakes and were ambulatory but were not permitted to perform vigorous exercise. $Ca^{47}Cl_2$ was administered intravenously in doses of 0.5 to 10 μC. Urine, stools, and serum were analyzed for radioactivity. By the end of the third day of antacid treatment urinary phosphorus excretion had decreased from control levels of 700 mg./day to 40 mg./day. Within one week urinary phosphorus excretion stabilized at less than 40 mg./day (and often undetectable values). Calcium balance became markedly negative as urinary calcium excretion rose to 600 to 750 mg./day (four to six times control values). Approximately twenty grams of calcium were lost in total. Serum calcium concentration remained stable within normal limits until day sixty-seven, when it fell to less than 8.0 mg./100 ml. and the volunteer required calcium supplementation. Hypophosphatemia, increased gastrointestinal absorption of calcium, and debility (anorexia and weakness) also occurred.

In 1968, Lotz, Zisman, and Bartter studied additional data from three normal volunteers, two patients with hypoparathyroidism, and one patient with pseudohypoparathyroidism. They found the following in normal subjects: a rapid, significant decrease in urinary phosphorus excretion, hypercalciuria, hypophosphatemia, increased resorption of skeletal calcium and phosphorus, increased gastrointestinal absorption of calcium, and a state of debility characterized by weakness, anorexia,

and malaise. The results from this study also indicate that these changes can occur in the absence of parathyroid hormone. A significant change in the serum calcium concentration from normal was not noted in these studies of phosphate depletion in man.

H. Other factors that affect calcium excretion

A significant diurnal variation in calcium excretion in man has been reported (Beeson et al., 1979). Under normal conditions the basic pattern includes a rapid rise in calcium excretion to a maximum during late morning, followed by an afternoon decrease and a rise again during the evening. A marked decrease in excretion rate usually occurs at night. Food appears to be the principle factor in determining the diurnal variation. For example, Heaton and Hodgkinson (1963) demonstrated that the sharp morning rise in calcium excretion could be completely abolished when breakfast was withheld. According to Coburn and Massry (1970) there is also a diurnal variation in calcium excretion in the dog. They reported an increase in calcium excretion in the morning, however, no additional information was given.

The ingestion of a variety of nutrients such as glucose, galactose, fructose, and protein has been observed to increase urinary calcium excretion even though GFR was not significantly altered (Lindeman, Adler, Yiengst, & Beard, 1967). For example, glucose ingestion (100 grams) by normal human subjects resulted in increased urinary excretion of calcium during experimentally decreased GFR and therefore filtered load of calcium. These results support the hypothesis that certain nutrients inhibit tubular reabsorption of calcium (Lemann, Lennon, Piering, Prien, & Ricanati, 1970).

Exercise decreases urinary calcium excretion (Heaton and Hodgkinson, 1963). Immobilization in healthy volunteers has been associated with an increased urinary calcium excretion with the excretion maximum attained by the fourth to fifth week (Deitrick, Whedon, & Shorr, 1948).

Calcitonin administration is associated with altered tubular transport of electrolytes but the specific actions are not well defined and are known to be variable in different species (Massry, Friedler, & Coburn, 1973). Thyroid hormone and growth hormone cause increased urinary calcium excretion (Massry et al., 1973). Mineralocorticoid administration (acutely) to both adrenalectomized dogs and normal man has been found to change the relationship of excretion between sodium and calcium by decreasing sodium excretion without exerting any apparent effect on calcium transport (Massry & Coburn, 1963). Acute glucocorticoid administration has no apparent effect on calcium excretion (Massry & Coburn, 1963).

Metabolic acidosis causes increased urinary calcium excretion. The mechanism of this increased urinary calcium excretion is currently being studied (Walser, 1973). Hypercalciuria has not been consistently demonstrated with respiratory acidosis. Findings regarding metabolic alkalosis are not consistent. Information is limited regarding the effects of respiratory alkalosis on calcium excretion but a decrease in calcium excretion has been found in one study (Siggard-Andersen, 1962).

III. EFFECTS OF CATECHOLAMINES ON CALCIUM BALANCE

In 1922 Takeo Inoue observed that subcutaneous injection of epinephrine in normal humans caused an increase in the hourly excretion of calcium, which later decreased (time frame not specified). This increased

calcium excretion was associated with an increase in phosphate excretion. Pincus, Natelson, and Lugovoy (1951) administered subcutaneous epinephrine (0.08 mg./Kg.) to intact fasted rabbits. Serum calcium concentration rose approximately 5 to 15% above control values and serum phosphate concentrations fell approximately 10% below control values.

Kenny (1964) reported a hypercalcemic response in parathyroidectomized rats to isoproterenol and, to a lesser extent, epinephrine and norepinephrine. The hypercalcemia was blocked by the beta-blocking agent nethalide and was not seen in rats with intact parathyroid glands.

Also in 1964, Morey and Kenny studied the effects of epinephrine, norepinephrine, and isoproterenol on urinary calcium and phosphate in both intact and parathyroidectomized rats. Several of each group of rats were treated with the alpha-adrenergic blocking agent phenoxybenzamine prior to catecholamine administration. They found that norepinephrine and epinephrine caused hypercalciuria in both intact and parathyroidectomized rats. Conversely, hypocalciuria was produced by epinephrine in the intact rats treated with the alpha-blocking agent. Isoproterenol had no effect in the intact rat but produced a hypocalciuric response in parathyroidectomized rats. The mechanism of the hypercalciuric response was not determined but a complete dependence on parathyroid function does not seem likely since similar responses were observed in parathyroidectomized rats. GFR was not directly measured but none of the catecholamines increased the urinary creatinine output. Epinephrine produced a varied response in urinary phosphorus excretion in both intact and parathyroidectomized rats. In intact rats isoproterenol produced a marked hypophosphaturia (greater than a seven-

fold decrease in phosphate excretion), while norepinephrine resulted in hyperphosphaturia (significant only at its highest dose of 0.5 mg./Kg.). Parathyroidectomized rats developed hyperphosphaturia in response to norepinephrine, hyperphosphaturia at the highest epinephrine dose of 0.5 mg./Kg., but did not develop marked hypophosphaturia in response to isoproterenol. Pretreatment with the alpha-blocking agent resulted in a hypophosphaturic response to epinephrine. Serum calcium and phosphorus concentrations were also done in this study for comparison with the previous results of Kenny (1964). The serum calcium and phosphorus concentrations were qualitatively the same in both studies.

Data from these studies indicate that catecholamines are associated with hypercalcemia. This hypercalcemia is inhibited by beta-adrenergic blockade and intact parathyroid function. Catecholamines that have alpha-adrenergic effects (such as epinephrine and norepinephrine) are associated with hypercalciuria. This hypercalciuria is inhibited by alpha-adrenergic blockade but occurs in both the presence and absence of parathyroid function. Skrabanek (1977) hypothesized the following in relation to the above data: catecholamines induce bone resorption and hypercalcemia by the beta-adrenergic effect in bone and hypercalciuria by the alpha-adrenergic effect in the kidney.

Catecholamines are associated with a decrease in serum phosphate concentrations. Catecholamines that have alpha-adrenergic effects are associated with hyperphosphaturia. This hyperphosphaturia appears to be dose related, is inhibited by alpha-adrenergic blockade, and is most consistently demonstrated in animals which have had their parathyroid glands removed.

Summary of the Review of the Literature

In summary, the following major points are found in this review of the literature:

A. DOPAMINE

1. Dopamine, a catecholamine, causes vasoconstriction in most vascular beds but selective vasodilation of renal vasculature. This vasodilation most likely results from stimulation of unique dopamine receptors and is dose related.
2. The effects produced by dopamine infusion on renal function are qualitatively comparable between man and dog.
3. Dopamine infusion is associated with increased GFR, ERPF, and sodium excretion. The effect of extracellular volume expansion on the degree of natriuresis caused by dopamine has not been clearly identified in the literature.
4. Dopamine has been associated with increased urinary calcium excretion in a single study. Changes in plasma calcium concentrations were not reported. No other studies were found in the literature that reported changes in plasma or urine calcium concentrations in relation to dopamine infusion.
5. In a single study dopamine was reported to be associated with phosphaturia.

B. CALCIUM

1. Calcium ion concentration in the extracellular fluid depends on a balancing interaction of uptake from the intestine, bone deposition and resorption, and gastrointestinal or urinary excretion.

2. Plasma concentrations of phosphate and calcium are closely related. A balance is maintained in this relationship and can be quantitatively estimated by a solubility product. A significant increase in urinary calcium excretion has been shown to occur during phosphate depletion in man and dog. Limited research about the effect of phosphate depletion on plasma calcium has yielded conflicting results.
3. The fraction of calcium that is filterable averages 0.63. This fraction includes ionized calcium and that complexed with certain organic ions. Protein bound calcium (approximately 40%) is nonfilterable. The majority of filtered calcium is reabsorbed in the proximal tubule and loop of Henle. There has been no report of a transport maximum or tubular secretion of calcium.
4. The renal handling of sodium and calcium are closely related throughout most of the nephron.
5. Vasodilation and increased perfusion pressure are associated with increased calcium excretion in the absence of changes in filtered load of calcium. Calcium excretion rates were correlated with sodium excretion.
6. Extracellular volume expansion with saline results in a decreased renal tubular reabsorption of calcium even when GFR and therefore filtered load of calcium is decreased.
7. Parathyroid hormone enhances tubular calcium reabsorption, initially decreases urinary calcium excretion, and increases urinary phosphate excretion.

8. There is a diurnal variation in calcium excretion in man and dog. This has been shown to be inhibited in man by withholding food.
9. Other factors, including certain nutrients, hormones, acid-base disturbances, and exercise can also affect urinary calcium excretion.

C. CATECHOLAMINES

1. Epinephrine, isoproterenol, and norepinephrine have been associated with hypercalcemia. This hypercalcemia is blocked by beta-blocking agents and is not consistently seen in animals with intact parathyroid gland function.
2. Epinephrine and norepinephrine (which have alpna-adrenergic effects) have been associated with hypercalciuria and hyperphosphaturia in both humans and experimental animals. The hypercalciuria is inhibited by alpha-adrenergic blockade but occurs in both the presence and absence of parathyroid gland function. The hyperphosphaturia appears to be dose related, is inhibited by alpha-adrenergic blockade and is most consistently demonstrated in animals which have had their parathyroid glands removed.

Statement of the Problem

Dopamine is a drug commonly used in the clinical setting. Many of the effects of dopamine on hemodynamic and renal function in both man and dog have been extensively studied. However, little has been reported of the effect of dopamine on plasma and urine calcium concentrations. Dopamine has been associated with increased urinary calcium excretion in a single study. Other catecholamines have been associated with significant changes in plasma and urinary calcium concentrations. There is evidence that dopamine may cause hyperphosphaturia. Calcium and phosphate balance are so closely related that a change in phosphate balance may be expected to produce some degree of change in calcium balance. Changes in extracellular calcium concentration may induce changes in contraction of cardiac, skeletal, and smooth muscle, nervous tissue excitability, and cerebral function. Thus, it seems reasonable to evaluate the effects of dopamine on calcium concentration in plasma and urine.

Three questions were addressed in this study:

1. What are the magnitude and time course of any changes in plasma calcium concentrations in relation to dopamine infusion?
2. What are the magnitude and time course of any changes in urinary calcium concentrations in relation to dopamine infusion?
3. What are the magnitude and time course of any changes in urinary calcium excretion in relation to dopamine infusion?

Nursing Implications

The role of the professional nurse has expanded as scientific knowledge has advanced. Today nurses are responsible for administering powerful drugs, assessing the intended therapeutic effect, and monitoring signs and symptoms related to side effects of drug therapy. In addition, nurses must often intervene to support physiological processes which return body chemistries to normal. Appropriate nursing assessment and intervention are particularly important in the critical care setting where physiological alterations are commonly severe and occur rapidly. Potent drugs are also commonly used in combination in the critical care setting.

Dopamine is a drug commonly used in the critical care setting for the management of patients with conditions such as shock and congestive heart failure. Dopamine may be used for a period as short as minutes or hours, or for as long as many days. There is evidence to suggest that dopamine may alter calcium balance. However, there is a paucity of specific research to determine the effect of dopamine on plasma and urinary calcium concentration. This information may be critically important since changes in extracellular calcium ion concentration may affect, for example, excitability of nervous tissue, renal function, cerebral function, skeletal stability, and contractility of cardiac, smooth, and skeletal muscle (Beeson et al., 1979). Therefore, nurses need to be aware of any significant effect of dopamine on calcium balance. This information is not currently available.

The purpose of this study was to determine the effect of dopamine on the plasma and urine concentration of calcium and thereby increase the base of knowledge available to guide nursing care.

CHAPTER II

METHODS

Protocol

In this study standard clearance techniques were used in eight mongrel dogs weighing between 18 and 33 Kg. Access to water was unrestricted but food was withheld from the dogs approximately 12 to 14 hours prior to the experiment. Experiments were conducted at the same time of day to minimize any effect of diurnal variation. Sodium pentobarbital (30 mg./Kg. of body weight) was used for anesthesia and endotracheal tubes were placed in the trachea. A catheter was placed in a femoral artery and used for continuous blood pressure monitoring as well as to obtain samples of blood. A catheter was placed in a femoral vein and used for infusion of maintenance fluid and dopamine.

Both ureters were ligated and cannulated following a midline abdominal incision. The abdominal incision was then closed by suture and covered by gauze saturated with isotonic saline to minimize insensible fluid loss.

Isotonic saline (250 ml.) was initially infused over 25 to 30 minutes to replace surgical losses. This was followed by an maintenance infusion (5% dextrose in a 0.2% sodium chloride solution with 1.75 gm. of inulin per liter) started at 2 ml./minute. The maintenance infusion was continued throughout the experiment and was delivered by a Harvard Infusion Pump that was calibrated before the experiment.

Clearance periods were started between 30 and 45 minutes after the maintenance fluid infusion was begun. The clearance periods continued from 20 to 60 minutes, depending on urine flow. At the midpoint of each clearance period 20 ml. of blood was withdrawn from the arterial

catheter, placed in heparinized tubes, and immediately centrifuged. The plasma was separated and refrigerated.

After three control clearance periods were completed, dopamine dissolved in isotonic saline was started. Dopamine in a dose of 1.05 µg./Kg. · minute was given to three dogs. Dopamine in a dose of 10 µg./Kg. · minute was given to three other dogs. Two dogs did not receive dopamine and served as control animals. A Harvard Infusion Pump infused the dopamine at 0.3 to 0.5 ml./minute. Body weight of the dog determined the actual rate of infusion. An equivalent volume of saline (without dopamine) was infused into the control dogs. During dopamine infusion four clearance periods were completed. Dopamine infusion was then stopped and three or four post-infusion clearance periods were completed.

The dog was sacrificed at the conclusion of the experiment. The kidneys were removed, weighed, and examined for gross abnormalities.

Chemical Methods

Standard spectrophotometric methods were used for analysis of blood and urine (Sunderman & Sunderman, 1969; and Tietz, 1976). Samples were read using a spectrophotometer (Beckman, model 25). See Appendices for a detailed discussion of the methods.

Analysis of Results

Results in the following categories will be discussed:

1. Urine flow
2. Glomerular filtration rate
3. Plasma calcium concentration
4. Filtered load of calcium
5. Clearance of calcium

6. Excretion rate of calcium

7. Fractional excretion of calcium

Comparisons were made between animals receiving no dopamine (controls) and those receiving 1.05 and 10 μg./Kg. · minute. A t-test was used to determine if differences between means are significant.

CHAPTER III

RESULTS AND DISCUSSION

Results

Results in the following categories are discussed:

1. Urine flow
2. Glomerular filtration rate
3. Plasma calcium concentration
4. Filtered load of calcium
5. Clearance of calcium
6. Excretion rate of calcium
7. Transport of calcium
8. Fractional excretion of calcium

Comparisons are made between three groups of animals: those (dogs 4 and 9) receiving no dopamine (controls), those dogs (2, 3, and 8) receiving dopamine at 1.05 µg./Kg. · minute (small dose) and those dogs (5, 6, and 7) receiving dopamine at 10 µg./Kg. · minute (moderate dose). A t-test was used to determine if differences between means of control periods ("C") and experimental periods ("D") in each of the three groups were statistically significant. Plasma inulin concentrations, integral to accurate GFR measurement, did not significantly change during the course of any individual experiment. Table 1 contains a summary of the results from all experiments.

Urine Flow

Urine flow did not vary in a consistent pattern during the experiments. Urine flow in the control dogs (4 and 9) ranged from 0.1 ml./minute to 0.3 ml./minute per one hundred grams of kidney weight.

Urine flows in dogs receiving dopamine at 1.05 µg./Kg. · minute ranged from 0.1 ml./minute to 1.5 ml./minute per one hundred grams of

kidney weight. Urine flow in dog 8 increased sharply before dopamine infusion, fell to its lowest value during dopamine infusion, and increased sharply again after dopamine infusion was stopped.

Urine flows in dogs receiving dopamine infusion at 10 µg./Kg. · minute ranged from approximately 0.1 ml./minute to 0.5 ml./minute per one hundred grams of kidney (Table 1).

Glomerular Filtration Rate (GFR)

Glomerular filtration rate increased in all animals during the course of the experiments. In control animals mean values of GFR ranged from 26.0 ml./minute ± 9.4 ml./minute to 113.0 ml./minute ± 7.6 ml./minute per one hundred grams of kidney weight. Glomerular filtration rate increased in both control dogs during the experimental periods equivalent to dopamine infusion and continued to increase in the post-infusion periods. Glomerular filtration rate increased by an average of 157% of control values during the experimental period and 181% of control values during the post-infusion period.

Dogs receiving dopamine at a rate of 1.05 µg./Kg. · minute showed a statistically significant increase in GFR compared to that observed during control periods ($p < 0.05$). Mean values for GFR ranged from 39.5 ml./minute ± 5.8 ml./minute to 60.8 ml./minute ± 15.2 ml./minute per one hundred grams kidney weight from control to post-infusion periods. This increase in GFR occurred in gradual increments. Mean GFR values during the experimental period were an average of 127% of control values. Except in one case (dog 3), the mean values for GFR continued to increase to an average of 139% of control values during the post-infusion period (Table 1).

Glomerular filtration rate also increased over control values in dogs receiving dopamine at a rate of 10 µg./Kg. · minute. Values for GFR during the experimental period were an average of 156% of control values. These increases in GFR were not statistically significant. Glomerular filtration rates during the post-infusion period were consistently greater (average value of 181% of control) than those observed during dopamine infusion.

Plasma Calcium Concentrations (P_{Ca})

Plasma calcium concentrations appeared to remain stable during the course of the experiments. Plasma calcium concentrations ranged from 4.3 µEq./ml. to 5.1 µEq./ml. These values for P_{Ca} are consistent with the range of P_{Ca} values (4.7 mEq./L. to 6.1 mEq./L.) found in the normal dog (Dittmer, 1961). There were no statistically significant differences in the mean values for plasma calcium concentration between control and experimental periods in any animal although in general a slight decrease in P_{Ca} did occur during the course of the experiments.

Filtered Load of Calcium (L_{Ca})

Filtered load of calcium increased over the course of the experiments in all animals. The mean values for filtered load of calcium ranged from a low value of 79.3 µEq./minute ± 27.4 (dog 4) and 320.0 µEq./minute ± 11.5 (dog 9) per one hundred grams of kidney weight. The L_{Ca} increased between the control period and the experimental period in every animal. The amount of increase in L_{Ca} was variable in individual animals. Values for L_{Ca} were increased by an average of 124% of control in animals receiving dopamine at 1.05 µg./Kg. · minute. Values for L_{Ca} in both control animals and animals receiving dopamine at

10 µg./Kg. · minute averaged 153% of control during the experimental period. However, only the increase in L_{Ca} during the experimental period in dogs receiving dopamine at 1.05 µg./Kg. · minute was statistically significant ($p < 0.05$). In all but one experiment (dog 3) the L_{Ca} continued to increase in the post-infusion period.

Calcium Clearance (C_{Ca})

The mean values for C_{Ca} did not vary in a consistent pattern between the control and experimental periods in either the control animals or those receiving dopamine. The mean clearance of calcium ranged between 0.06 ml./minute ± 0.002 and 1.29 ml./minute ± 0.66 per one hundred grams of kidney weight. The mean value of C_{Ca} in the control animals during the experimental period was 66% of the value during the control period in dog 4 and 307% of the value during the control period in dog 9. The mean C_{Ca} in animals receiving dopamine at 1.05 µg./Kg. · minute decreased in two animals (dogs 2 and 8) to an average of 71% of control values, while C_{Ca} increased in one animal (dog 3) to 113% of control values. The mean C_{Ca} increased in all three animals receiving dopamine at 10 µg./Kg. · minute. This increase ranged between 106% and 190% of the control value. The difference between means in control and experimental periods was not statistically significant.

During the post-infusion period there was a decrease in C_{Ca} in all experiments except one (dog 9). Values for C_{Ca} during the post-infusion period in all dogs except 9 averaged 55% of control. In dog 9 the value for C_{Ca} during the post-infusion period decreased below that for the experimental period but remained 183% of the control value.

Excretion Rate of Calcium (E_{Ca})

The mean excretion rate of calcium did not vary in a predictable

manner throughout the course of the experiments. Mean values for E_{Ca} ranged from 0.2 µEq./minute ± 0.02 µEq./minute to 5.7 µEq./minute ± 2.8 µEq./minute per one hundred grams of kidney weight. The mean value of E_{Ca} in the control animals during the experimental period was 64% of the control value in dog 4 and 298% of the control value in dog 9. The mean value of E_{Ca} in animals receiving dopamine at 1.05 µg./Kg. · minute decreased in two animals (dogs 2 and 8) to an average of 69% of control values, while E_{Ca} increased in one animal (dog 3) to 111% of control values. In animals receiving dopamine at 10 µg./Kg. · minute the mean E_{Ca} equaled the control value in one dog (5) and increased to an average of 190% of control in two dogs (6 and 7). No pattern was found between the excretion rate of calcium and any particular dose of dopamine.

There was a decrease in E_{Ca} during the post-infusion period in all experiments except one control (dog 9). In all animals except dog 9 values for E_{Ca} during the post-infusion period averaged 52% of control. In dog 9 the value for E_{Ca} during the post-infusion period decreased below that for the experimental period but was still 173% of the control values.

Reabsorption of Calcium (T_{Ca})

Reabsorption of calcium generally increased throughout the course of the experiments. The mean values for T_{Ca} ranged from 77.0 µEq./minute ± 27.2 µEq./minute (dog 4) to 319 µEq./minute ± 11.2 Eq./minute (dog 9) per one hundred grams of kidney weight. Calcium reabsorption increased in every animal between the control and experimental periods. In all dogs except 7 and 9 this increase in T_{Ca} occurred in gradual increments

with experimental values averaging 127% of control. In dogs 7 and 9 the increase in T_{Ca} appeared to be abrupt with mean values averaging 166% (dog 9) and 211% (dog 7) of control. The difference between means in control and experimental periods was statistically significant only in the dogs receiving dopamine at 1.05 µg./Kg. · minute ($p < 0.05$).

Calcium reabsorption continued to increase in gradual increments during the post-infusion period in all dogs except one (dog 3) with values averaging 161% of control. In dog 3 T_{Ca} decreased in comparison to experimental period values but was still 120% of control.

Fractional Excretion of Calcium (FE_{Ca})

Fractional excretion of calcium generally decreased throughout the course of the experiments. Mean values for FE_{Ca} ranged from 0.0297 ± 0.0150 to 0.0006 ± 0.0001. Fractional excretion of calcium changed in opposite directions in control animals (dogs 4 and 9) during the experimental period. The mean value of FE_{Ca} in dog 4 was 43% of control while that of dog 9 was 159% of control. Mean values for FE_{Ca} during the experimental period decreased to an average of 65% of control in dogs receiving dopamine at 1.05 µg./Kg. · minute. In dogs receiving dopamine at 10 µg./Kg. · minute mean values for FE_{Ca} decreased to 92% of control in two animals (dogs 5 and 7), while FE_{Ca} rose to 133% of control in one dog (dog 6). However, the differences between means in control and experimental periods were not statistically significant. In all animals post-infusion values for FE_{Ca} decreased below values for both the experimental and control periods.

Discussion

In general there were no statistically significant changes in plasma and urine concentrations of calcium following dopamine infusion

at rates of 1.05 µg./Kg. · minute or 10 µg./Kg. · minute.

The GFR increased in all animals during the course of the experiments. Glomerular filtration rate increased over control values in both experimental and post-infusion periods. In addition, GFR continued to be increased over both control and experimental values during the post-infusion period in all experiments except one (dog 3). While an increase in GFR is a predictable effect of dopamine (McDonald et al., 1964, and Meyer et al., 1967), the increase in GFR in the control animals (Table 1) places in question the interpretation of increased GFR resulting from drug effect alone.

The increase in GFR may have resulted from a slight increase in extracellular fluid volume necessitated by the experimental design (a standard clearance technique) that required the infusion of a small to moderate amount of fluid for dopamine administration and fluid maintenance. Extracellular volume expansion (particularly with isotonic saline) has been reported to increase calcium excretion when sodium excretion was enhanced (Massry et al., 1967). Even though plasma and urine sodium concentrations were not measured it is probable that a degree of extracellular volume expansion occurred during these present experiments.

The maintenance fluid used in this study was 5% dextrose in a solution of 0.2% sodium chloride. This was infused at a rate of 2 ml./minute. If the fluid infusion had been isotonic saline the extracellular volume of the dogs would have been expanded by a mean value of 17% (SD ± 5%). Insensible loss is not included in this calculation. However, this amount of volume expansion is unlikely because of the following considerations. (1) 5% dextrose in a solution of 0.2% sodium

chloride will not remain in the extracellular fluid compartment alone. The dextrose is transported intracellularly to be metabolized and water follows osmotically. (2) The internal tissue exposure inherent in the surgical procedure of the experiments can be anticipated to result in considerable insensible fluid loss. (3) The physical trauma inherent in the experimental procedure which involved catheterizing ureters and manipulating peritoneum may result in some shift of fluid to sites of damaged tissue, "third-spacing". Also, since GFR continued to increase through the experiments, in all animals, it may be that dogs are particularly sensitive to volume expansion. As a result of these other considerations, extracellular volume expansion was undoubtedly much less than 17% but may still have been the cause, in part, of the increased GFR seen throughout the experiments. As noted above, the marked increase in GFR throughout the experiments seen in the control dogs that did not receive dopamine makes it impossible to assume that dopamine is the sole cause of the increase in GFR seen in the dogs receiving the drug.

The dopamine doses used in this study were chosen to begin development of a dopamine dose response curve for plasma and urine calcium concentrations. Intravenous dopamine infusion at a rate of 1.05 µg./Kg. · minute corresponds to a low dose of the drug while 10 µg./Kg. · minute corresponds to a moderate dose (Ebie, 1964). In a single study the 10 µg./Kg. · minute dose has been reported to result in a significant (up to 400%) increase in calcium excretion in association with increased sodium excretion when GFR is increased acutely without extracellular fluid volume expansion (Massry & Kleeman, 1972). In this same study

similar acute increments in GFR produced from extracellular volume expansion with saline infusion were associated with significantly greater increases in sodium and calcium excretion. This 10 ug./Kg. · minute dose of dopamine is also comparable to a dose used by Cuche et al. (1976) which was associated with a phosphaturic effect independent of changes in parathyroid hormone, calcitonin, renal blood flow, and sodium excretion. An effect on urine or plasma calcium concentration might also then be expected at this dose of dopamine because of the reciprocal relationship of phosphate and calcium relative to their solubility products (Massry et al., 1973).

According to the findings of Massry and Kleeman (1972) the use of dopamine, and the increase in GFR with or without extracellular fluid volume expansion would be expected to result in a significant increase in calcium excretion. This effect was not seen in the present experiments. Of interest in the present experiments is the fact that calcium fractional excretion decreasedin general throughout the course of the experiments in all dogs receiving dopamine except one (dog 6) while tubular reabsorption of calcium generally increased. However, the changes were not statistically significant. As noted above, the decrease in FE_{Ca} and increase in T_{Ca} occurred in the setting of a marked increase in GFR. These findings do not support the conclusions of Massry and Kleeman (1972) or, indirectly, Cuche et al. (1976). One might conclude that dopamine may have contributed to the increase in calcium reabsorption. However, the variability of calcium fractional excretion and reabsorption in the control animals makes it impossible to conclude that the increase in calcium reabsorption was an effect of dopamine alone.

Initially this study proposed to address the magnitude and time course of any changes in plasma calcium concentration, urinary calcium concentration, and urinary calcium excretion in relation to dopamine infusion. As noted above, no statistically significant changes occurred consistently in plasma or urine calcium concentrations at either of the two dopamine doses used.

LEGEND FOR TABLE 1

C is control period

D is drug infusion period

P is post-infusion period

N = 3 unless noted

* = N of 2

** = N of 1

$\dot{V}_U$ Urine flow rate

GFR Glomerular filtration rate

P_{Ca} Plasma calcium concentration

L_{Ca} Filtered load of calcium

C_{Ca} Clearance of calcium

E_{Ca} Excretion rate of calcium

T_{Ca} Transport or reabsorptive rate of calcium

FE_{Ca} Fractional excretion of calcium

P_{In} Plasma inulin concentration

Values for $\dot{V}_U$, GFR, L_{Ca}, C_{Ca}, E_{Ca}, T_{Ca}, are per 100 grams of kidney weight.

TABLE 1 (Continued)

		CONTROL		DOPAMINE AT 1.05 µg./Kg. . MINUTE			DOPAMINE AT 10 µg./Kg. . MINUTE		
		Dog 4	Dog 9	Dog 2	Dog 3	Dog 8	Dog 5	Dog 6	Dog 7
P_{Ca} µEq/ml	C $\overline{X}$	4.90	4.80	5.10	4.80	4.50	4.90	5.10	4.70 (**)
	SD	±0.10	±0	±0.10	±0	±0.10	±0.05	±0 (*)	±0
	D $\overline{X}$	4.70	4.60	4.90	4.70	4.40	4.70	5.10	4.70
	SD	±0	±0.05	±0.06 (*)	±0.05	±0.20 (*)	±0.10 (*)	±0.07	±0.05 (*)
	P $\overline{X}$	4.60	4.50	4.70	4.60	4.30	4.60	4.90	4.50
	SD	±0.05	±0.10	±0.10	±0.05	±0.10	±0.10	±0.10	±0
L_{Ca} µEq/min	C $\overline{X}$	79.3	176.3	131.0	119.4	122.1	149.7	129.3	93.8 (**)
	SD	±27.4	±70.9	±41.5	±17.5	±7.7	±49.5	±22.2 (*)	±0
	D $\overline{X}$	106.2	292.6	164.0	157.9	138.8	182.4	172.0	197.4
	SD	±24.8	±24.2	±43.4 (*)	±18.3	±4.6 (*)	±84.5 (*)	±12.0	±10.4 (*)
	P $\overline{X}$	127.0	320.0	179.3	143.0	150.2	222.7	198.7	201.6
	SD	±31.0	±11.5	±39.5	±20.3	±19.1	±93.1	±3.6	±14.9

TABLE 1 (Continued)

		CONTROL		DOPAMINE AT 1.05 µg./Kg. · MINUTE			DOPAMINE AT 10 µg./Kg. · MINUTE		
		Dog 4	Dog 9	Dog 2	Dog 3	Dog 8	Dog 5	Dog 6	Dog 7
C_{Ca} ml/min	C $\bar{X}$	0.47	0.10	0.13	0.13	1.29	0.13	0.08	0.17 (**)
	SD	±0.05	±0.02	±0.03	±0.02	±0.66	±0.04	±0.01 (*)	±0
	D $\bar{X}$	0.31	0.31	0.11	0.15	0.76	0.14	0.15	0.32
	SD	±0.12	±0.12	±0.04 (*)	±0.03	±0.10 (*)	±0.01 (*)	±0.06	±0.08 (*)
	P $\bar{X}$	0.15	0.19	0.06	0.12	0.69	0.09	0.04	0.09
	SD	±0.05	±0.08	±0	±0.02	±0.11	±0.01	±0.01	±0.02
E_{Ca} µEq/min	C $\bar{X}$	2.30	0.50	0.70	0.60	5.70	0.60	0.40	0.80 (**)
	±SD	±0.20	±0.07	±0.20	±0.10	±2.80	±0.20	±0.06 (*)	±0
	D $\bar{X}$	1.50	1.40	0.50	0.70	3.30	0.60	0.80	1.50
	SD	±0.50	±0.60	±0.20 (*)	±0.20	±0.40 (*)	±0.03 (*)	±0.30	±0.40 (*)
	P $\bar{X}$	0.70	0.80	0.30	0.50	3.00	0.40	0.20	0.40
	SD	±0.20	±0.30	±0.01	±0.08	±0.40	±0.04	±0.02	±0.09

TABLE 1 (Continued)

		CONTROL		DOPAMINE 1.05 µg./Kg. · MINUTE			DOPAMINE 10 µg./Kg. · MINUTE		
		Dog 4	Dog 9	Dog 2	Dog 3	Dog 8	Dog 5	Dog 6	Dog 7
T_{Ca} µEq/min	C $\overline{X}$	77.0	175.8	130.3	118.7	116.3	149.1	128.9	93.0 (**)
	SD	±27.2	±70.9	±41.4	±17.4	±8.4	±49.3	±22.2 (*)	±0
	D $\overline{X}$	104.8	291.2	163.4	157.2	135.5	181.7	171.2	195.9
	SD	±24.2	±24.4	±43.2 (*)	±18.2	±4.4 (*)	±84.5 (*)	±11.6	±10.7 (*)
	P $\overline{X}$	126.3	319.1	179.1	142.4	147.3	222.3	198.5	201.2
	SD	±30.9	±11.2	±39.4	±20.4	±18.7	±93.0	±3.6	±14.8
FE_{Ca}	C $\overline{X}$	0.0196	0.0020	0.0034	0.0034	0.0297	0.0028	0.0020	0.0052 (**)
	SD	±0.0058	±0.0009	±0.0004	±0.0005	±0.0150	±0.0005	±0.0006 (*)	±0
	D $\overline{X}$	0.0085	0.0031	0.0021	0.0028	0.0150	0.0025	0.0027	0.0048
	SD	0.0014	±0.0014	±0.0003 (*)	±0.0006	±0.0012 (*)	±0.0009 (*)	±0.0010	±0.0015 (*)
	P $\overline{X}$	0.0034	0.0016	0.0010	0.0024	0.0124	0.0012	0.0006	0.0012
	SD	±0.0008	±0.0006	±0.0002	±0.0006	±0.0001	±0.0004	±0.0001	±0.0002

TABLE 1 (Continued)

		CONTROL		DOPAMINE 1.05 µg./Kg. . MINUTE			DOPAMINE 10 µg./Kg. . MINUTE		
		Dog 4	Dog 9	Dog 2	Dog 3	Dog 8	Dog 5	Dog 6	Dog 7
P_{In} mg%	C $\overline{X}$	7.10	3.70	7.10	4.90	7.00	7.00	4.50 (**)	2.60
	SD	±1.50	±0.60	±0.10	±0.60	±0.90	±1.00	±0.50 (*)	±0
	D $\overline{X}$	6.30	3.20	5.50	5.60	8.40	6.30	5.30	3.40
	SD	±0.10	±0.40	±0.40 (*)	±0.40	±0.40 (*)	±1.40 (*)	±0.10	±0.20 (*)
	P $\overline{X}$	6.50	3.10	6.00	6.30	7.70	5.70	4.80	3.10
	SD	±0.60	±0.40	±0.60	±0.60	±2.10	±1.00	±0.20	±0.40

TABLE 1. SUMMARY OF EXPERIMENTAL RESULTS FROM CONTROL DOGS, DOGS RECEIVING DOPAMINE AT 1.05 µg./Kg. · MINUTE, AND DOGS RECEIVING DOPAMINE AT 10 µg./Kg. · MINUTE.

		CONTROL		DOPAMINE AT 1.05 µg./Kg. · MINUTE			DOPAMINE AT 10 µg./Kg. · MINUTE		
		Dog 4	Dog 9	Dog 2	Dog 3	Dog 8	Dog 5	Dog 6	Dog 7
$\dot{V}_U$ ml/min	C $\bar{X}$	0.30	0.10	0.10	0.20	1.00	0.10	0.20	0.20 (**)
	SD	±0.01	±0.02	±0.03	±0.01	±0.36	±0.01	±0.02 (*)	±0
	D $\bar{X}$	0.20	0.20	0.20	0.30	0.70	0.20	0.30	0.50
	SD	±0.06	±0.02	±0.02 (*)	±0.03	±0.12 (*)	±0.02 (*)	±0.01	±0.03 (*)
	P $\bar{X}$	0.20	0.30	0.20	0.40	1.30	0.10	0.20	0.30
	SD	±0.06	±0.02	±0.01	±0.03	±0.24	±0.02	±0.01	±0.02
GFR ml/min	C $\bar{X}$	26.0	58.3	40.6	39.5	43.4	48.3	40.2	31.7 (**)
	SD	±9.4	±23.5	±13.0	±5.8	±3.7	±16.4	±6.9 (*)	±0
	D $\bar{X}$	35.9	101.8	52.3	53.0	50.6	61.1	54.1	66.2
	SD	±8.4	±9.0	±13.4 (*)	±6.3	±4.0 (*)	±27.6 (*)	±3.0	±4.2 (*)
	P $\bar{X}$	43.6	113.0	60.8	49.0	55.6	77.4	64.8	71.1
	SD	±11.1	±7.6	±15.2	±7.2	±8.9	±34.5	±0.8	±5.3

CHAPTER IV

SUMMARY, CONCLUSIONS, AND SUGGESTIONS FOR FURTHER STUDY

Dopamine is a drug commonly used in the care of acutely ill patients in the clinical setting. However, little has been reported of the effect of dopamine on plasma and urine calcium concentrations. Dopamine has been associated with increased urinary calcium excretion in a single study (Massry & Kleeman, 1972). Other catecholamines have been associated with significant changes in plasma and urinary calcium concentrations. There is evidence that dopamine may cause hyperphosphaturia (Cuche et al., 1976). Calcium and phosphate balance are so closely related that a change in phosphate balance may be expected to produce some reciprocal degree of change in calcium balance.

Dopamine was given intravenously to six dogs in this study to evaluate the effect of this drug on plasma and urine calcium concentrations. Three dogs received dopamine at 1.05 µg./Kg. · minute, three dogs received dopamine at 10 µg./Kg. · minute, while two dogs, used as controls, were given equivalent amounts of 5% dextrose in a solution of 0.2% sodium chloride and isotonic saline without dopamine. The dopamine doses used in the study were chosen to begin development of a dopamine dose response curve in relation to plasma and urine calcium concentrations.

In general the results of study did not show statistically significant changes in plasma and urine concentrations following dopamine infusion at the doses noted above. Glomerular filtration rate increased in all animals, including controls, throughout the course of the experiments. As a result, it is not possible to assume that dopamine is the

sole cause of the increasedGFR in the dogs receiving the drug. The increase in GFR may have resulted from a slight increase in extracellular fluid volume necessitated by the experimental design. However, the extracellular fluid volume expansion may be considered to be minimal because of distribution of the intravenous maintenance fluid to all body fluid compartments, and uncalculable but significant insensible fluid loss and fluid shift to damaged tissue.

According to the findings of Massry and Kleeman (1972) the use of dopamine, and the increase in GFR with or without extracellular fluid volume expansion would be expected to result in a significant increase in calcium excretion. This effect was not seen in the present experiments and thus it is not possible to support the conclusions of Massry and Kleeman (1972) or, indirectly, Cuche et al., (1976). Of interest in the present experiments, however, is the fact that fractional excretion of calcium decreased throughout the course of the experiments in all but one dog receiving dopamine while tubular reabsorption of calcium generally increased. This decrease was not statistically significant. One might conclude that dopamine may have contributed to the increase in calcium reabsorption. However, the variability of fractional excretion and reabsorption of calcium in the control animals makes it impossible to conclude that the increase in calcium reabsorption is an effect of dopamine alone.

If further studies are carried out calcium loading of the experimental animal prior to clearance measurements might be a useful technique to determine whether changes in transport maximum of calcium actually occur. The standard clearance technique used in this study

is a good screening technique but preliminary calcium loading would help make drug effects on calcium more visible. One disadvantage of the clearance technique is the difficulty of not overloading the experimental animal with fluid. In addition, using increased doses of dopamine might make the drug effect on calcium more visible.

The expanded role of the professional nurse today includes responsibility for administering potent drugs such as dopamine, assessing the intended therapeutic effect, and monitoring signs and symptoms related to side effects of drug therapy. Changes in extracellular calcium concentration may induce changes in such critical functions as contraction of cardiac, skeletal, and smooth muscle, nervous tissue excitability and cerebral function. Therefore nurses need to be aware of any significant effect on calcium balance.

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APPENDIX A

CHEMICAL METHOD: INULIN

Inulin Determination (Method of Heyrovsky)

Procedure for Plasma (1:4 dilution)

1. Pipette 1 ml. of plasma into a test tube.
2. Add 3 ml. of 20% trichloroacetic acid, cover, and mix by shaking.
3. Allow to stand for 5 minutes, then centrifuge at full speed for 10 minutes.
4. Place 1 ml. of the clear supernatant in a clean test tube. All samples are done in duplicate.
5. Add 0.2 ml. of indole-3-acetic acid (500 mg. in 100 ml. of 95% ethanol).
6. Add 7 ml. of 37% hydrochloric acid, cover, mix by shaking.
7. Place in a 37^{o}C water bath for exactly one hour.
8. Remove from water bath, cool under running tap water.
9. Read in a spectrophotometer at 528 nm. absorbance. Set blank at zero.

Procedure for Urine

Urine at 1:100 or 1:150 dilution with deionized water may be used. Treat as for plasma beginning at step 4.

Standards

Standards at 1, 2, 5, 7.5, and 10 mg./100 ml. solutions are made by diluting the inulin stock standard solution (50 mg./100 ml.) with deionized water. Duplicate samples are treated as for plasma beginning at step 4.

Inulin Determination (continued)

Principle

When inulin is treated with indole-3-acetic acid and concentrated hydrochloric acid at a controlled temperature a purple color develops. Inulin is hydrolyzed to fructose, forming the purple complex, by the combination of heat and acid. This method is sensitive in the range of 0.01 to 0.1 mg./ml. (Sunderman & Sunderman, 1969).

APPENDIX B

CHEMICAL METHOD: CALCIUM

Calcium Determination by Precipitation with Chloranilic Acid

Procedure for Plasma

1. Pipette 2.0 ml. of plasma (heparinized) into a 15 ml. conical centrifuge tube in duplicate.
2. Add forcefully to all tubes 1 ml. of saturated sodium chloranilate (6.13 g. of sodium chloranilate in 500 ml. of deionized water, shake to saturate, filter).
3. Place tubes into a 37°C water bath for at least 3 hours.
4. Centrifuge for 10 minutes at approximately 2000 rpm, decant the supernatant immediately, and drain tubes for approximately 2 minutes. Wipe the mouth of the tube to remove excess chloranilate.
5. Add 1 drop of isopropyl alcohol, 50% (v/v), to each tube and break up the precipitate by tapping the tube or with a Vortex mixer. Wash the precipitate with 6 to 7 ml. of 50% isopropyl alcohol.
6. Centrifuge and drain tubes of filter paper for approximately 2 minutes; wipe the mouth of the tube dry.
7. Add 1 drop of EDTA (dissolve 25 g. of tetrasodium ethylene-diaminetetraacetate in deionized water and dilute to 500 ml.) to the precipitate and break up the precipitate as outlined in step 5.
8. Add exactly 6 ml. of EDTA to each tube.
9. Allow all tubes to stand for approximately 10 minutes, then read at 520 nm. against an EDTA blank. The color is stable.

Calcium Determination (continued)

Procedure for Urine

Pipette 2.0 ml. of urine into a 15 ml. conical centrifuge tube in duplicate and proceed as for plasma from step 2.

Standards

Standards of 1, 2, 4, 6, 8, and 10 mEq./100 ml. solutions are made by diluting the calcium stock standard with deionized water. The stock standard is made by placing 1 g. of dried calcium carbonate, AR, into a 1000 ml. volumetric flask, adding approximately 9 ml. of deionized water and 1 ml. of concentrated HCL. Shake until dissolved and fill with deionized water to volume. The solution is stable and contains 20 mEq. Ca^{++}/liter.

Principle

Addition of a saturated solution of sodium chloranilate to the experimental sample results in precipitation of calcium as calcium chloranilate. Excess chloranilic acid is washed away from the precipitate with isopropyl alcohol. The precipitate is then treated with EDTA to chelate with calcium and release chloranilic acid which is colored and can be measured in a spectrophotometer (Tietz, 1976).

Ca^{++} + Chloranilate $\longrightarrow$ Ca^{++} Chloranilate $\downarrow$

CaChloranilate + EDTA $\longrightarrow$ CaEDTA + Chloranilic Acid

AN ABSTRACT OF THE THESIS OF

NANCY J. BINDER

For the MASTER OF NURSING

Date of Receiving this Degree: June 12, 1981

Title: CHANGES IN PLASMA AND URINE CALCIUM CONCENTRATIONS INDUCED BY DOPAMINE

Approved: _____
Jack L. Keyes, Ph.D., Thesis Advisor

Dopamine is a drug commonly used in the clinical setting. Dopamine has been associated with increased urinary calcium excretion in a single study. Other studies support the theoretical possibility of such an effect.

Dopamine was given intravenously to six dogs in this study to evaluate the effect of the drug on plasma and urine calcium concentrations. Three dogs received dopamine at 1.05 µg./Kg. · minute, three dogs received dopamine at 10 µg./Kg. · minute, and two dogs (controls) were given equivalent fluid without dopamine.

In general the results of this study did not show statistically significant changes in plasma and urine concentrations following dopamine infusion at the doses noted above. Glomerular filtration rate increased in all animals (including controls) throughout the course of the experiments. As a result, it is not possible to assume that dopamine is the sole cause of the increased GFR in the dogs receiving the

ABSTRACT OF THESIS CONTINUED

drug. Increased GFR with or without extracellular fluid volume expansion would be expected to result in a significant increase in calcium excretion. This effect was not seen in the present experiments.

Fractional excretion of calcium decreased throughout the course of the experiments in all but one dog receiving dopamine. Tubular reabsorption of calcium also increased. However, variability of fractional excretion and reabsorption of calcium in the control animals makes it impossible to conclude that the increase in calcium reabsorption was an effect of dopamine alone.