RENAL PROSTAGLANDINS
AND
RELATED CLINICAL DISORDERS

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I. HISTORICAL INTRODUCTION

Prostaglandins are a ubiquitous group of unsaturated fatty acids with widely varying physiological effects. Kurzrok and Lieb (1) while working with artificial insemination in 1930 noted that when semen was injected into the uterine cavity that it often was expelled promptly. They subsequently extended this observation by conducting in vitro experiments and noting that semen may cause either contraction or relaxation of a uterine strip. Though in retrospect they probably were describing the effects of prostaglandins, their conclusions were simply that certain types of sterility may be due to an unknown factor in the semen. Subsequently in 1933 Goldblatt (2) and in 1934 von Euler (3) isolated then an unknown "active principle" from the prostate secretions of adult males as well as from seminal vesicle fluid of sheep. von Euler (3) further gave a detailed account of his methods, and based on his extraction techniques, he concluded he was examining a fatty acid which was "not previously identified with something already known in chemistry" (as translated from ref. 3). In 1935 von Euler (4) coined the active principle as "vesiglandin". In a further article in 1936 he coined the term "prostaglandin", and noted that it was a potent vasodilator (5). Though von Euler's group continued with some physiological studies with the prostaglandins, the modern era of prostaglandins did not start until the early 1960's. In 1960 Bergstrom and Sjovall elucidated the exact chemical structure of both prostaglandin F (6) and E (7) and subsequently in 1962 they described the prostaglandins PGF_1 and PGF_2 (8). It is about this time also that the American literature started appreciating potential physiological role of prostaglandins with Lee and co-workers description that extracts from rabbit renal medulla can cause sustained vasodepressor effects in rats (9). Since this time there has been a great explosion in the number of papers published in the field of prostaglandins as evidenced by a journal, Prostaglandins, which is devoted solely to prostaglandin research.

II. BIOCHEMICAL SYNTHESIS AND METABOLISM

Figure 1 schematically summarizes the renal synthesis and degradation of prostaglandins, while Figure 2 represents the chemical structure and nomenclature of the various prostaglandins.

Prostaglandins are biosynthesized from arachidonic acid. The rate limiting step in the biosynthesis of prostaglandins is the conversion of the phospholipids to arachidonic acid as regulated by the activity of phospholipase A_2. It appears that the conversion of phospholipid to arachidonic acid is stimulated by bradykinin, angiotensin II, antidiuretic hormone, (10) and high tissue pO_2 levels (11). If arachidonic acid is injected into the renal artery, it is rapidly converted by cyclooxygenase first to cyclic endoperoxidases (PGG_2 and PGH_2). This step is inhibited by various agents including aspirin, indomethacin, meclofenamate, and glucocorticoids. The prostaglandins G_2 and H_2 are unstable intermediates which in turn are rapidly converted into one of three identified products: PGE_2 (via isomerase) PGI_2 or prostacycline (via prostacycline synthetase) or thromboxane (via thromboxane synthetase). PGE_2 in turn may be converted to $PGF_{2\alpha}$ by 9-keto-reductase or to metabolites PGA_2 (by 11-dehydrase) or to 15 keto-PGE_2 (by 15-OH-PG dehydrogenase). Ethacrynic acid or furosemide might increase PGE_2 levels by inhibiting 15-OH-PGDH (12).

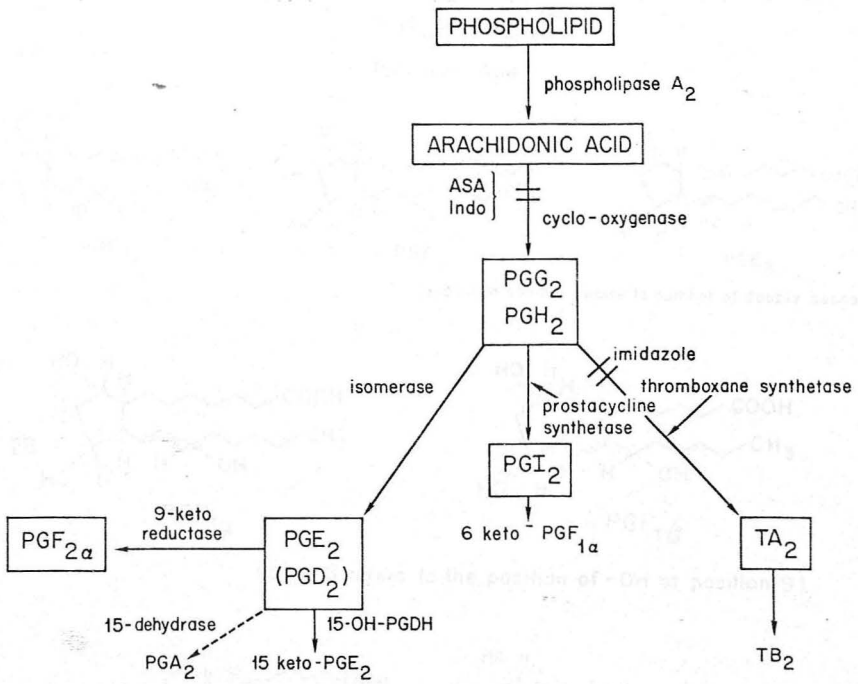

Figure 1. Renal synthesis and degradation of prostaglandins.

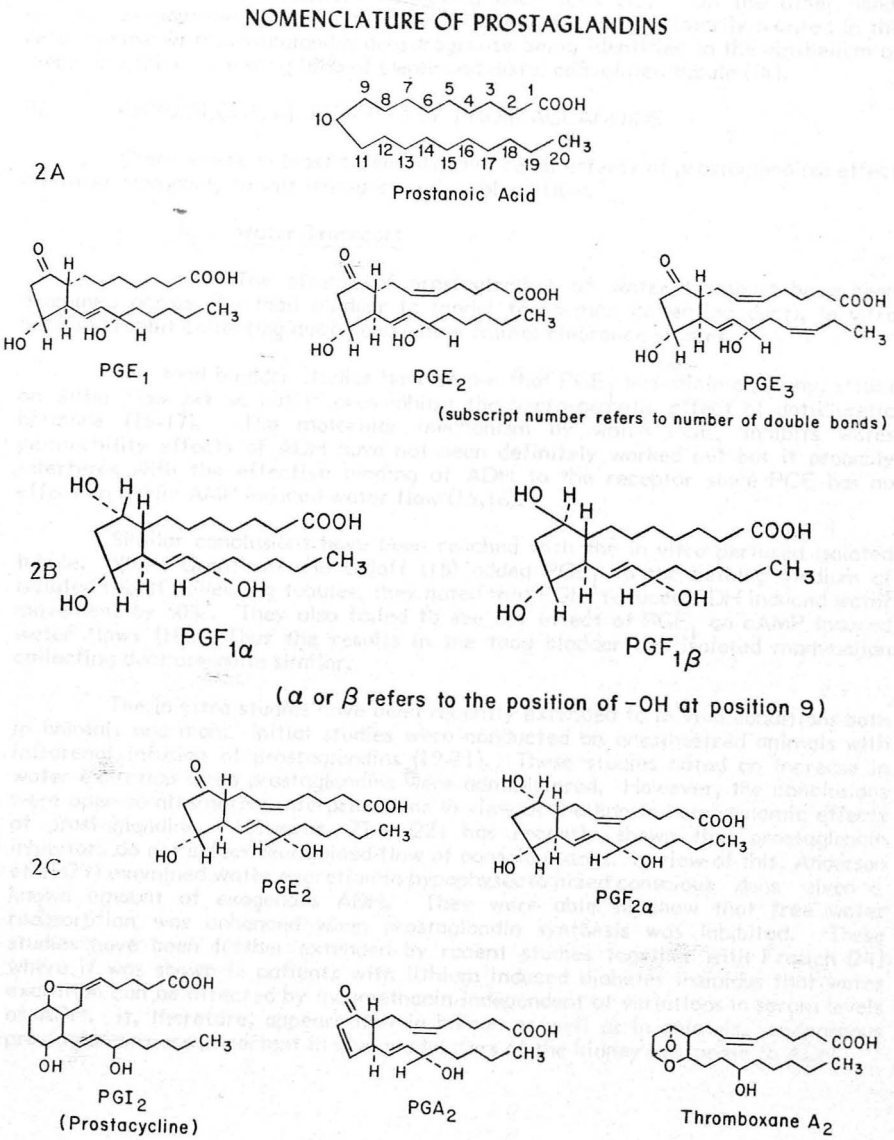

Figure 2. Nomenclature of prostaglandin. 2A depicts the significance of the subscript number; 2B demonstrates the difference between α and β compounds; 2C includes the structure of the major biologically active prostaglandins.

The basic site of prostaglandin synthesis in the kidney is the medulla. Prostaglandin synthetase has been identified predominantly in the medullary interstitial cells and medullary collecting duct cells (13). On the other hand, enzymes responsible for degradation of prostaglandins are primarily located in the renal cortex with prostaglandin dehydrogenase being identified in the epithelium of medullary thick ascending limb of Henle and distal convoluted tubule (14).

III. PHYSIOLOGICAL EFFECTS OF PROSTAGLANDINS

There exists at least three different renal effects of prostaglandins: effect on water transport, on salt transport and on blood flow.

A. Water Transport

The effects of prostaglandins on water transport have been examined across the toad bladder (a model for human collecting duct), in vitro perfused rabbit collecting ducts, and whole animal clearance studies.

The toad bladder studies have shown that PGE_1 has minimal,if any, effect on water flow per se but it does inhibit the hydro-osmotic effect of antidiuretic hormone (15-17). The molecular mechanism by which PGE_1 inhibits water permeability effects of ADH have not been definitely worked out but it probably interferes with the effective binding of ADH to the receptor since PGE has no effect on cyclic AMP induced water flow (15,16).

Similar conclusions have been reached with the in vitro perfused isolated tubule. When Grantham and Orloff (18) added PGE_1 to the bathing medium of isolated rabbit collecting tubules, they noted that PGE_1 reduced ADH induced water movement by 50%. They also failed to see any effect of PGE_1 on cAMP induced water flows (18). Thus the results in the toad bladder and isolated mammalian collecting duct are quite similar.

The in vitro studies have been recently extended to in vivo conditions both in animals and man. Initial studies were conducted on anesthesized animals with intrarenal infusion of prostaglandins (19-21). These studies noted an increase in water excretion when prostaglandins were administered. However, the conclusions were open to alternative interpretations in view of the known hemodynamic effects of prostaglandins. However, Zins (22) has recently shown that prostaglandin inhibitors do not effect renal blood flow of conscious dogs. In view of this, Anderson et al (23) examined water excretion in hypophysectomized conscious dogs given a known amount of exogenous ADH. They were able to show that free water reabsorption was enhanced when prostaglandin synthesis was inhibited. These studies have been further extended by recent studies together with Frolich (24) where it was shown in patients with lithium induced diabetes insipidus that water excretion can be affected by indomethacin independent of variations in serum levels of ADH. It, therefore, appears that in human as well as in animals, endogenous prostaglandins are important in vivo modulators of the kidney's response to ADH.

B. Sodium Transport

The effect of prostaglandin on sodium excretion are more controversial than their effect on water metabolism even though there is general agreement that when prostaglandins are infused into renal artery of anesthesized dogs that there is prompt natriuresis (19, 21, 25-27). Similarly, when prostaglandin A_1 is infused intravenously into conscious man there is a significant increase in sodium excretion (28, 29). However, all of these findings may be secondary to hemodynamic effects known to occur with pharmacologic doses of prostaglandins since previous studies have shown that infusions of variety of vasodilating agents into renal circulation causes an increase in sodium excretion (21).

The controversy in regard to sodium excretion and prostaglandins arises from use of inhibitors of prostaglandin synthesis. A number of studies have actually shown a slight increase in sodium excretion with meclofenamate in both the conscious (30) and anesthesized (31) dog. These studies, however, were conducted during water diuresis and baseline low sodium excretion. Tannenbaum, et al (32) on the other hand have infused arachidonic acid intrarenally and have noted ipsilateral natriuresis without changes in renal blood flow or glomerular filtration rate. These studies would support the concept that prostaglandins inhibit sodium reabsorption as would the recent clinical observations (to be discussed later) which demonstrate that sodium excretion can be decreased with indomethacin in patients with Bartter's Syndrome.

The most convincing demonstration that PGE_2 affects renal sodium transport directly is the recent in vitro studies which revealed that sodium transport was directly inhibited by PGE_2 across the cortical and outer medullary collecting tubules (3). This effect was rapid, reversible and dose dependent. Thus, decreased concentrations of prostaglandin would be associated with increased sodium reabsorption. In agreement with these in vitro studies are the studies of Ganguli, et al (34). They treated rats with indomethacin and noted that papillary sodium concentration (in part a reflection of sodium transport across the collecting duct) was twice as high as in similarly prepared control "non-indomethacin" rats. Thus, in aggregate, it is my personal feeling that the various published and unpublished studies constitute strong evidence to suggest that PGE_2 directly inhibits sodium transport across the collecting duct system. Further studies are needed to examine whether various prostaglandins affect salt transport across other nephron segments.

C. Prostaglandins and Renal Hemodynamics

The majority of evidence supports the concept that prostaglandins increase renal blood flow by vasodilating its vascular bed. These conclusions have been reached with intrarenal infusions of either prostaglandin A or E series (21, 25-27, 35-38). Also high doses of intrarenally administered arachidonic acid increases renal blood flow (32). Further studies with radiolabelled microspheres have noted that there is a disproportionately greater increase in the juxtamedullary blood flow as compared to the superficial cortical blood flow (39-42). Furthermore, there is an increase in renal venous prostaglandin like material with various maneuvers which normally decrease renal blood flow (43-48).

Somewhat contrary to the above summarized studies are those observations when indomethacin has not been shown to decrease renal blood flow in conscious dogs (22, 30). However, it is quite possible that the noncompetitive inhibitors of prostaglandins may themselves have effects on the renal hemodynamics which would obscure the effects of changing prostaglandin levels.

IV. CLINICAL DISORDERS INVOLVING PROSTAGLANDINS

A. Bartter's Syndrome

Bartter's Syndrome is a clinical disorder characterized by hypokalemic alkalosis, elevated serum renin and aldosterone levels but with normal or low blood pressure. Under normal circumstances these patients are resistant to pressor doses of Angiotensin II, and they require prolonged and severe salt restriction to form sodium-free urine. Thus these patients have "relative salt wasting" (50) and, therefore, are in a chronic volume and salt depleted state.

A number of theories have evolved in regard to the pathogenesis of this syndrome. The two principle ones are the primary vascular defect to the vasopressor action of angiotensin or primary renal salt wasting leading to decreased response to angiotensin either due to volume contraction per se or to the associated potassium depletion which occurs with increased natriuresis. However, neither of these two theories have been entirely satisfactory.

Recently three groups have independently reported successful correction of the metabolic defects in Bartter's Syndrome with the use of indomethacin (51-53). In addition, Frolich, working with Gill, et al (53) measured urinary PGE_2 by gas chromatograph mass spectrometer-computer system in patients with Bartter's Syndrome both with and without inhibition of prostaglandin synthesis. In six patients there was a definite elevation in urinary PGE_2 in patients with Bartter's Syndrome which was decreased with indomethacin. In addition, plasma renin activity and urinary aldosterone were decreased from the elevated control values. All of these findings were associated with a correction towards normal in potassium balance, sodium balance and body weight. Also, the pressor dose of angiotensin was normalized by indomethacin and by ibuprofen (53). Thus these findings suggest[1] that the primary event in Bartter's Syndrome may be the overproduction of PGE_2 and that the metabolic consequences of the overproduction of PGE_2 may be reversed by inhibitors of prostaglandin synthesis. Whether this mode of therapy will prove to be effective or chronic basis has not been established. Flory, et al (54) have a recent abstract suggesting that two patients with Bartter's Syndrome "escaped" the beneficial effect of indomethacin after two months of therapy.

B. Syndrome of Inappropriate ADH Secretion (SIADH)

The characteristic clinical features of the syndrome of inappropriate secretion of antidiuretic hormone result from unusually high rates of water retention at a time when serum osmolality is low. The salient findings of the SIADH are: 1) decreased serum sodium concentration (with associated decreased serum osmolality); 2) urine osmolality which is higher than the plasma osmolality;

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[1] It is quite possible that the overproduction of PGE in turn may be secondary to some other primary stimulus.

and 3) inappropriately high urinary excretion of sodium when the patient is allowed free access to salt and water. A number of hypotheses have been put forth to explain the natriuresis associated with SIADH. However, none of these have been satisfactory.

Recent studies (10) have demonstrated that arginine vasopressin increases biosynthesis of PGE in toad bladders. The biosynthesis of PGE was inhibited by phospholipase inhibitors. In addition they were able to show that ADH released arachidonic acid from the intracellular lipid stores without affecting the conversion of arachidonic acid to PGE.

It, therefore, is possible that some of the natriuretic responses of ADH might be mediated by prostaglandins. Supportive of this are the recent studies of Fejis-Toth, et al (55) who noted first that administration of ADH to conscious dogs caused antidiuresis and natriuresis while inhibition of prostaglandin synthesis abolished the natriuresis. These studies therefore suggest that the natriuresis of SIADH probably is, in part, mediated by prostaglandins.

C. Renal Artery Stenosis

It is well appreciated that acute renal artery stenosis leads to contralateral polyuria. The mechanism of this has been variously attributed to inhibition of ADH release, development of hypertension, or changes in renal hemodynamics. None of these postulated mechanisms have proven to be satisfactory.

The recent studies of Galvez, et al (56) have advanced our knowledge significantly in regard to the mechanism of contralateral polyuria after renal artery stenosis. In a control group of dogs with left renal artery stenosis they noted an increase in blood pressure, decrease in urine osmolality, increase in free water clearance, increase urinary sodium, and increase in plasma renin. Same directional changes were noted if blood pressure rise was prevented with simultaneous infusion of Arfonad. Thus it was concluded that blood pressure rise could not account for polyuria. However, Saralasin (competitive inhibitor of Angiotensin II) when infused on top of renal artery stenosis, decreased the previous contralateral polyuria to control levels. It, therefore, was concluded that angiotensin somehow mediated the polyuria. That the polyuria was not a conseqeunce of angiotensin inhibiting angiotensin release was evidenced in a group of experiments when polyuria occurred in hypophysectomized animals. If animals were first treated with indomethacin and then underwent renal artery stenosis, they still became hypertensive but now were without polyuria. These findings in connection with the recent demonstration that Angiotensin II stimulates the formation of PGE by increasing the release of arachidonic acid, suggest that the contralateral polyuria after renal stenosis is mediated by the following cascade of events. Renal artery stenosis → increased Angiotensin II → increased PGE → inhibition of water permeability of the collecting duct. This set of events may be applicable only in acute states (56) since decreased PGE synthesis have been noted in rats with chronic renal artery stenosis (57, 58) and hyponatremia is frequently seen in patients with high renin hypertension (59).

D. Post Obstructive Diuresis

It is now well accepted that chronic hydronephrosis is associated with renal vasoconstriction and an increase in fractional sodium excretion. Also, it is well known that post obstructive natriuresis is not uncommon. With this background, Nishikewa, Morrison and Needleman (60) examined in rabbits whether elevation in PGE might occur in hydronephrosis as a protective mechanism to overcome the decrease in renal blood flow and as an explanation for the decrease in fractional sodium reabsorption. They chose to measure the release of PGE in response to various stimuli as an index of prostaglandin synthesis in hydronephrotic kidneys (ureteral ligation) as compared to the counterlateral control kidneys. They chose Angiotensin II, bradykinin and norepinephrine as stimuli for prostaglandin synthesis. In each case there was an exaggerated response in the hydronephrotic kidney to the given stimulus. They also infused arachidonic acid intrarenally using this same model. In this instance there was no difference in the PGE synthesized in the hydronephrotic kidney and contralateral control. These studies suggested to them there was no increase in cyclo-oxygenase activity in the hydronephrotic kidney but rather the enhanced release of PGE with ureteral ligation represents exaggerated biosynthesis of PGE. Whether these findings can be extrapolated into the human remains to be elucidated. Certainly other additional factors also contribute to the decreased sodium reabsorption in the obstructed and post obstructed models as was reviewed by Dr. Jim Gross in the Medical Grand rounds given at UTHSC in 1976.

E. Volume Expansion

Acute volume expansion is associated with natriuresis. Since deWardener, et al (61) postulated the existence of natriuretic hormone, there has been an intensive search for the identity or the very existance of the natriuretic substance. It now appears that the volume expansion natriuresis occurs independent of changes in glomerular filtration rate or changes in circulating mineralocorticoid activity. Since prostaglandins have been shown to affect sodium transport across the toad bladder and in the kidney, a number of studies have evaluated its possible role in natriuresis of volume expansion.

Two studies on anesthetized rats have now shown that the degree of natriuresis of acute volume expansion with sodium (10% of total body weight) can be significantly blunted by pretreating the animals with oral doses of indomethacin (62, 63). Indomethacin pretreatment had no effect on GFR in these studies. These authors interpreted their findings to suggest that prostaglandins are involved in the natriuresis of acute volume expansion (62, 63). However, the studies of Bohan and Wernor (64) and those of Kirschenbaum and Stein (65) failed to confirm these studies. However, the latter studies were conducted in anesthetized dogs. They were also examined after volume expansion either without PG synthesis inhibitor or with pretreatment of dogs with either meclofenamate or indomethacin. In neither study was there a significant difference in the natriuresis of acute volume expansion whether the dogs did or did not have prostaglandin synthetase inhibitors. Though the data are presently meager, it is felt that the evidence is not convincing that prostaglandin per se is the elusive natriuretic hormone.

F. Preeclampsia

Normal pregnancy is not associated with elevations of blood pressure even though it is characterized by significantly elevated renin and angiotensin values when compared to nonpregnant women (66-78). Also, the nonhypertensive pregnant women are quite resistant to the pressor effects of AII (77-80) while those women who develop pregnancy-induced hypertension lose their resistance and become pressor sensitive to infused doses of AII (76, 77, 80, 81). Gant and associates (75) have extended these observations and shown that development of pregnancy induced hypertension can be predicted as early as 26 weeks of pregnancy by noting that the hypertensive-to-be women required significantly lower dose of AII to observe a given pressor response as compared to that group of women who remained normotensive throughout their pregnancy. This is especially important since these findings occurred before the clinical signs of preeclampsia. This apparent unresponsiveness of the blood pressure to angiotensin could either be due to a decrease in effective circulatory volume or some type of vascular unresponsiveness to angiotensin II. That the apparent unresponsiveness to AII in normal pregnant women is not due to volume deficit was shown in those sets of studies where either 5% NaCl solution was infused to normal pregnant women near term (76) or high hematocrit blood was infused to pregnant patients with various types of anemia (SS, SC or S-B-Thal disease) (77). In both cases there was a rapid volume expansion, however, there was no change in dose of AII required to elicit a pressor response. These studies are convincing demonstrations that decreased circulatory volume is not responsible for decreased response to AII and suggest that there is some type of arteriolar hyporesponsiveness to AII.

Insight into the possible mechanism of AII unresponsiveness may be obtained from a recent series of studies examining factors controlling uteroplacental blood flow. Studies have shown that the uteroplacenta unit is a rich source of prostaglandins (82-84). Further the studies of Venuto, et al (85) have shown that prostaglandin inhibition is associated with a significant fall in uterine blood flow in a pregnant rabbit. Thus, these studies suggest that the prostaglandins may have a central role in regulating the uteroplacental blood flow during pregnancy (85). This conclusion is further strengthened by the recent observation where placental PGE from preeclamptic women was much lower than from control normotensive women (86). Using this observation, and the recent report that indomethacin increases blood pressure of a pregnant rabbit while having no effect on blood pressure of nonpregnant rabbit (87) suggests that renin angiotensin may be elevated in pregnancy as a compensatory phenomena to antagonize the vasodilatory effects of prostaglandins.

G. Pre-renal Azotemia

Under normal circumstances the kidney can effectively regulate its blood flow. The mechanism of this autoregulation is poorly understood. However, there is a significant body of literature which can be interpreted to suggest that prostaglandins might play a role. Thus, during ischemic circumstances it can be argued that renal prostaglandins are increased as a protective mechanism to increase blood flow by renal vasodilitation. In fact, to support this hypothesis is a recent abstract by Zipser, et al (88) where they noted marked deterioration of renal function in a group of patients with cirrhosis after they were given indomethacin. The creatine clearance fell from 73±10 to 32±7 cc/min in association with a decrease in urinary PGE from 3.3±0.5 µg/d to 0.8±0.4 µg/d. We have seen similar cases at Parkland Memorial Hospital. From these preliminary observations we should conclude that extreme caution should be exercised if prostaglandin synthetase inhibitors are used in patients with prerenal azotemia.

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