Elevated plasma 4-pyridoxic acid in renal insufficiency


ABSTRACT

Background: Renal insufficiency is associated with altered vitamin B-6 metabolism. We have observed high concentrations of 4-pyridoxic acid, the major catabolite of vitamin B-6 metabolism, in plasma during renal insufficiency.

Objective: The objective was to evaluate the renal handling of 4-pyridoxic acid and the effects of renal dysfunction on vitamin B-6 metabolism.

Design: We measured the renal clearance of 4-pyridoxic acid and creatinine in 17 nonpregnant, 17 pregnant, and 16 lactating women. We then examined the influence of vitamin B-6 or alkaline phosphatase activity on the ratio of 4-pyridoxic acid to pyridoxal (PA:PL) in plasma in 10 men receiving a low (0.4 mg pyridoxine·HCl/d) or high (200 mg pyridoxine·HCl/d) vitamin B-6 intake for 6 wk, in 10 healthy subjects during a 21-d fast, in 1235 plasma samples from 799 people screened for hypophosphatasia, and in 67 subjects with a range of serum creatinine concentrations.

Results: Renal clearance of 4-pyridoxic acid was 232 ± 94 mL/min in nonpregnant women, 337 ± 140 mL/min in pregnant women, and 215 ± 103 mL/min in lactating healthy women. These values were approximately twice the creatinine clearance, indicating that 4-pyridoxic acid is at least partially eliminated by tubular secretion. Elevated plasma creatinine concentrations were associated with marked elevations in 4-pyridoxic acid and PA:PL. PA:PL was not affected by wide variations in vitamin B-6 intake or by the wide range of pyridoxal-P concentrations encountered while screening for hypophosphatasia.

Conclusions: Plasma 4-pyridoxic acid concentrations are markedly elevated in renal insufficiency. Plasma PA:PL can distinguish between increases in 4-pyridoxic acid concentrations due to increased dietary intake and those due to renal insufficiency.


KEY WORDS 4-Pyridoxic acid, vitamin B-6, pyridoxal-P, pyridoxal, renal function, pregnancy, lactation, women

INTRODUCTION

Previous studies of vitamin B-6 and renal function have focused primarily on the effect of dietary deficiencies and the metabolism of the biologically active vitamers. Kleiner et al (1) showed that vitamin B-6 supplementation improves fasting plasma amino acid and serum HDL concentrations in renal dialysis patients, leading these authors to conclude that vitamin B-6 deficiency may have a pathogenic role in renal dysfunction. Moreover, vitamin B-6 deficiency was shown to cause microscopic renal lesions in rats (2, 3) and to increase oxalate excretion in humans (4), whereas vitamin B-6 supplements may reduce the occurrence of renal oxalate stones (5), particularly in patients with increased endogenous oxalate production (6, 7). In prospective studies, a high vitamin B-6 intake was associated with a reduced incidence of kidney stones in women (8) but not in men (9). A low vitamin B-6 status could also contribute to the increased plasma homocysteine concentrations observed in renal insufficiency (10).

Vitamin B-6 occurs as an alcohol (pyridoxine), aldehyde (pyridoxal), and amine (pyridoxamine). These forms can be phosphorylated in the 5'-position and interconverted. Pyridoxal-P is the major coenzyme form and 4-pyridoxic acid is the major urinary metabolite (11). 4-Pyridoxic acid is not produced during renal processing of pyridoxine because it is not detected after exposure of renal tubular cells (12) or perfused rat kidney (13) to pyridoxine. However, 4-pyridoxic acid accounts for ∼10% of the tissue radioactivity in kidneys perfused with radiolabeled pyridoxal (13), but the percentage of label in 4-pyridoxic acid in the urine is variable. Studies of vitamin B-6 metabolism in humans taking large doses of vitamin B-6, comparable with doses used during parenteral nutrition, showed that renal clearance of 4-pyridoxic acid is approximately twice the creatinine clearance (14). This finding indicates that 4-pyridoxic acid can be eliminated by tubular secretion as well as glomerular filtration.

1From the Department of Biochemistry, Fort Wayne State Developmental Center, Fort Wayne, IN; the Department of Human Nutrition and Dietetics, University of Illinois, Chicago; the Metabolic Research Unit, Shriners Hospitals for Children, St Louis; the Department of Mathematical Sciences, Indiana University–Purdue University, Fort Wayne, IN; the Human Performance Laboratory and the Department of Nutrition, Ball State University, Muncie, IN; and the Department of Medicine, Southern Illinois University School of Medicine, Springfield, IL.

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4Address reprint requests to SP Coburn, Fort Wayne State Developmental Center, 4900 St Joe Road, Fort Wayne, IN 46835. E-mail: coburn@fww.edu. Received November 14, 2000. Accepted for publication February 13, 2001.
Plasma 4-pyridoxic acid reportedly has a strong, positive correlation with plasma urea and creatinine (15).

While studying B-6 vitamers with HPLC, we noted that chromatograms of plasma from patients with renal disease contained a variety of fluorescent peaks not found in healthy control subjects (J Mahuren, S Coburn, J Wortsman, unpublished observations, 1997). These included a large peak with the elution time of 4-pyridoxic acid. We initially assumed that this peak contained an interfering compound. However, heating 4-pyridoxic acid in acid forms an internal lactone that alters the elution time of the peak in a predictable way (16). Heating the urine with acid resulted in recovery of most of the peak as 4-pyridoxic acid lactone, confirming that the original large peak was predominantly 4-pyridoxic acid and not an interfering compound. This observation stimulated the following study of the effect of low, normal, and high vitamin B-6 intakes and renal disease on the renal handling of 4-pyridoxic acid.

SUBJECTS AND METHODS

Subjects

All protocols were approved by the Human Subject Committees of the appropriate institutions, and informed consent was obtained. Nonpregnant (x ± SD age: 28.8 ± 3.9 y; n = 17), pregnant (age: 26.6 ± 5.6 y; gestational age: 36.5 ± 1.9 wk; n = 17), and lactating women (age: 26.6 ± 5.4 y; time postpartum: 11.8 ± 10.3 wk; n = 16) consumed a self-selected diet plus a daily multivitamin supplement containing 2 mg pyridoxine·HCl for 4 wk before the study date. On the study day, subjects consumed a meal low in vitamin B-6 at 0700; 2 h later they ingested 100 mL of an aqueous solution containing 5 μmol each of [1H3]pyridoxamine, [3H3]pyridoxine, and [2H5]pyridoxal (18). Blood and urine samples were collected over the next 7 h. After each voiding, subjects consumed 100 mL of a solution containing 5% glucose polymer (Polycose; Ross Product Division, Abbott Laboratories, Columbus, OH) as the sole source of nutrition during the collection period. The tracer data are reported elsewhere (18).

The metabolism of a large dose of vitamin B-6 was examined in 10 men (38 ± 8 y) who ingested 200 mg pyridoxine·HCl. Urine samples were collected at −2, −1, 0, 3.5, 4.5, 5.5, and 7 h. Blood samples were drawn at −1, 3.5, 4.5, and 5.5 h.

Data from a variety of sources were used to evaluate the influence of various factors on the ratio of 4-pyridoxic acid to pyridoxal (PA:PL). The effect of kidney dysfunction was examined by analyzing residual clinical plasma samples selected for a range of creatinine concentrations in 27 women (median age: 64 y; range: 17–91 y; 25th–75th percentiles: 45–75 y) and in 40 men (median age: 66 y; range: 15–85 y; 25th–75th percentiles: 48–74 y). The effect of the dietary vitamin B-6 intake was examined with the use of data from previously reported studies of 10 healthy men who received low (0.4 mg pyridoxine·HCl/d) followed by high (200 mg pyridoxine·HCl/d) vitamin B-6 intakes (19) for 6 wk each and of 10 healthy volunteers who participated in a 21-d fast (20).

Our screening of subjects for hypophosphatasia, which is associated with marked elevations in pyridoxal-P concentrations (21), gave us a pool of 1235 plasma samples from 799 individuals with an extremely wide range of pyridoxal-P concentrations. This provided a unique opportunity to examine the possible effect of pyridoxal-P on PA:PL. These individuals were normal, heterozygous, or homozygous for hypophosphatasia. For 365 samples from 207 females for whom we had background data, the median age was 24 y (range: 0–72 y; 25th–75th percentiles: 6–37 y). For 342 samples from 163 males, the median age was 10 y (range: 0–78 y; 25th–75th percentiles: 5–24 y). Because samples were often referred through third parties, we had no background data on the remaining 528 samples (271 samples from 218 females, 214 samples from 168 males, and 43 samples from individuals whose sex was undetermined).

Methods

Plasma and urinary creatinine concentrations were measured with use of the Abbott Vision instrument (Abbott Laboratories, Abbott Park, IL). B-6 vitamers in plasma and urine were determined by cation-exchange HPLC (22). 4-Pyridoxic acid clearance was determined from the slope of the line obtained from the regression of the average [starting concentration + ending concentration]/2 plasma 4-pyridoxic acid concentration (mmol/L) associated with urine samples from each collection period against the urinary 4-pyridoxic acid excretion (mmol/min).

The regression analysis was performed with the use of WINSAAM (version 2.0.17; Laboratory of Experimental and Computational Biology, National Cancer Institute, Bethesda, MD). The population feature of WINSAAM (23) was used to combine the individual regression data to obtain the mean value for each of the 3 subject groups.

Data relating plasma 4-pyridoxic acid concentrations to renal clearance after the large dose of vitamin B-6 were evaluated assuming that creatinine clearance was equal to the glomerular filtration rate and that excretion by secretion could be described by noncooperative binding, cooperative binding, or substrate inhibition. We expressed the binding sites in units of μmol/min. An alternative would have been to express the binding sites as a concentration and to then multiply by a rate constant to obtain a rate. The latter approach creates 2 unknowns, whereas the former creates only 1. Because we had no direct measurements of either the binding sites or the rate constant, the former approach, which combines the 2 unknowns into a single term, was selected as the most appropriate.

For noncooperative binding,

\[
\text{Total clearance (mL plasma/min)} = \text{creatinine clearance + bound ligand (μmol/min)/plasma 4-pyridoxic acid (mmol/L)} \quad (1)
\]

Bound ligand was calculated by solving the equation for the dissociation constant in terms of total ligand and total binding sites (24), yielding a quadratic equation with the following solution:

\[
B = [\text{PA} + S + K - ([\text{PA} + S + K]^2 - 4 \times \text{PA} \times S^{0.5})/2] \quad (2)
\]

where \(B\) is bound ligand (μmol/min), \(\text{PA}\) is plasma 4-pyridoxic acid (μmol/L), \(S\) is total binding sites (μmol/min), and \(K\) is the dissociation constant. Values for \(S\) and \(K\) were arbitrarily selected to attempt to fit the data.

For cooperative binding,

\[
\text{Rate of secretion (μmol/min)} = V_{max} \times \frac{\text{PA}^n}{(K_{ap} + \text{PA}^n)} \quad (3)
\]

where \(V_{max}\) is the maximum velocity, \(n\) is the number of binding sites per molecule, and \(K_{ap}\) is the complex constant in Hill’s equation (25), and
TABLE 1
Renal clearance of creatinine and 4-pyridoxic acid in healthy nonpregnant, pregnant, and lactating women

<table>
<thead>
<tr>
<th></th>
<th>Nonpregnant (n = 17)</th>
<th>Pregnant (n = 17)</th>
<th>Lactating (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine (μmol/L)(^2)</td>
<td>62 (51–71)(^a)</td>
<td>44 (42–53)(^b)</td>
<td>62 (62–71)(^a)</td>
</tr>
<tr>
<td>Creatinine excretion (μmol/min)(^1)</td>
<td>6.3 ± 2.4</td>
<td>7.2 ± 2.7</td>
<td>6.5 ± 1.9</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)(^1)</td>
<td>97 ± 29(^a)</td>
<td>161 ± 62(^b)</td>
<td>100 ± 37(^a)</td>
</tr>
<tr>
<td>Baseline plasma pyridoxal-P (nmol/L)(^1)</td>
<td>49 (25–65)(^a)</td>
<td>12 (7–17)(^b)</td>
<td>46 (37–56)(^a)</td>
</tr>
<tr>
<td>Baseline plasma pyridoxal (nmol/L)(^1)</td>
<td>36 ± 19</td>
<td>16 ± 8(^b)</td>
<td>36 ± 15(^a)</td>
</tr>
<tr>
<td>Baseline plasma 4-pyridoxic acid (nmol/L)(^1)</td>
<td>43 ± 17(^a)</td>
<td>54 ± 10(^b)</td>
<td>40 ± 11(^a)</td>
</tr>
<tr>
<td>4-Pyridoxic acid clearance (mL/min)(^1)</td>
<td>232 ± 94(^a)</td>
<td>337 ± 140(^a)</td>
<td>215 ± 103(^a)</td>
</tr>
</tbody>
</table>

\(^1\)Values within a row with different superscript letters are significantly different, P < 0.05.
\(^2\)Median; 25th–75th percentiles in parentheses. Kruskal-Wallis ANOVA on ranks with Dunn’s method used to compare groups.
\(^\pm\)\(\pm\) ± SD. ANOVA and Tukey’s test used to compare groups.

Total clearance (mL/min) = creatinine clearance (mL/min) + secretion (μmol/min)/PA (mmol/L)

For substrate inhibition,

Total clearance (μmol/min) = creatinine clearance (mL/min) + clearance by secretion (mL/min)

The secretion process was simulated by the following equations:

\[
\text{Secretion (μmol/min)} = \frac{\text{Vmax (μmol/min) × PA (μmol/L)}}{\left[\frac{\text{Km + PA × (1 + PA/Km)}}{\text{PA (mmol/L)}}\right]} \tag{6}
\]

where \(K_m\) is the Michaelis constant and \(K_i\) is the inhibition constant, and

\[
\text{Clearance (mL/min) from secretion} = \frac{\text{secretion (μmol/min)}}{\text{PA (mmol/L)}} \tag{7}
\]

Data analysis

Statistical analysis was performed with the use of SIGMASTAT (version 2.03; Jandel Scientific, San Rafael, CA). The sensitivity and specificity of PA:PL were analyzed in the 67 clinical samples and in 224 of the hypophosphatasia screening samples for which we had both creatinine and PA:PL data. On the basis of a plasma creatinine value > 133 μmol/L as indicative of renal dysfunction, 40 subjects had renal dysfunction and 251 subjects did not. Subjects were cross-classified according to their renal status and PA:PL was used as a threshold for determining the positive or negative status of the screening test. Several threshold values were investigated; in each case, the estimates of the sensitivity and specificity of the associated test were calculated with the use of appropriate proportions of the available data. A nonparametric receiver operating characteristic (ROC) curve was plotted (27) to compare the effectiveness of PA:PL to a cutoff value of 133 μmol creatinine/L as a decision making tool. An ROC plot provides a graphic display of all possible sensitivity and specificity pairs that result from changing the threshold value for decision making based on the screening test. For a specified decision threshold, a point on the ROC plot provides an estimate of the sensitivity and 1 – specificity associated with that threshold value. The closer the curve approaches the upper left corner, the more effective the tool is.

RESULTS

Renal clearance of 4-pyridoxic acid in the nonpregnant, pregnant, and lactating women was approximately twice the creatinine clearance (Table 1), confirming that tubular secretion and probably glomerular filtration are involved in the renal elimination of 4-pyridoxic acid. Because plasma 4-pyridoxic acid increased 2–3-fold after administration of the B-6 vitamins, plasma clearance of 4-pyridoxic acid was determined for each subject from the slope of the linear regression of urinary excretion against the plasma concentration for each collection period (Figure 1). Clearances of both 4-pyridoxic acid and creatinine increased during pregnancy (Table 1). Pyridoxal-P and pyridoxal concentrations were significantly lower in pregnant women than in the nonpregnant and lactating women.

These data indicate that in healthy women the relation between plasma 4-pyridoxic acid and renal excretion is reasonably linear over a range of ≈100 nmol/L. However, at the larger range of 4-pyridoxic acid concentrations seen in the 10 men who ingested 200 mg vitamin B-6, there was decreased 4-pyridoxic acid clearance at plasma concentrations > 1 μmol/L (Figure 2). This could reflect saturation of the secretion process. We attempted to describe the curve relating plasma 4-pyridoxic acid to renal clearance, assuming that excretion was a combination of filtration...
and a secretory process involving either noncooperative binding, cooperative binding, or substrate inhibition. Only the cooperative-binding simulation produced a reasonable fit to the data (Figure 2). Because the noncooperative binding and substrate inhibition equations did not produce appropriate curves, the lines for these 2 equations in the figure are arbitrary examples. The contribution of filtration and secretion at various plasma 4-pyridoxic acid concentrations, as predicted by the cooperative-binding equation, is depicted in Figure 3. Although the cooperative-binding curve in Figure 2 fits this particular data set well, the predicted clearances at plasma values <100 nmol/L are less than the values in excess of 200 mL/min reported in Table 1 for different experimental conditions. Further studies are needed to determine whether the combination of filtration and cooperative binding best describes the renal processing of 4-pyridoxic acid. However, the results clearly indicate the existence of a concentration-dependent renal secretory process that contributes to the elimination of 4-pyridoxic acid.

The observations that 4-pyridoxic acid excretion appears to involve both filtration and secretion and that plasma 4-pyridoxic acid concentrations are markedly elevated in renal disease suggest that plasma 4-pyridoxic acid might be a useful indicator of renal function. However, plasma 4-pyridoxic acid concentrations also increase in response to vitamin B-6 administration. Therefore, we investigated whether PA:PL might differentiate changes due to diet from those due to renal disease. Ingestion of 5 μmol each of pyridoxine, pyridoxal, and pyridoxamine (Figure 4) or lactating (Figure 5) women produced little change in the PA:PL during the first hour even though the plasma concentrations of both compounds increased 3–4-fold. After 1 h, the ratio increased slightly because pyridoxal declined more rapidly than did 4-pyridoxic acid. In pregnant women (Figure 6) the ratio declined during the initial rise in plasma concentrations because pyridoxal increased faster than did 4-pyridoxic acid. After that, the ratio increased slightly because pyridoxal declined faster than did 4-pyridoxic acid. In men who received a low vitamin B-6 intake of 0.4 mg pyridoxine·HCl/d (19), the ratio declined during the first 4 d because 4-pyridoxic acid declined faster than did pyridoxal (Figure 7). 4-Pyridoxic acid then increased slightly, causing the PA:PL to increase and then gradually decline as plasma pyridoxal increased. Neither increasing the vitamin B-6 intake to 200 mg pyridoxine·HCl/d (Figure 7) nor reducing the intake by fasting for 21 d (Figure 8) (20) markedly influenced the PA:PL. Furthermore, the ratio was not influenced by the wide range of pyridoxal-P concentrations encountered during screening for hypophosphatasia (Figure 9). However, in the 67 clinical samples, elevations in serum creatinine—even when mild—were associated with a markedly increased PA:PL (Figure 10). Therefore, PA:PL is not influenced by vitamin B-6 intake or alkaline phosphatase activity but is sensitive to impairment of renal function. Results of the sensitivity and specificity analysis show that a PA:PL of 2.5 would provide...
a sensitivity of 85% and a specificity of 82.9% for the diagnosis of renal impairment (ie, serum creatinine > 133 μmol/L) (Table 2). The nonparametric ROC curve (Figure 11) raises the possibility that with additional data relating changes in renal handling of 4-pyridoxic acid to specific renal disorders, the PA:PL might become an auxiliary tool for evaluating renal function.

**DISCUSSION**

The increased renal clearances of both creatinine and 4-pyridoxic acid in pregnant women presumably result from increased renal perfusion (28). The lower pyridoxal-\( P \) concentrations in pregnancy are likely due to the hydrolytic activity of placental alkaline phosphatase (29). The lower plasma pyridoxal values observed in the pregnant women conflict with previous reports in which pyridoxal concentrations were higher in pregnant than in nonpregnant women (30, 31). Although pyridoxal concentrations in pregnant women in the present study were comparable with those from previous reports, concentrations in the nonpregnant group were 2–3 times higher. The higher values in the nonpregnant group probably reflect the effect of the vitamin B-6 supplement given in the present study. Our pregnant group was also of a more advanced gestational age (36 ± 2 wk) than were the groups in the earlier reports: 22 ± 1 wk (30) and 28–36 wk (31).

The 4-pyridoxic acid clearance of 249.8 ± 48.2 mL·min·1.73 m\(^2\) obtained by others after intravenous infusion of 100 mg pyridoxine (14) is similar to the values obtained in the present study. PA:PL remained at ~1 under those conditions (32) and also after oral administration of 600 mg pyridoxine·HCl (33).
Therefore, various vitamin B-6 intakes over a wide range rarely produce a PA:PL markedly >2.

Although the high activity of aldehyde oxidase in liver (34) supports the hypothesis that liver is the primary source of 4-pyridoxic acid, the occurrence of up to 30% of the label in urine as 4-pyridoxic acid after perfusion of isolated rat kidney with pyridoxal (13) raises the possibility that some urinary 4-pyridoxic acid may be produced in the kidney. However, the high 4-pyridoxic acid concentrations found in association with renal dysfunction probably are the result of an accumulation of 4-pyridoxic acid produced in the liver rather than in the kidney. Further research should clarify the relative importance of glomerular filtration and tubular secretion in the renal processing of 4-pyridoxic acid.

Another question is whether the high plasma concentrations of 4-pyridoxic acid observed in renal disease might influence the metabolism of vitamin B-6 or other pathways in these patients.

Renal insufficiency is accompanied by elevated plasma homocysteine concentrations and an increased risk of atherosclerosis (10). Because vitamin B-6 is a cofactor for cystathionine β-synthase, which is required for the degradation of homocysteine, vitamin B-6 status is important in controlling the homocysteine concentration after a methionine load (35). Vitamin B-6 status may also affect cardiovascular disease risk by mechanisms independent of homocysteine (35). When human platelets were incubated with 3 μmol [3H]pyridoxine/L, the uptake and phosphorylation of pyridoxine as indicated by the distribution gradient (activity in platelets/activity outside platelets) was inhibited 50% by 500 μmol 4-pyridoxic acid/L (36). Use of 500 μmol 4-pyridoxic acid/L and 3 μmol pyridoxine/L yields an inhibitor-substrate ratio of 167. Because the normal concentration of pyridoxal in plasma is <100 nmol/L, 4-pyridoxic acid concentrations >10000 nmol/L might produce inhibitor-substrate ratios that could have a negative effect on vitamin B-6 metabolism. Because renal dysfunction is one of the most common causes of increased plasma phosphate concentrations, it is not unexpected that some of the high-phosphate sera used in our alkaline phosphatase study (37) had 4-pyridoxic acid concentrations >10000 nmol/L (J Mahuren et al, unpublished observations, 1997). However, in those samples, pyridoxal was also elevated, presumably as a

<table>
<thead>
<tr>
<th>Upper limit of normal for PA:PL</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>97.5</td>
<td>66.5</td>
</tr>
<tr>
<td>2.0</td>
<td>92.5</td>
<td>77.3</td>
</tr>
<tr>
<td>2.5</td>
<td>85.0</td>
<td>82.9</td>
</tr>
<tr>
<td>3.0</td>
<td>82.5</td>
<td>88.4</td>
</tr>
<tr>
<td>3.5</td>
<td>77.5</td>
<td>93.2</td>
</tr>
<tr>
<td>4.0</td>
<td>72.5</td>
<td>94.8</td>
</tr>
</tbody>
</table>

1Creatinine ≤ 133 μmol/L, n = 251; creatinine > 133 μmol/L, n = 40.

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**FIGURE 9.** Lack of correlation between pyridoxal- and the ratio of 4-pyridoxic acid to pyridoxal (PA:PL) in 1235 plasma samples from people screened for hypophosphatasia (r = −0.007, P = 0.81). The axes are shown in log scale to give more uniform visualization of the wide range of data.

**TABLE 2**

Sensitivity and specificity of the ratio of plasma 4-pyridoxic acid to pyridoxal (PA:PL) for detecting individuals with plasma creatinine values > 133 μmol/L, indicating renal dysfunction

**FIGURE 10.** Regression between log ratios of 4-pyridoxic acid to pyridoxal (PA:PL) and log plasma creatinine for 67 samples selected for a range of creatinine concentrations: log PA:PL = 1.10 × log creatinine − 1.77; r = 0.72, P < 0.001. The logarithmic transformation was selected because it produced the most linear relation.

**FIGURE 11.** Nonparametric receiver operating characteristic plot for the diagnostic accuracy of the ratio of 4-pyridoxic acid to pyridoxal to detect serum creatinine concentrations >133 μmol/L, which indicate renal dysfunction.
result of vitamin B-6 supplementation, with the result that the PA:PL remained <100.

Although an inhibitor-substrate ratio of 167 was needed to achieve 50% inhibition in the platelet uptake studies, pyridoxamine-phosphate oxidase, which oxidizes pyridoxine-P and pyridoxamine-P to pyridoxal-P, was inhibited 52% by 200 µmol pyridoxic acid 5'-phosphate at a substrate concentration of 258 µmol/L (38). This is a substrate-inhibitor ratio of ≈1 to 1 and raises the possibility that some enzymes required for normal vitamin B-6 metabolism might be susceptible to inhibition by pyridoxic acid 5'-phosphate. The only report of pyridoxic acid 5'-phosphate in tissues (39) was later attributed to photolytic oxidation of pyridoxal-P during sample processing (40). Pyridoxic acid 5'-phosphate was not detected in rat liver after perfusion with pyridoxine (41). These observations raise the possibility that the high plasma 4-pyridoxic acid concentrations associated with renal dysfunction might interfere with the uptake and metabolism of vitamin B-6 by platelets and possibly other cells and tissues and might lead to formation of sufficient pyridoxic acid 5'-phosphate to interfere with some reactions in vitamin B-6 metabolism. In conclusion, our data indicate disproportionate increases in plasma 4-pyridoxic acid 5'-phosphate to interfere with pyridoxic acid 5'-phosphate in tissues (39) was later attributed to photolytic oxidation of pyridoxal-P at a substrate concentration of 258 µmol/L (38).

We acknowledge the technical assistance of R Frederick.

REFERENCES