Retention of an albumin-bound furan dicarboxylic acid in patients with chronic renal failure or after a kidney transplant

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Abstract

Background. 3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (5-propyl FPA) is a furan dicarboxylic acid which accumulates in the plasma of patients with renal impairment. 5-Propyl FPA is an inhibitor of the binding of drugs to albumin and is also implicated in other aspects of the uraemic syndrome.

Methods. Plasma concentrations of propyl FPA have been measured in non-dialysis-dependent, chronic renal failure patients and in renal transplant patients by high-performance liquid chromatography. Concentrations of haemoglobin, albumin and creatinine were also determined.

Results. There was a positive correlation between serum creatinine and 5-propyl FPA and a negative correlation between haemoglobin concentration and 5-propyl FPA in chronic renal failure patients. There was a negative correlation between 5-propyl FPA and duration of transplant only when the serum creatinine was > 200 µM. The mean plasma concentration of 5-propyl FPA in chronic renal failure patients with plasma creatinine < 200 µM was similar to controls but the mean concentrations were significantly elevated in these patients and also in transplant patients when their plasma creatinine > 200 µM. Despite a successful renal transplant the plasma concentration of 5-propyl FPA remained higher than in either controls or in patients with an equivalent degree of renal impairment from miscellaneous causes.

Conclusions. This retention of 5-propyl FPA may therefore reflect a specific tubular defect in renal transplant patients treated with cyclosporin and points to the possibility that 5-propyl FPA may serve as a marker of tubular dysfunction.

Key words: furan dicarboxylic acid; 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; chronic renal failure; renal transplant; albumin; protein binding

Introduction

3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (5-propyl FPA), a furan dicarboxylic acid, was discovered in normal human urine by Spiteller and Spiteller [1] and in blood by Pfordt et al. [2]. 5-Propyl FPA may originate from the diet [3,4] and also from the breakdown of long-chain fatty acids [5]. Liebich et al. [6] first identified 5-propyl FPA in the plasma of uraemic patients and observed that it was not removed by haemodialysis; they attributed this to protein binding, although this was not studied. Shortly afterwards we found that 5-propyl FPA was a potent inhibitor of binding [7-10] and had a high affinity for albumin [11,12] and was thus an important contributor to the drug binding defect of uraemic plasma.

Many organic acids are retained in the bloodstream in chronic renal failure and there is increasing evidence of their toxicity. Identification of the major uraemic toxins is, however, a difficult and slow process [13,14] but 5-propyl FPA is involved with several aspects of the uraemic syndrome: it inhibits the binding of organic acids (including drugs and endogenous acids) to albumin [7-11, 15-18] and also the renal uptake of PAH by rat kidney cortical slices in vitro [18-20]. Conversely the clearance of 5-propyl FPA from rat plasma in vivo is decreased by both PAH and probenecid [21], which is further indication that this furan acid may inhibit the transport of drugs which are actively secreted via the 'PAH' pathway. Earlier work by Depner [22] had confirmed that the unidentified binding inhibitors in an extract of human uraemic plasma also inhibited the uptake of PAH by rat kidney slices and suppressed its secretion by the isolated rat kidney [23]. Another inhibitory effect of 5-propyl FPA is on the cellular transport of thyroxine in the cultured rat hepatocyte [24]. There are also indications that 5-propyl FPA may be involved in the neurological symptoms of chronic renal failure [25] and inhibition of the transport of organic acids in the brain across the choroid plexus (sometimes referred to as the 'kidney in the brain') is one of the hypothetical mechanisms.

The plasma concentrations of 5-propyl FPA have...
been measured in chronic renal failure (CRF) patients and in renal transplant patients in order to make a comparison with previous studies in both Germany [6,26–28] and Japan [17,29,30] to establish whether dietary or genetic factors affect 5-propyl FPA levels. The haemoglobin levels were measured in both sets of patients to investigate the link postulated by Niwa et al. [30] between the anaemia associated with renal failure and 5-propyl FPA.

Subjects and methods

The CRF group comprised 31 patients (10 female; ages 29–74 years; the diagnoses were glomerular nephritis, 13; CRF of uncertain aetiology, 7; polycystic kidney disease, 6; hypertension, 5) and the transplant group 30 patients (10 female; ages 17–70 years). An equal number of patients received frusemide or bumetanide (organic acids) as the diuretic. Antihypertensive therapy in both groups was similar with previous studies in both Germany [5–Propyl FPA] (μM) and in renal transplant patients to investigate the link postulated by Niwa et al. [30] between the anaemia associated with renal failure and 5-propyl FPA.

Results

The mean plasma concentration of 5-propyl FPA in the control group was 14 ± 7 μM (± SD; n = 21; 95% confidence interval 11–17 μM) in agreement with findings from other studies [32].

Chronic renal failure patients

The CRF patients studied were all non-dialysis dependent and had not undergone transplantation (Table 1). The mean concentration of 5-propyl FPA did not differ significantly from control levels. The haemoglobin levels were low compared with controls, the serum creatinine concentrations were high but the serum albumin concentrations were within the reference range. There was a positive correlation between the concentration of 5-propyl FPA and serum creatinine concentration (r = 0.58, P < 0.001) and a negative correlation between 5-propyl FPA and haemoglobin concentration (r = 0.59, P < 0.001). There was no correlation between the concentration of 5-propyl FPA and either the duration of renal disease or the serum albumin concentration.

Although the serum creatinine concentrations of the renal patients as a whole were higher than normal, there was a large variation in the serum creatinine concentrations (74–989 μM) and so for further analysis of the data the patients with chronic renal failure were split into two groups depending on whether the serum creatinine concentration was greater or less than 200 μM. This value was chosen arbitrarily because it is indicative of the loss of critical renal mass and usually determines significant renal failure. There were 11 patients with serum creatinine > 200 μM and 20 patients where serum creatinine < 200 μM. There were no significant differences between age, duration of renal disease or serum albumin concentration between the two groups (Table 1).

The plasma concentration of 5-propyl FPA was significantly higher when serum creatinine > 200 μM compared with serum creatinine < 200 μM and this was significantly higher (P < 0.001) than control values. The haemoglobin concentration was significantly

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Total (n = 31)</th>
<th>SC &lt;200 μM (n = 20)</th>
<th>SC &gt;200 μM (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 ± 16</td>
<td>58 ± 13</td>
<td>48 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of CRF (years)</td>
<td>5.2 ± 4.6</td>
<td>6.5 ± 4.2</td>
<td>4.5 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>[Haemoglobin] (g/dl)</td>
<td>13.2 ± 2.4</td>
<td>14.4 ± 1.8</td>
<td>11.1 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[Serum albumin] (g/l)</td>
<td>42 ± 6</td>
<td>41 ± 7</td>
<td>43 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>[Serum creatinine] (μM)</td>
<td>246 ± 217</td>
<td>128 ± 39</td>
<td>461 ± 243</td>
<td>-</td>
</tr>
<tr>
<td>[5-Propyl FPA] (μM)</td>
<td>29 ± 34</td>
<td>11 ± 10</td>
<td>61 ± 39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>(17–41)</td>
<td>(6–16)</td>
<td>(35–87)</td>
<td></td>
</tr>
</tbody>
</table>

NS, non-significant.
Statistical analyses were performed with the Student's unpaired t-test between the two serum creatinine groups.
Furan acid in renal failure

Table 2. Clinical data obtained from all renal transplant patients, in patients with serum creatinine <200 uM, and with serum creatinine >200 uM

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 30)</th>
<th>SC &lt; 200 uM (n = 15)</th>
<th>SC &gt; 200 uM (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42 ± 14</td>
<td>40 ± 14</td>
<td>44 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of transplant (years)</td>
<td>3.3 ± 3.4</td>
<td>2.8 ± 3.5</td>
<td>3.7 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>[Haemoglobin] (g/dl)</td>
<td>12.7 ± 3</td>
<td>13.8 ± 1.6</td>
<td>11.7 ± 1.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>[Serum albumin] (g/l)</td>
<td>42 ± 4</td>
<td>44 ± 4</td>
<td>41 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>[Serum creatinine] (µM)</td>
<td>240 ± 153</td>
<td>141 ± 47</td>
<td>339 ± 158</td>
<td>-</td>
</tr>
<tr>
<td>[5-Propyl FPA] (µM)</td>
<td>34 ± 19</td>
<td>28 ± 19</td>
<td>39 ± 19</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, non-significant.
Statistical analyses were performed with the Student’s unpaired t-test between the two serum creatinine groups.

higher when serum creatinine <200 uM. There were no correlations between plasma 5-propyl FPA and any other factor in either of the two groups.

Renal transplant patients

The mean plasma concentration of 5-propyl FPA in these patients was significantly higher than that found in controls (Table 2). Haemoglobin concentration was lower than controls, serum creatinine was higher and serum albumin concentration was within the reference range, as was found in the CRF patients.

There was no correlation between the concentration of 5-propyl FPA and the duration of transplant, haemoglobin, serum creatinine or serum albumin. As with the CRF patients there was a large variation in the serum creatinine concentrations of the transplant patients (31–706 uM) and so again for further analysis the patients were split into two groups depending on whether serum creatinine was greater than or less than 200 uM (Table 2).

There was no significant difference between age, duration of transplant, serum albumin concentration or 5-propyl FPA concentration between the groups. However, in both groups 5-propyl FPA concentrations were significantly higher than controls (P < 0.05, serum creatinine <200 uM and P < 0.001, serum creatinine >200 uM respectively). The haemoglobin concentration was significantly higher when serum creatinine was <200 uM.

There was a negative correlation between 5-propyl FPA concentration and duration of transplant when serum creatinine >200 uM (Figure 1). It appears therefore that the transplanted kidney can, given time, decrease the 5-propyl FPA concentration in plasma. No other correlations were found with 5-propyl FPA in either group.

Comparison of CRF patients and transplant patients

The CRF patients tended to be older than the transplant patients, but the difference was not statistically significant. The plasma concentration of 5-propyl FPA was significantly higher (P < 0.05) in transplant patients than that in CRF patients but there were no significant differences between haemoglobin concentrations or serum albumin concentrations.

When the serum creatinine <200 uM, the plasma concentration of 5-propyl FPA was significantly higher in transplant patients than in CRF patients (P < 0.001), however when serum creatinine >200 uM, this was not significant. There were no statistically significant differences in the values of haemoglobin, serum creatinine or serum albumin when the patients were divided into two groups on the basis of their serum creatinine concentration.

Discussion

The mean plasma concentration of 5-propyl FPA in CRF patients overall did not differ significantly from controls and this is in agreement with the observations of Liebich et al. [26,27] in a German population. Furthermore there was no obvious influence of genetics or diet. It is clear from the data reported here, however, that as serum creatinine concentration increases there...
is a subsequent increase in the plasma concentration of 5-propyl FPA, and there is a good correlation between these two parameters. The negative correlation between 5-propyl FPA levels and haemoglobin concentration in CRF patients suggests that 5-propyl FPA may have a role in the anaemia associated with renal failure [30,32].

The plasma concentrations of 5-propyl FPA in patients following renal transplant were significantly higher than those seen in either controls or CRF patients, even 3 years (on average) after transplantation. Mabuchi et al. [29] and Liebich et al. [26] both reported a slow decline in the plasma levels of 5-propyl FPA after a transplant, Liebich suggesting that it may require 2–4 months before the normal range is reached, whereas Mabuchi did not comment. The results presented here, from a larger group of patients, indicate that the levels may never return to those of controls. The reason for the slow decline of 5-propyl FPA concentration is not clear. There may be a large body burden of such organic acids competing for tubular secretion and also the slow decline in 5-propyl FPA concentration may be due to the immunosuppressant drugs used in the post-transplant period [29].

The patients in this study received cyclosporin as the only immunosuppressant; its nephrotoxicity occurs in three stages: immediately after transplant, 2–3 weeks after transplant, and long-term, with a slow decline of renal function and interstitial fibrosis [33]. This may explain the continued elevation of 5-propyl FPA concentrations after transplant, although even when serum creatinine concentrations fell below 200 μM the concentration was still significantly higher than control levels, indicating that other factors, such as a large tissue burden of 5-propyl FPA may be responsible. When serum creatinine concentrations were greater than 200 μM there was a significant correlation between plasma concentration of 5-propyl FPA and duration of transplant, which suggested that a slow decline in 5-propyl FPA concentration occurred with time. However, once serum creatinine concentrations fell below 200 μM and renal function approached normality, this correlation was not seen. Thus it appears that the transplanted kidney can excrete 5-propyl FPA, but the concentration levels off at a concentration which is significantly higher than control values, even though kidney function as defined by the creatinine marker appears to be adequate. It should also be noted that when serum creatinine concentration was less than 200 μM in CRF patients, the 5-propyl FPA concentration was similar to controls.

Another reason for the persistent elevation in the concentration of 5-propyl FPA may well be competition for active secretion between 5-propyl FPA and a metabolite of cyclosporin, which is primarily metabolized by the cytochrome P450 III system [34]. The competition or indeed inhibition is not likely to be due to cyclosporin itself, because cyclosporin did not affect the uptake of 5-propyl FPA by rat kidney cortical slices, even at a cyclosporin:5-propyl FPA ratio of 5:1 (unpublished observation). Cyclosporin or one of its metabolites is thought to impair the tubular secretion of uric acid and thus induce hyperuricaemia in patients [35]. This implies that if it is cyclosporin or a metabolite that affects the excretion of 5-propyl FPA, it acts on more than one pathway of active tubular secretion, because uric acid (400 μM) had no effect on the active uptake of 5-propyl FPA (75 μM) by rat kidney slices (unpublished observation).

The concentrations of other organic acids in transplant patients decrease more rapidly than 5-propyl FPA, for example indole-3-acetic acid decreases rapidly during the first 1–3 days after a transplant [29] and hippuric acid returns to normal levels after 3–7 days [26]. These two organic acids are only weakly bound to plasma albumin, and so another possible contributory factor to the elevation of 5-propyl FPA post-transplant is its high affinity for albumin. This would also explain the prolonged protein-binding defect observed after a transplant despite an initial improvement in binding [29]. Mabuchi and Nakahashi [11] suggested that the binding defect following transplantation may be due to hypoalbuminaemia; however, in our patients there was no evidence of this. The continued binding defect is therefore probably caused by the presence of highly protein-bound organic acids, including 5-propyl FPA, which are not excreted efficiently by the kidney in transplant patients.

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References


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