Plasma Changes of Pituitary Protein 7B2 in Chronic Renal Failure Before and After Haemodialysis, Comparisons with Pituitary Hormones and Neuropeptides

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Plasma Changes of Pituitary Protein 7B2 in Chronic Renal Failure Before and After Haemodialysis, Comparisons with Pituitary Hormones and Neuropeptides

**Author(s):** Venetikou M S, Meleagros L, Bloom S R, Ghatei M

**Abstract**

Pituitary protein 7B2, is a highly conserved molecule, located in the gonadotrophs and released by luteinising hormone releasing hormone (LHRH), in vitro and in vivo.

7B2-immunoreactivity (7B2-IR) was estimated in patients with chronic renal failure (CRF) before and after haemodialysis.

Twenty patients (twelve male, eight female) aged 18-67 (43.9 ± 17.7 [SD]) years with CRF were studied before and after haemodialysis. A blood sample was taken from the haemodialysis access site (Cimino fistula) [n=13] or Scribner shunt [n=7]. Haemodialysis was then carried out using a hollow fibre AK 10 dialyser and Gambro control unit. A second blood sample was taken ten minutes after the end of haemodialysis. Pre and post-dialysis blood pressure, pulse and weight were recorded. Plasma creatinine was also recorded before and after haemodialysis. 7B2-IR was estimated using a sensitive radioimmunoassay (RIA). Chromatography was used to verify the expected elution position of 7B2.

Mean plasma creatinine fell from 1223 ± 52 (645 - 1500) µmol/l before to 546 ± 40 (230-900) µmol/l after haemodialysis (p < 0.001).

7B2 concentrations in 20 patients with CRF before haemodialysis were found to be 123 + 7.4 pmol/l, post-dialysis 7B2 levels were 262 + 19.5 pmol/l, significantly increased compared to those seen during pre-dialysis (p < 0.01). 7B2 levels in patients with CRF correlated positively with plasma creatinine (r = 0.48, p < 0.04). A representative chromatographic profile of 7B2– IR in plasma of CRF patients eluted at the expected position.

7B2-IR is increased in CRF patients and is further increased after haemodialysis.

**Introduction**

A protein of approximately 180 amino acids designated 7B2 was isolated from the anterior porcine pituitary and was found to be mostly in the pituitary and the hypothalamus (Hsi et al.1982). 7B2 was found to be located mainly in the gonadotrophs (Marcinkiewicks et al.1986) and to be secreted by LHRH by the normal rat pituitary cells in vitro (Deng et al.1986). Natori et al. (1989) noticed that LHRH when given IV (100 µg) in humans could increase 7B2 in the plasma of healthy volunteers; functionless pituitary adenomas which are known to secrete in vitro high alpha subunit or luteinising hormone (LH) levels (Mashiter et al.1981) have been shown to secrete the highest 7B2 levels in vitro among other pituitary adenomas (Venetikou et al., 1988).

Through the years it was found to be also located in tissues that are either primary neuronal (the brain and the adrenal medulla) or endocrine (pituitary, thyroid, pancreas), or are known to carry a sub–population of neuroendocrine cells (gastrointestinal tract); the highest amounts are found in the anterior lobe of the pituitary, followed by the neurointermediate lobe, the hypothalamus, the adrenal medulla, the thyroid gland and the pancreas (Mbkay et al., 2001). Apart from the gonadotrophs, 7B2 was found to be located inside secretory granules of various neuroendocrine cells and to be co-localised with arginine vasopressin (AVP) (supraoptic nucleus), AVP, galanin, oxytocin, neuremedin B and U (paraventricular nucleus), LH, follicular stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), growth hormone (GH) and prolactin (PRL) (anterior lobe of the pituitary), proopiomelanocortin (POMC), melanocyte stimulating hormone (MSH) (neurointermediate lobe), AVP (posterior pituitary lobe), calcitonin (parafollicular cells of thyroid), calcitonin gene related peptide (CGRP) (lung), somatotrophin release inhibiting hormone (SRH), metenkephalin (met – ENK), neuropeptide Y (NPY) (adrenal medulla), insulin, glucagon, SRIH and pancreatic polypeptide (PP) (gastrointestinal tract and pancreas). (Mbkay et al. 2001). After processing, 7B2 protein is packaged into dense-core vesicles and secreted upon exocytotic stimulation. In cell cultures (normal cells), its secretion seems unaffected by growth hormone releasing hormone (GHRH) and
corticotrophin releasing hormone (CRH) and secretion is increased by LHRH (Deng et al. 1986; Venetikou et al. 1992)

Cloning of the cDNA of POMC mRNA led to the characterisation of the ACTH precursor and established the molecular links between ACTH, beta-lipotropin (beta-LPH) and gamma-LPH and beta-END. Further, previously unidentified POMC-derived peptides were also unravelled, including the N-terminal fragment. POMC is a precursor polypeptide that contains the amino acid sequences of numerous small polypeptide products. It contains eight pairs of basic amino acids and one sequence of four basic amino acids, which are the sites of cleavage for the recently identified prohormone convertases (PC1 and PC2), which have different specificities. PC1 but not PC2 is found in the corticotroph cells of the anterior pituitary and cleaves POMC to generate neurotensin (NT), ACTH, beta-LPH and small amounts of gamma-LPH and beta-END. In the melanotroph cells of the intermediate pituitary, both PC1 and PC2 are present and the proteolysis of POMC is thus more extensive resulting in a series of smaller peptides including gamma-MSHs, corticotrophin intermediate lobe peptide (CLIP), alpha-MSH, beta-MSH, beta-END. Equimolar quantities of the above are released in the circulation. For practical reasons, LPH RIA is used as an overall indication of function of the corticotroph cells (Bertagna 1994).

The pituitary protein 7B2 has been isolated while purifying the N-terminal glycol-segment of POMC from pig anterior pituitaries and it was shown to elute as a distinct peak in a reverse-phase high pressure liquid chromatography (HPLC) of tissue extracts (Hsi et al. 1982).


In the past, Iguchi and co-workers showed that 7B2-IR could be increased in patients with CRF compared to healthy controls. Positive correlations between plasma 7B2, urea, creatinine and b2-microglobulin were shown (Iguchi et al., 1988).

We report 7B2 levels in another group of CRF patients before and after haemodialysis, and the possible mechanisms in view of the very intriguing research data on 7B2 pituitary literature which links 7B2 biological role to the function of the proconvertases.

Patients and Methods

A. Patients

This study was undertaken in collaboration with Dr L Meleagros (Endocrine Unit, Hammersmith Hospital, London). The patients studied were under the care of Drs C Savage and CG Winearls, and were treated at the Renal Unit, Hammersmith Hospital, London. Pulse and blood pressure measurements were carried out by the nursing staff of the Renal Unit, who also took all the blood samples. Twenty patients (twelve male, eight female) aged 18-67 (43.9 ± 17.7 [SD]) years with chronic renal failure (CRF) were studied before and after haemodialysis. The causes of CRF and the medication patients were receiving are shown in table 1. All medication was withheld on the morning of the study. Eleven of these patients had previously received renal transplants (two patients had two transplants each) which had failed. The length of time on haemodialysis, in the group as a whole, ranged from one month to five years and seven months. (median one year, ten months). Fourteen patients received 2 and six patients 3 haemodialysis treatments per week. The duration of each treatment was 3 hours (n=1), 4 hours (n=9), 5 hours (n=3), 6 hours (n=5) and 7 hours (n=2). Immediately before the start of haemodialysis, the patients were weighed and supine pulse and blood pressure were recorded by counting the radial pulse at the wrist and with a standard mercury sphygmomanometer, respectively. A blood sample was then taken from the haemodialysis access site (Cimino fistula) [n=13] or Scribner shunt [n=7]. Haemodialysis was then carried out using a hollow fibre AK 10 dialyser and Gambro control unit. A second blood sample was taken ten minutes after the end of haemodialysis. The post-dialysis blood pressure, pulse and weight were also recorded. Plasma creatinine was estimated before and after haemodialysis.

Blood samples were collected in heparinised tubes for 7B2 and creatinine estimations.

The plasma obtained for 7B2 RIA was stored at -20°C and thawed only once, prior to the assay (100 µl aliquot used). Plasma creatinine was measured (Technicon RA - 1000 automated analyser) by the staff of the Renal Dialysis Unit.

B. Methods

7B2 RIA

A sensitive RIA for 7B2-IR was developed in our laboratory (Suzuki et al 1985).
**Immunization . Preparation of antisera**

A peptide fragment corresponding to residues 23-39 of authentic 7B2 was custom synthesized (CRB, Cambridge, UK) and conjugated to bovine serum albumin (BSA) (Sigma Chemical Co, Dorset, Poole, UK) by carbodiimide. The conjugated material was emulsified in complete Freund’s adjuvant for the primary immunization and in incomplete adjuvant for booster injections. Freund’s adjuvant was prepared by mixing 8.5 ml of n-hexadecane (Koch Light Laboratories Ltd) with 1.5 ml of Arasel A (Sigma) and was then made complete by the addition of heat-killed mycobacteria (1 mg/ml).

Two ml of the emulsified conjugate containing 80 pg of conjugated peptide were injected into New Zealand white rabbits via 0.5 ml subcutaneous injections, one into each groin and axilla. Three months after the primary immunization, booster injections were given at two monthly intervals. Each contained 40 µg of conjugated 7B2 23-39 in 2 ml of incomplete Freund’s adjuvant (i.e. without mycobacteria). The rabbits were bled from the marginal ear vein, seven to ten days after each booster injection. Blood was allowed to clot at room temperature and serum separated by centrifugation. Each harvested serum was then examined to bind $^{125}$I-7B2 (23-39). For this test, 20 µl of undiluted serum was added to each assay tube (in duplicate) containing assay buffer and label to a total volume of 700 µl.

The antisera which exhibited greater than 70% binding after one hour incubation at room temperature followed by charcoal / dextran separation were subsequently tested at three different dilutions in order to determine the optimal working dilution. The antisera used in these studies labelled AG7 was used at a final dilution of 1/160,000 and the affinity constant was 1.9 $\times$ 10$^{11}$ l/mmol with respect to the synthetic fragment. The antibody has been shown to cross-react by 33% with authentic porcine 7B2 on a molar basis. 7B2 cross-reactivities were observed with human insulin, proinsulin, glucagon, secretin, SRIH, human PP, ACTH, N-terminal of POMC, beta-LPH, beta-END, GH, AVP, oxytocin, ovine CRF and vasoactive intestinal peptide (VIP).

**Iodination procedure**


**Standards**

Standards were prepared gravimetrically using synthetic 7B2 fragment. Ten µl aliquots each containing 2 pmol of 7B2 23-39 were lyophilised to 10$^{-2}$ torr and stored in vacuo at -20°C.

**Assay conditions**

All samples were assayed in duplicate in 2 ml polystyrene tubes (LKB, Luckham Ltd). Sample addition was 100 µl in each assay tube. 0.4 ml of 0.6 M phosphate buffer (pH: 7.4), containing 10 mM EDTA, 7.5 mM sodium azide and 150 mM BSA was used as assay buffer. The label and antisera were made up in the same buffer and 100 µl of each was added in every assay tube to give a final volume of 700 µl.

**Separation**

After a five day incubation at 4°C antibody bound label was separated from free by adding 250 µl of a suspension containing 4 mg of charcoal (Norit GSX: Hopkin and Williams) coated with 0.4 mg clinical grade dextran (Sigma) to each tube. The tubes were centrifuged at 1600 g for 20 minutes at 4°C and the supernatant was aspirated immediately.

**Gamma counting**

Following separation, both the charcoal pellet and supernatant were counted in multi-well gamma counters (Nuclear Enterprises 1600). Since synthetic 7B2 23-39 is used as standard, results are expressed as 7B2 Immunoreactive Equivalents (7B2-IE).

Changes of 7B2-IE of 0.9 fmol/assay tube were detected with 95% confidence limits with intra and inter-assay variations of under 15%.

**Chromatographic profiles**

Samples containing 7B2-IE were subjected to gel permeation chromatography. A 1.4 $\times$ 90 cm column of Sephadex G-100 was used to separate the components present in plasma. The column was eluted with a 0.06 M phosphate buffer (pH: 7.4) containing 10 mM EDTA 0.3% BSA and 0.2 M NaCl, at a flow rate of 3.2 ml/h at 4°C.

The column was pre-calibrated with dextran blue ((molecular weight)(MW) 2,000,000), horse heart cytochrome C (MW 12,384) and a trace amount of Na$^{125}$I - Dextran blue, cytochrome C and a trace amount of Na$^{125}$I were added to each sample as internal markers. The elution coefficient (Kav) for each immunoreactive peak was calculated according to Laurent & Killander (1964). Gel permeation chromatography of porcine pituitary extracts showed a major peak (90% of total immunoreactivity), eluting before cytochrome C (Suzuki et al. 1985).

**Statistics**

Statistical analyses were performed using two – tailed t tests.
Results

A. Patients
Haemodialysis resulted in a significant fall in systolic blood pressure from the pre-dialysis value of 149.8 ± 3.7 (120-190) mmHg to 131.8 ± 4.6 (100-170) mmHg (p < 0.01). Mean diastolic blood pressure also fell from 81.5 ± 2.6 (60-100) to 78.5 ± 2.1 (60-90) mmHg but this was not significant. At the same time, the pulse rose from 79 ± 3 (70-96) to 87 ± 3 (74-108) beats/minute (p < 0.05). However, not all patients reacted the same way: systolic blood pressure increased in five patients and was unaltered in one, while pulse decreased in three and remained the same in one. All patients lost weight as a result of dialysis. Mean weight fell from 62.5 ± 3.05 (40.2 - 95.7) kg before, to 60.12 ± 2.84 (39.7 - 90.6) kg after haemodialysis (p < 0.05). Mean plasma creatinine fell from 1223 ± 52 (645 - 1500) µmol/l before to 546 ± 40 (230-900) µmol/l after haemodialysis (p < 0.001) (table 2).

7B2 concentrations in 20 patients with CRF before haemodialysis were found to be 123 ± 7.4 pmol/l; these levels are increased compared to healthy controls studied in our laboratory; post-dialysis 7B2 levels were 262 ± 19.5 pmol/l, significantly increased compared to those levels seen during pre-dialysis (p < 0.01) (figure 1). 7B2 levels in patients with CRF correlated positively with plasma levels of creatinine (r = 0.48, p < 0.04).

B. Chromatography
Representative chromatographic profile of 7B2 plasma in CRF patients is seen in figure 2.

Discussion

7B2-IR was increased in our patients with renal failure. There was a significant increase after haemodialysis compared to pre-dialysis levels.

In our study 7B2 values correlated significantly with plasma levels of creatinine. Our results are in accordance with a previously published report which showed increased 7B2-IR in 27 patients undergoing haemodialysis for treatment of their renal failure (Iguchi et al. 1988). The 7B2 molecule did not seem to permeate through the dialysis membrane due to its large molecular weight; therefore, the elevation of 7B2-IR during haemodialysis was thought to be due to haemoconcentration.

7B2 may be metabolised in the kidney; chromatographic profiles showed that 7B2 circulates as a monomer in plasma of patients with CRF. Iguchi et al (1988) noted the presence of a smaller molecular weight 7B2-IR in the urine of CRF patients. It is therefore possible that the 7B2-IR is also present in urine and that the molecular forms differ from those in plasma. Perhaps this is due to degradation of 7B2 in the kidney.

From the previous literature which showed various hypothalamic-pituitary abnormalities in CRF, and in view that 7B2 is primarily a hypothalamic-pituitary component we may also consider our renal failure data together with other pituitary correlates, especially classical hormones, neuropeptides and various neurotransmitters and their associated changes.

CRF has long been associated with endocrine abnormalities. Various alterations in hormonal levels and responses have been detected in patients with CRF by many investigators. Basal LH and FSH may be either normal or slightly elevated in these patients; LH and FSH responses to LHRH although not different in peak values after stimulation in CRF patients compared to controls, persist significantly in elevation during the second and third hours after the administration of LHRH due to either increased secretion or diminished rate of metabolic clearance of LHRH or the gonadotrophins or both (Schalch et al.1975). Some attenuation of the gonadotrophins’ response to LHRH has been shown in other studies; increased response of LH and FSH to LHRH post-dialysis has been also noticed. TSH response to thyrotropin releasing hormone (TRH) was found to be attenuated in most of the renal failure patients. It was thought that a dissociation in glycoprotein hormone responses to releazoning hormones exists in uremia; whereas the gonadotrophs retain their responsiveness to LHRH, the thyrotrophs appear to be more affected by the ureamic process and demonstrate an impaired response to TRH (LeRoith et al.1980). Higher basal LH and FSH levels were found in 20 end-stage renal failure patients maintained in haemodialysis, and poststimulatory levels of the hormones to LHRH test were significantly lower to normals (Jecht et al.1980). LH and FSH levels were found to be increased in CRF patients which reflect decreased feedback inhibition by primary gonadal failure (frequently seen in renal failure) and that plasma LHRH is not bound to plasma proteins (Matsubara et al.1983). Experimental renal failure in rats suggests that reproductive abnormalities found in CRF may be due to alterations in pituitary LH responses (Nazian et al.1989). Evidence of attenuation of LHRH response impulse strength with preservation of LHRH pulse frequency in men with CRF was reported by Veldhuis et al. (1993). Since
7B2 has been initially linked with the gonadotrophins and responds to LHRH, the increase of its levels in CRF may be due to other involved mechanisms apart from the inability of the kidney to clear 7B2-IR.

Patients with CRF and growth retardation have a higher number of GH peaks and slightly elevated mean GH levels compared to transplant patients (Ferraris et al. 1997). Disturbances of the somatotropic hormone axis play an important pathogenic role for growth retardation and catabolism in children with CRF. The GH secretion in CRF is variable but a prolonged half life of GH as a result of reduced renal metabolic clearance rate is a consistent finding. Insulin growth factor-1 (IGF-1) and IGF-2 levels are normal in pre-terminal CRF, while in end stage renal disease (ESRN), IGF-1 levels are slightly decreased and IGF-2 levels slightly increased; in view to the GH increase, these IGF levels appear inappropriately low in these patients. Increased insulin growth factor binding proteins (IGFBPs) are reported, which may inhibit tissue actions of IGFs (Tonshoff et al. 1997). Basal SRIH levels in patients with CRH were similar in CRF patients and in controls, while SRIH response to oral glucose tolerance test (OGTT) was significantly lower in CRF patients compared to controls, suggesting a loss of SRIH secretory cell responsiveness to glucose in uraemia (Franceschini et al. 1998).

In a study, 10 chronically haemodialysed for 10 years patients with CRF were compared with 7 controls. These CRF patients were studied on the day preceding haemodialysis and received ovine CRH (100 μg IV) and ACTH (Synacten 0.25 mg IV in bolus). Although both ACTH and cortisol levels seemed more increased in haemodialysed patients, the means were not significantly different compared to controls (Vigna et al. 1995).

Various neuropeptides, especially those associated with the gut – brain axis are also disregulated in CRF and renal dialysis patients. Raised plasma levels of pancreatic glucagon are also found in patients with renal failure probably due to the inability of the kidney to clear biologically inactive glucagon fragments (Christofides, 1982). In another study which included 15 CRF patients requiring haemodialysis plasma was assayed before and 4 hours post haemodialysis for gastrointestinal hormonal profile. Before haemodialysis gastrin was minimally increased, but gastrin inhibitory peptide (GIP) and PP were grossly increased compared to normals. Haemodialysis showed no changes in levels of GIP, VIP, PP, SRIH, MOT and NT. Slight increases of insulin and gastrin may be due after haemodialysis to the calcium levels increase. The kidneys appear to be the major site for inactivation of insulin, gastrin, GIP and PP (Sirinek et al., 1984). Plasma atrial natriuretic factor (ANF) was found to be significantly increased in end-stage renal failure patients (Tonolo et al 1989). Most of the known neuroendocrine substances are therefore increased in CRF and 7B2-IR seems to follow the same pattern.

In neuroendocrine cells, 7B2 functions as a specific chaperone for the proprotein convertase PC2 (Braks & Martens 1994). These investigators have proposed that 7B2 serves as an intracellular proPC2 chaperone and prevents the premature activation of thezymogen during its transit in the regulated secretory pathway. It appears that pro7B2 attaches to proPC2 in the ergatoplasm reticulum (ER). This attachment is facilitated by the relative alkaline conditions of this compartment. The inactive complex is transported to the trans Golgi network (TGN) where pro7B2 is cleaved into an N-terminal protein and a C-terminal peptide. ProPC2 then gets autocatalytically cleaved after the prodomain as the complex is transported into secretory granules. In these organelles, the prodomain and the 7B2 fragments dissociate from the enzyme, which then becomes fully activated. Thus, 7B2 regulates PC2 activation (Braks & Martens 1994). 7B2 and PC2 proteins are both packaged into secretory granules. The PC2-7B2 model defines a new neuroendocrine paradigm whereby proteolytic activation of prohormones and proneuropeptides in the secretory pathway is spatially and temporally regulated by the dynamics of interactions between converting enzymes and their binding proteins. 7B2 has also been grouped with the chromogranins and secretogranins in the so called granin family of proteins, one of whose presumed functions is to facilitate the sorting of neuroendocrine proteins from the secretory granules (Ozawa & Takata 1995). Therefore it can be co-released when some of the above mentioned substances are overproduced.

By studying POMC expressing non-pituitary tumours, corticotrophin-like-intermediate lobe peptide (CLIP), a product of corticotrophin cleavage by PC2, was found only in those tumours that express this convertase (Vieau et al 1994) and it can be assumed that these tumours also contain 7B2. Immunological analysis of pathological tissues has revealed more extensive association of 7B2 with neuroendocrine tumours than titration of its circulating levels. It has been shown in the majority of benign and approximately half of the malignant pancreatic tumours, mostly in insulin – producing ones (Suzuki et al. 1986; Azzoni et al. 1992; Vieau et al. 1994), but insulinomas containing only proinsulin (and not its active mature form) were found.
to lack also 7B2 (Azzoni et al. 1992). It has also been detected in pituitary tumours (Venetikou et al 1988; Lloyd et al. 1995; Takumi et al. 1998).

It is also of interest, that unlike PC2-null mice which are viable, 7B2 null mutants die early in life from Cushing’s disease due to “ACTH” hypersecretion by the intermediate lobe, suggesting a possible involvement of 7B2 in secretory granule formation and in secretion regulation (Westphall et al. 1999). The 7B2-null mice with “Cushing’s” can be saved early in life by adrenalectomy (Laurent et al 2002). Neither our plasma ACTH tumours of Cushing’s patients (Venetikou 1992), nor these seen by Natori et al (1988, 1990) in the past, allow us to conclude that 7B2-IR in plasma is increased in Cushing’s disease. Corticotrophic adenomas in vitro have not shown increased 7B2 secretion, although 7B2 is concomitantly secreted with ACTH by AtT-20 tumourous cells in vitro (Venetikou et al 2008).

Besides being useful in PC2 physiology, 7B2 is also important as a tumour marker and its plasma levels do not necessarily unravel its function.

7B2 is an intriguing molecule which has been linked with many metabolic changes in tissues of null cell mice (Sarac et al. 2002) and whose definite function remains to be elucidated in view of the fact that it appears to exist in cells where PC2 activity is not evident (Seidel et al., 1998), suggesting a bigger biological role for 7B2 than PC2.

Systemic disorders clearly may exert a significant influence on neuroendocrine function. Disorders that cause significant stress to the body, either physical or psychological, may cause a resetting upward of the hypothalamic-pituitary-adrenal (HPA) axis to provide sufficient cortisol to counteract the stress and to help sustain energy substrate levels. GH levels also increase in many of these situations, again promoting sufficient energy substrate levels. In some circumstances the concomitantly low IGF activity may be speculated to be adaptive to prevent the insulin-like agonist activity of these substances as well as to prevent energy expenditure in body growth. In situations such as CRF, the decreased IGF activity may be primary, causing decreased feedback at the hypothalamic-pituitary level and increased GH levels. (Molitch & Hou 1983). It could be argued that 7B2 increase in a systemic illness such as CRF may also follow the pattern of the above mentioned pituitary hormones and neuropeptides. Thus its plasma changes could be more than a clearance matter.

To date, no elucidation of the hypothalamic-pituitary target-gland changes in such illnesses such as CRF has been totally conclusive either as far classical hormones or other neuropeptides are concerned. Studies with various designs and patient numbers may be further required to give definite conclusions.

References


Causes of CRF in twenty patients treated with haemodialysis. Also listed are the drugs these patients were receiving at the time of the study.

**DIAGNOSIS AND DRUG THERAPY IN CRF PATIENTS**

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<tr>
<td>Pyelonephritis</td>
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<td>Diabetes</td>
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<tr>
<td>Drug Therapy</td>
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</tr>
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<td>----------------</td>
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<td>Ranitidine</td>
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<td>Frusemide</td>
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<td>Tolbutamide</td>
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Illustration 2

Table 2

Haemodynamic variables, weight and plasma creatinine (mean±SEM); P value (two tailed t-test); quoted ns = non significant.

<table>
<thead>
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<th>Post-dialysis</th>
<th>p value</th>
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<td>Diastolic BP</td>
<td>81.5±2.6</td>
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<tr>
<td>Pulse</td>
<td>79±3</td>
<td>87±3</td>
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<tr>
<td>Weight</td>
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<td>60.12±2</td>
<td>p&lt;0.05</td>
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<tr>
<td>Plasma creatinine</td>
<td>1223±52</td>
<td>546±40</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
Illustration 3

Figure 1

7B2 concentrations in patients with CRF (n=20) before and after haemodialysis ** p< 0.01
Representative plasma 7B2 chromatographic profile obtained from patients with CRF. The column was calibrated with dextran blue (Vo), horse heart cytochrome C (CC) and NaI 125 (Vt) as molecular size markers.

Illustration 4

Figure 2
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