Letters and Replies

Preservation of renal function: the spectrum of effects by calcium channel blockers

Sir, N. Tarif and L. Bakris recently pointed out that non-dihydropyridine calcium channel blockers (DHPCCBs) may offer protection to the kidney not available with DHPCCBs alone [1]. They however failed to outline that marked differences exist among DHPCCBs. It is well recognized that antihypertensive agents that normalize glomerular capillary pressure \( P_{\text{GC}} \) most likely slow the progression of renal disease, whereas drugs that control systemic, but not glomerular, hypertension do not necessarily afford renal protection [2]. In experiments nifedipine, nicardipine and amloidipine dilate only the afferent arteriole [3–5] whereas other DHPCCBs such as felodipine [6], manidipine and efonidipine [3–4] dilate both the afferent and the efferent arterioles, and may decrease \( P_{\text{GC}} \).

In hypertensive patients amloidipine has been shown to increase filtration fraction [7] suggesting only preglomerular vasodilation. On the other hand felodipine perfusion has been shown to decreased filtration fraction in hypertensive renal insufficiency patients and healthy subjects [8] with only minor changes in systemic blood pressure, thus clearly indicating that in addition to dilating afferent arteriole felodipine dilates efferent arteriole.

As outlined by Tarif and Bakris very few studies have addressed the effects of DHPCCBs on progression of renal disease in humans [9,10]. However, with the exception of nifedipine, most of them have shown that DHPCCBs have equivalent effects to ACE inhibitors on proteinuria and renal function [9,10]. I therefore agree that further studies should make precise the effects of DHPCCBs in patients with overt proteinuria and renal insufficiency.

DHPCCBs should not be viewed as a uniform class. Further studies should probably focus on the effect of DHPCCBs which have favourable intrarenal effects (i.e. which decrease \( P_{\text{GC}} \)), on progression of renal disease in humans.

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Reply

Sir,

We read with interest Dr Deray’s comments regarding a possible difference in the renal haemodynamic effects within the subclass of dihydropyridine calcium channel blockers (DHPCCBs). While we agree with Dr Deray that some of the newer DHPCCBs possess the ability to dilate the efferent arteriole, specifically, efonidipine and possibly manidipine, the fact remains that these data are garnered from acute animal studies. Moreover, the data with felodipine are not only acute but are performed in humans. Thus, we can only conjecture about the intrarenal haemodynamic effects of felodipine.

It is interesting to note, however, that all of the animal data in either diabetes or remnant kidney models with ACE inhibitors show protection against glomerulosclerosis [1–4]. The exact opposite is seen with DHPCCBs. DHPCCBs uniformly fail to prevent either glomerulosclerosis or reduce proteinuria in these animal models [1–4]. Nevertheless, the author makes the statement that ‘… with the exception of nifedipine, most of them have shown that DHPCCBs have equivalent effects on proteinuria and renal function.’ We strongly disagree with this assertion. What is particularly disturbing is that he has selected two studies with a small number of patients, one of which is a short-term, 6-month study and the other published in a journal supplement.

While there are no long term randomized clinical trials as yet with DHPCCBs, other than nifedipine, that address progression of renal disease, there are two long-term randomized trials that evaluate two different CCBs. The first is the FACET trial that randomized close to 400 patients with type II diabetes to either fosinopril or amloidipine and evaluated cardiovascular events over a 3-year period [5]. The second is the ABCD trial that randomized over 900 patients with type II diabetes and nephropathy to either an ACE inhibitor or nisoldipine and evaluated progression of renal disease and cardiovascular events for a period of approximately 3 years [6]. The FACET trial was stopped early due to a high cardiovascular event rate in the amloidipine group [5]. The results of the second trial will soon be available. Additionally, the PRAISE trial that evaluated amloidipine in...
heart failure noted that more than twice as many people had a rise in serum creatinine in the amlodipine group when compared to placebo [7]. Everyone in this trial received an ACE inhibitor. These results could not be explained by differences in blood pressure control or by the differential use of ACE inhibitors.

Thus, to truly define whether the haemodynamic effects possessed by this subclass of DHPCCBs will ultimately translate into clinical benefit remains to be seen. A large randomized, double blind trial that extends over a period of at least 3 years in high-risk patients needs to be performed. Unfortunately, no such data exist and that presented by the author lacks sufficient duration of follow-up and power as defined by patient number. Additionally, the majority of the studies are published in a supplement rather than the actual journal, thus, bringing into question whether they were peer-reviewed.

As is well known, increases in intraglomerular pressure are only one mechanism that contributes to renal injury in diabetes. Diabetes is a chronic disease that mechanically involves not only changes in intraglomerular pressure but also loss of renal autoregulation and alterations in mesangial matrix. These latter changes are mediated through mechanisms that do not involve haemodynamics. Thus, based on the current data from animal and human studies, DHPCCBs, in general, have the same renal profiles as nifedipine. Efonidipine and possibly manidipine may yield different outcomes with regard to the development of glomerulosclerosis in animal models. However, results of human trials will ultimately guide therapeutic decisions and at this time these are lacking.

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Letters (extended clinical observations)

Interferon-induced acute renal failure in nephrotic syndrome

Case

A 38-year-old Saudi male presented to another hospital in 1994 with uncontrolled hypertension. He was known to have bronchial asthma for many years controlled by beta_2_ agonist inhalers and occasionally steroid inhalers. He was known to have hypertension for which he was getting treatment. In late 1994 he was admitted to his local hospital because of progressive lower limb oedema and was found to have nephrotic syndrome. His 24 h urine protein collection was 15 g and his renal function was normal. A renal biopsy was done which revealed a diagnosis of membranous glomerulopathy. He was treated with oral steroids for 6 weeks but without any improvement.

In October 1995 he was first seen in our hospital when he presented with exacerbation of bronchial asthma, progressive swelling of lower limbs and uncontrolled hypertension. He was admitted and started on steroids to which he responded very well and were tapered quickly. He was kept on beta_2_ agonists and steroid inhalers. His blood pressure was better controlled after increasing the enalapril to 10 mg a day and adding amlodipine 10 mg daily. At this stage his liver function tests were normal except serum albumin which was 19 mg/dl and his renal function was normal. His serum creatinine was 158 µmol/l and urea 9.6 mmol/l. His CBC was normal and he was hepatitis C antibody negative but hepatitis surface antigen positive, E antigen negative. Serum cryoglobulins were negative and anti-GBM antibodies were negative. Anti-DNA was negative and complements were all within normal, P and C ANCA are negative and his blood sugar was within normal, ESR was 32. He had ultrasound of the abdomen which showed normal size kidneys and his PT and PTT were both normal. His total serum cholesterol was 10.9 mg/dl and his triglycerides were high at 2.4 mg/dl. Chest X-ray revealed mild cardiomegaly and his ECG showed left ventricular hypertrophy. Urine analysis did not show RBC casts or white blood cell casts, but showed some granular casts. The renal biopsy was reviewed and confirmed the diagnosis of membranous glomerulonephropathy and special stains were positive for hepatitis B antigen and core antibodies. Our working diagnosis was that this patient had nephrotic syndrome secondary to membranous glomerulopathy as a result of persistent hepatitis surface antigenaemia.

He was started on frusemide, albumin infusion, bed rest, fluid and salt restriction. Gradually his oedema improved and he was discharged on amlodipine 10 mg, enalapril 10 mg and 40 mg Lasix daily, cholesterol lowering agents (Lipostat 20 mg daily) and beta_2_ agonist inhalers for his bronchial asthma. At discharge his serum creatinine was normal (101 µmol/l). He was seen in the clinic with a stable renal function and controlled blood pressure. Since October 1995 he was admitted three times because of exacerbation of his bronchial asthma, and worsening oedema. He was seen lately in November 1996 because of exacerbation and worsening of his lower limb oedema. A repeated 24 h urine collection showed 11 g/24 h, and his renal and liver functions were normal. Blood pressure was controlled. This time the possibility of treating him with interferon was entertained and it
was explained to the patient the risks and hazards, and the possibility of failure of treatment, and he accepted the idea. He was started on alpha interferon 3 million units subcutaneously three times a week. The first dose was given on 4 December 1996 which he tolerated well except for a mild grade fever and arthralgia which subsided while in the hospital, and he continued to have normal renal function and controlled blood pressure. Just before discharge his serum creatinine was 104 μmol/l and his urea was 7.1 mmol/l. On follow-up (after five doses of interferon) his creatinine was high for the first time at 213 μmol/l and his urea was 11.2 mmol/l, interferon was stopped and the patient admitted to hospital for evaluation. Two days later his serum creatinine was 622 μmol/l and urea 22.9 mmol/l. His renal function was progressively rising, he was clinically not dehydrated, not febrile. He was not taking any drugs which could cause deterioration of his renal function (no nephrotoxics given to him). He did not have any symptoms apart from feeling fatigued, dizzy and nauseated. In 5 days his serum creatinine reached 1183 μmol/l and his urea was 37 mmol/l with bicarbonate of 14. Ultrasound of the kidneys was done which showed enlarged kidneys with increased cortical echogenicity and free ascitic fluid. He had Doppler ultrasound which showed normal flow in both renal veins and arteries. DTPA scan was done which showed good uptake and delayed excretion suggestive of acute tubular necrosis. His CBC was normal and his urine sodium was 33 mmol, potassium 23 mmol. Again his urine microscopy showed abundant granular casts but no RBC casts. PT and PTT were both normal. Our working diagnosis was acute renal failure secondary to interferon. He was kept on bed rest, low salt diet and restriction of his fluid. He was challenged with large doses of Lasix without improvement and we started him on dopamine at a renal dose (3–5 μg/kg/min). Within 2 days he started to pass more urine which rose from 400 ml per day, reaching about 1 l daily. Gradually his renal function improved. By day 15 after admission he had a serum creatinine of 234 mmol/l and urea of 21 mmol/l. By the end of the third week he had normal renal function, serum creatinine 113 μmol/l, urea 13.6 mmol/l (Figure 1). His total serum protein was 45 mg/l, serum albumin was 21 mg/dl and his repeated 24 h urine collection was 8 g of protein. His blood pressure was controlled, oedema was minimal and he was discharged in a good condition on beta agonist inhaler for his bronchial asthma, enalapril 10 mg daily, Lipostat 20 mg daily for his cholesterol and amlodipine 10 mg daily. He was kept on Aspirin 100 mg per day. A month later he was seen in the clinic with normal renal function.

Our patient suffers from nephrotic syndrome. The renal biopsy clearly showing membranous glomerulonephropathy with positive stain for core antibodies and surface antigen. He was suffering from severe proteinuria to the extent that required many admissions and it was limiting his daily activity, especially in his work as a driver. We elected to treat him with interferon hoping he would respond to such treatment.

Glomerulonephritis induced by viral hepatitis has been treated in uncontrolled studies with interferon therapy in a small number of patients in an effort to eradicate the hepatitis B virus antigenemia. Some of these reports show improvement, either complete or partial remission in their proteinuria [1]. Mesangiproliferative and membranous glomerulonephritis have been reported in association with hepatitis B surface antigen infection [1]. However, all three major hepatitis B virus antigens including hepatitis surface antigen, E antigen and B core antigen had been localized by immunofluorescence in the glomerular capillary walls of such patients [2]. In our patient repeated renal biopsy was positive for hepatitis surface antigen and core antigen. Based on observations clearance or loss of hepatitis B virus serology marker is frequently associated with the resolution of the nephrotic syndrome [3,4]. A report from Taiwan showing two groups of patients treated with interferon had a remarkable response to interferon with regression of their proteinuria almost to normal range, and some of these patients even seroconverted to hepatitis E antigen negative, follow-up of these patients up to 1 year shows good response without recurrence of hepatitis serology status to positive, and there were no complications reported [5]. Our patient was suffering from massive proteinuria and oedema limiting...
his daily activity and we chose to treat him with interferon based on the above mentioned literature. We followed him very closely because there are various reports of patients treated with interferon who develop acute renal failure and/or proteinuria [6–8]. In some of these reports, renal biopsies were done and the pathology shows either interstitial nephritis or acute tubular necrosis [9–11]. In most of these reports such patients were on chemotherapy and their primary diagnosis was malignancy, especially haematological malignancies. A recent report on 16 patients who had a kidney transplant and had hepatitis C treated with interferon, there is a conclusion that up to 40% of these patients develop renal failure and their histological finding mainly showed diffuse interstitial oedema [12].

The question remains how interferon causes acute renal failure. One explanation by Eleanor Laderer, based on a pathological finding in which she suggests induction of an autoimmune state by interferon, may play a role in such renal insult [8]. However, acute renal failure induced by interferon remains a dilemma, though some authors believe it has a direct nephrotoxic effect [10], others think it is an alteration of T lymphocytes [9]. Whatever the mechanism of renal failure, the usual pathological finding includes either acute severe tubular necrosis or interstitial nephritis, haemolytic uraemic syndrome like picture, or some features of focal sclerosis [6,9–11]. In general interferon can cause renal dysfunction which ranges from subclinical to severe dysfunction which is usually self-limiting with discontinuation of the drug as seen in our patient. Renal biopsy in our patients was not done but the clinical and radiological picture suggests acute tubular necrosis because of abundant granular casts in urine.

From literature we learn that there might be a beneficial effect of interferon to patients with viral hepatitis induced glomerulonephritis and the question remains which patient to select for such therapy. We have to be reminded that interferon has its own potential side effects on kidneys including proteinuria, and even acute renal failure requiring dialysis [13]. We think it should be used carefully and patients should be monitored very closely, and if there is any change in renal function, this drug should be withdrawn.

Letters

Severe nephrotic syndrome requiring bilateral renal embolization for control: repeated recanalization despite presence of a hypercoagulable state

Sir,

Patients with nephrotic syndrome have an increased risk (10–40%) of thromboembolic phenomena [1,2], which constitute a major threat to this group of patients. We describe a patient with collapsing glomerulopathy who required bilateral renal artery embolization for control of his steroid and cyclosporine-resistant nephrotic syndrome complications. His clinical course was unusual since he paradoxically recanalized his right renal artery twice, following the embolization procedures, despite his hypercoagulable state.

Case

A 20-year-old black Ethiopian man was seen in the emergency room, 2 days after arrival from Africa, with a 3-week history of progressive weakness, anorexia, increasing abdominal swelling, and shortness of breath. He had no history of tuberculosis, schistosomiasis, malaria or other unusual tropical infections and denied any intravenous drug use, high risk sexual exposure, or blood transfusions. There were no current symptoms or family history of a systemic disorder with renal manifestations. On physical examination, he appeared emaciated with blood pressure 130/90 mmHg and fever 38.5°C. He had a large left, and a very small right renal. He also had moderate ascites with a small umbilical hernia. There was no lymphadenopathy or hepatosplenomegaly. The rest of the examination was unremarkable. On laboratory investigations he had normocytic anaemia (haemoglobin 98 g/l, MCV 85 fl). Serum creatinine was 106 μmol/l, urea 6.4 mmol/l, albumin 6 g/l, total protein 25 g/l, and cholesterol 5.84 mmol/l. Liver enzymes were normal. Urinalysis revealed >5 g/l proteinuria and 3+ haematuria with dysmorphic RBCs, granular, and fatty casts. ANA, rheumatoid factor, and complements C3 and C4 were normal.

Nephrotic syndrome is considered to be a hypercoaguable state where thromboembolic phenomena have been described to occur in approximately 35% of all patients [1] and patients with membranous glomerulonephritis and heavy proteinuria tend to have the highest risk [2]. The high prevalence of abnormal ventilation perfusion scans in patients without any clinical symptoms suggests that the real incidence of thromboembolism in the nephrotic syndrome may be even higher [3]. Several areas have been the focus of attention, however, platelet abnormalities and enhancement of platelets-vessel wall interaction seem to be the most significant. Thrombocytes is often present in patients with membranous glomerulonephritis and heavy proteinuria [4]. Decreased red blood cell deformability and increased Von Willebrand factor are present in this group of patients [5] and have been associated with increased platelet transport toward the vessel wall and increased platelet adhesion [6,7]. In vitro studies have demonstrated marked platelet hyperaggregability [5,7] related to factors such as hypoalbuminemia with increased availability of otherwise normal albumin-bound pro-aggregatory agent thromboxane A2; hypercholesterolemia with increased in vitro platelet aggre-
gation related to elevated LDL levels [9] and increased levels of fibrinogen a ligand of glycoprotein IIb–IIIa rece-
ptors on activated platelets enhancing spontaneous platelet aggragation [5].

Increased formation of fibrin may also contribute to the hypercoaguable state at least in part related to increased thrombin formation. The latter may be caused by increased levels of clotting factors V and VIII, which are frequently found in nephrotic syndrome [4,10]. Although increased plasma levels of protein C, which inactivates factors V and VIII, and its co-factor S have been described in most studies, the free (active) levels of these proteins may be reduced [11–13]. Also there may be antithrombin III deficiency with less effective inhibition of thrombin resulting in increased coagulant activity and fibrin formation. The extent of this latter abnormality seems to be amplified in presence of gross proteinuria [14].

The thrombotic state is further enhanced by decreased fibrinolytic activity, which may be related to decreased levels of plasminogen [15], which has also been shown to correlate with the magnitude of proteinuria [16]. Albumin appears to be a co-factor for the binding of plasminogen to fibrin and the subsequent interaction with tissue plasminogen activator [17].

The explanation for the paradoxic recanalization in our patient is not clear. It is quite possible that with cessation of proteinuria following renal embolization, the levels of plasminogen normalized (not measured), as did the albumin level, the latter an important factor for the binding of plasminogen to fibrin, and subsequent interaction with tissue plasminogen activator. Additionally, platelet function abnormality related to induction of uremic state by embolization, as well as improvement in other clotting factor abnormalities may have contributed.

In summary, bilateral renal embolization can be attempted as a last resort for control of severe nephrotic syndrome, however, recanalization of the embolized vessels can occur and manifest as recurrence of clinical symptoms, as well as proteinuria and other laboratory abnormalities.

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Treatment of relapsing thrombotic thrombocytopenic purpura with cyclophosphamide pulse therapy

Sir,

Thrombotic thrombocytopenic purpura (TTP) is clinically characterized by the pentad of microangiopathic anaemia, consumptive thrombocytopenia, neurologic abnormalities, renal involvement and fever [1]. TTP shares many features with haemolytic uraemic syndrome (HUS), in fact both diseases have been described as variable expression of one disease entity [2]. Both disorders are characterized by very similar histopathologic lesions which have been described as thrombotic microangiopathy. While treatment is essentially identical in both diseases, the efficacy of therapy has been best evaluated in TTP. Plasma infusion or exchange is currently the mainstay of therapeutic intervention [3,4]. However, 10–20% of patients have only an incomplete, transient or no response to plasma therapy. Here we describe the case of a patient with relapsing TTP in whom complete remission was obtained only after the administration of cyclophosphamide.

A 46-year-old woman was admitted to our hospital because of unexplained anaemia, thrombocytopenia and multiple neurologic symptoms. A few days before admission, she had noticed several episodes of gingival bleeding and the formation of multiple haematomas. She had developed a slight fever (38.5 °C) and recurrent episodes of blurred vision and short-lasting motoric aphasia. On admission, her appearance was pale and she presented with multiple haematomas on all extremities. Laboratory tests demonstrated anaemia with an haematocrit of 22.5% and thrombocytopenia with 22,000/mm³. Her creatinine was normal but LDH was markedly elevated at 828 U/l as were reticulocytes at 7.6% whereas haptoglobin was not detectable. Her Coombs-tests were negative, differential count demonstrated 2.2% fragmentocytes. Bone marrow aspiration was consistent with haemolysis and consumptive thrombocytopenia, and a diagnosis of thrombotic-thrombocytopenic purpura (TTP) was made. Plasmapheresis was initiated with 3 l fresh frozen plasma. Three days later her thrombocytes had increased to 85,000/mm³ and LDH was only slightly increased at 268 U/l, thus, plasma exchange was stopped. However, plasma exchange had to be reinitiated 3 days later due to a renewed increase of LDH and fall in thrombocytes. Shortly afterwards thrombocytes started to rise whereas the LDH fell again. Nevertheless, 2 weeks after admission the patient developed left sided paresis despite continued (every other day) plasmapheresis treatment. Whereas a CT-scan taken the same day revealed no abnormality, an MRI-scan taken 3 days later demonstrated multiple ischaemic areas including the temporoparietal region, the basal ganglia and the internal capsule on the right side (Figure 1a) though leftsided ischaemic lesions were present as well (Figure 1b). Thus, plasma exchange was continued and prednisone therapy initiated. Four weeks after admission thrombocytes had increased to 135,000/mm³ and LDH was down to 240 U/l, and the patient had recovered mostly from her stroke complaining mainly of paresthesias in her left arm and hand. However, soon afterwards thrombocytes fell again and haemolysis parameters showed renewed activity, prompting an increase in volume of plasma exchange to 4.5 l. Thereafter, thrombocytes again recovered and haemolytic activity was not detectable, so 6 weeks after admission plasma exchange was stopped for the second time. Unfortunately, only few days later plasma exchange had to be reinitiated due to another relapse. Again, disease activity was efficiently lowered for 1 week, followed yet by another relapse. A decision was made to add cyclophosphamide to the therapy which was given as a pulse of 1 g intravenously. This resulted finally in a steady increase in thrombocytes and no indication for haemolysis. The patient recovered mostly even from this second ischaemic event and had no more neurologic occurrences. Plasma exchange therapy was stopped almost 11 weeks after admission, a total of 44 treatment sessions were performed. A second pulse of cyclophosphamide was administered 4 weeks after the first despite normal values for thrombocytes and no indication for haemolysis. The patient was discharged.

Fig. 1. MRI-scan indicating ischaemic areas in the basal ganglia and the internal capsule on the right side (a) as well as the temporoparietal region on both sides (b). Ischaemic regions are marked by arrows.
was discharged almost 14 weeks after admission. She has remained in ambulatory control for 18 months without relapse and with almost complete recovery with occasional numbness in her right hand being her only complaint.

The pathogenesis of TTP is only incompletely understood. In 1991, two large studies demonstrated convincingly the effectiveness of plasma exchange in TTP [3,4]. Despite plasmapheresis relapses remain common. In that case, a repeat course of plasma exchange is usually able to reverse the disease course [5]. However, 10–20% of patients will have only a transient or no response to plasmapheresis. Patients with resistant disease have been treated with cryosupernatant [6], vincristine [7,8], splenectomy [3] or intravenous immune globulins [9]. However, cryosupernatant is not available in all centres (including ours) and the effectiveness of immune globulins is questionable (besides being very expensive) [10]. Splenectomy gave mixed results in small studies and is rather a method of last choice [1]. Vincristine is thought to act by disruption of platelet microtubules and is thus often used by clinicians in resistant disease. However, vincristine may cause severe and irreversible peripheral neuropathy and was therefore not applicable in our patient who already had strong paresthesias in her upper left extremity. In 1990, Bird and coworkers published a report on the usage of cyclophosphamide for chronic relapsing TTP [11]. Similarly, our patient had had multiple relapses despite continuous plasma exchange and high dose steroids. Her clinical situation did not stabilize until cyclophosphamide was added. However, unlike Bird et al, we opted for a cyclophosphamide pulse therapy since it has fewer side effects. The patient is relapse-free ever since. Cyclophosphamide is a strong immunosuppressant. Autoimmune mechanisms may be involved in the pathogenesis of TTP [12], though that has not been demonstrated conclusively. Antiendothelial and antiplatelet antibodies have been described in quinine-induced forms of TTP [13]. Though the pathogenesis of the disease in our patient is not clear, our report demonstrates that cyclophosphamide may be a therapeutic alternative for resistant disease.

Fig. 2. CT-scan demonstrating the novel ischemic area in the left occipital lobe (arrows in a,b). In addition, a small ischaemic area is shown in the right occipital lobe as well (arrow in a).

Hydrocarbon exposure and glomerulonephritis due to systemic vasculitis

Sir,

Hydrocarbons (HC) have been implicated in the development of various renal diseases [1,2]. Because many patients with Wegener’s granulomatosis (WG) as well as some patients with microscopic polyangiitis (MPA) have kidney involvement accompanied by upper and/or lower respiratory tract lesions, we hypothesized that inhalation of volatile HC may play a role in the development of these vasculitides.

To investigate this hypothesis, we invited all (surviving) patients with WG and MPA who were diagnosed between 1980 and 1994 at the Liverpool Regional Renal Unit, and who fulfilled the following criteria, to participate in a validated and carefully designed occupational questionnaire [2]. The inclusion criteria were as follows.

1. Idiopathic crescentic necrotizing GN—patients with rapidly progressive glomerulonephritis (RPGN), with crescentic necrotizing glomerulonephritis (NGN) in renal biopsy, with scarce or no immune deposits on fluorescence.

2. MPA—like group 1, but with necrotizing vasculitis with few or no immune deposits affecting small blood vessels,
4. Patients with NGN in a renal biopsy, with clinical signs of respiratory tract involvement compatible with WG without definite histology, but with a positive anti-proteinase-3 ANCA.

5. Patients with NGN in a renal biopsy, and granulomatous inflammation and necrotizing vasculitis in any organ outside the respiratory tract, with a positive c-ANCA (anti-proteinase-3 ANCA).

Patients with RPGN or NGN with evidence of any secondary causes were excluded.

Twenty-eight patients fulfilled the inclusion criteria and were pair matched with normal community based controls derived randomly from blood donors attending the regional blood transfusion service. Thirteen other acute medical patients with older ages (60–73 years) were recruited for comparison. All cases and controls were pair matched for age (±3 years), gender and social class, and they all came from the same area, namely Merseyside, in the Northwest of England. None of the controls were known to have any systemic disease or chronic illnesses that might have prevented them from employment. All controls had normal urinalysis and plasma biochemistry.

All interviews were conducted at the end of 1994 by a research assistant without any knowledge of the subject’s status. The exposure score was calculated until individual’s illness began in both the patient and then control.

The contents of the questionnaire include enquiries about the types of activities (occupational and hobbies) which result to various types of HC exposure, the duration of exposure and the intensity of exposure. The exposure scores were estimated as the products of exposure to each type of HC and the intensity of exposure. HD exposure scores were estimated as the products of the

\[ \text{Exposure Score} = \text{Exposure Type} \times \text{Intensity of Exposure} \]

### Table 1

The patients’ characteristics and diagnosis, main HC exposure, ANCAs serology, evidence of pulmonary haemorrhage (hge), and serum creatinine (μmol/l) at presentation.

<table>
<thead>
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<th>Case</th>
<th>Gender</th>
<th>Age</th>
<th>Social class</th>
<th>Diagnosis</th>
<th>Occupational exposure</th>
<th>Lung hge</th>
<th>Creatinine (μmol/l)</th>
<th>ANCA</th>
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<td>652</td>
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</table>

HD, haemodialysis.
appropriate intensity factor and the total number of hours of exposure to individual HC.

A total of 19 males and nine females were recruited. The personal characteristics of the cases were shown in Table 1 which also illustrated the main HC exposure, ANCA serology, evidence of any pulmonary haemorrhage, and serum creatinine (μmol/l) at presentation.

A history of heavy occupational HC exposure (score >5000) was demonstrated in 13 of the male cases. Figure 1 illustrates the HC exposure score of the cases compared to controls. The Mann–Whitney U test was used to compare the score between different groups.

The overall cases demonstrated a significantly greater mean (15.231, median (9698) and range (0–81 262) of HC exposure score compared to controls (mean 49.59, median 378, range 0–59 520), P <0.01. The male cases, similarly, demonstrated a greater HC exposure score (mean 20.866, median 9608, range 0–81 262) as compared to male controls (mean 6847, median 1468, range 0–59 520), P <0.01. There was also a greater HC exposure score (mean 3335, median 400 and range 0–22400) in the female cases in comparison with female controls (mean 1067, median 0, range 0–9400) but the difference was insignificant.

Patients with pulmonary haemorrhage had a greater mean (21.960), median (9400) and range (0–81 262) of HC exposure score compared to those without (mean 11 045, median 3248, range 0–42 300) but the difference was not significant (P = 0.2).

Previous studies examining HC exposure in RPGN have produced conflicting results [3, 4]. Although our study comprised only a small number of patients, our observation supports a positive association between HC exposure and development of systemic vasculitis affecting the kidneys.

Two patients in this series (7 and 13) were brothers who worked as welders with heavy background paint and other HC exposure. Familial WG is very rare [5], so it is possible that HC exposure triggered ANCA-related vasculitis in genetically predisposed individuals.

Further studies examining the relationship between HC exposure and onset and relapse of WG and MPA may help us in our understanding further the pathomechanisms of these vasculitides.

Acknowledgements. Dr P. Pai was a research fellow funded jointly by Mersey Kidney Research and Health and Safety Executive.

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Royal Liverpool University Hospital
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**Plasma α-glutathione S-transferase (α-GST) as a marker of liver damage in hemodialysis patients**

Sir, Current liver function is analysed by the detection and monitoring of liver enzymes such as alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and aspartate aminotransferase (AST). The main disadvantage of these markers is that they are not distributed uniformly throughout the liver since the periportal concentrations is greater than that found in the centrilobular region [1]. Recently, α-glutathione S-transferase (α-GST) has been proposed as an alternative marker of hepatocellular damage and a better and more sensitive index than the transaminases [2, 3]. To determine the clinical utility of α-GST in patients with chronic hepatitis B, G, C, Delta viraemia, serum α-GST levels (Hepkit, Biotrin Int, Stillorgan, Dublin, Ireland) were measured in 80 haemodialysed patients. Patients were simultaneously evaluated with conventional liver biochemistry. Fifty-one patients tested negative and 29 patients tested positive for HC infection by enzyme-linked immunoabsorbant assay [2]. Two out of 51 HCV antibody-negative patients and 14 out of 29 HCV antibody-positive patients had positive HCV RNA by RT-PCR. Five of those negative for anti-HCV antibodies and HCV RNA-positive patients had a positive HGV RNA by RT-PCR and seven of those positive for anti-HCV antibodies and negative for HCV RNA had a positive HGV RNA. Two of those positive for anti-HCV antibodies and positive for HCV RNA were hepatitis B surface antigen (HBsAg) positive and positive for Delta viraemia, whereas two of those negative for anti-HCV antibodies and negative for HCV RNA were HBsAg-positive and negative for Delta viraemia patients. Thus, in 80 haemodialysed patients we found 50 nonviraemic patients (16 female, 34 male, mean age 41.12 ± 15.5 years, mean haemodialysis time 31.76 ± 36.7 months) and 30 viraemic patients (13 female, 17 male, mean age 37.73 ± 9.5 years, mean haemodialysis time 50.97 ± 40.0 months).

The α-GST concentrations were significantly above reference values in 100% (30/30) of viraemic patients (compared with 40% (12/30) for ALT, 56% (17/30) for GGT and 20% (6/30) for AST). The mean values of α-GST, ALT, GGT and AST were significantly higher in the viraemic group compared with the normal values of nonviraemic group. As a comparison, the mean values of α-GST, ALT, GGT and AST in the viraemic patients were 15.46 ± 8.17, 48.83 ± 42.12, 70.7 ± 70.77, 29.03 ± 17.54, respectively, whereas in the nonviraemic patients were 3.16 ± 1.56, 16.18 ± 6.59, 20.36 ± 10.08, 14.58 ± 5.82, respectively. The periporal hepatocytes contain the highest concentrations of the transaminases, but the centrilobular hepatocytes are relatively deficient in transaminases [1]. Basic and acidic GSTs are in contrast to the conventional transaminases widely distributed throughout the liver and are equally expressed in both perportal and centrilobular hepatocytes [1]. This differences between transaminases and GST as markers explained the better specificity of α-GST. On the other hand, simultaneous determination of serum α-GST concentration and transaminase activities may serve as a better indicator of hepatocellular damage in haemodialysed patients than evaluation of transaminase level alone. The normal values of transaminases are lower in dialysis patients than in the general population [4–6]. It is necessary to consider also, that both AST and ALT levels are depressed in the haemodialysed patients even after adjusting for confounding variables [7]. Thus, association of...
plasma α-GST with transaminases determination improves the biochemical assessment of liver damage in haemodialysis patients and might provide a sensitive measurement of antivi-
raemic treatment efficacy.

It can be concluded from the present finding that α-GST and transaminases in conjunction could be more sensitive indication of liver damage in haemodialysis patients.


Measurement of gamma glutamyl transpeptidase activity: a useful and low-cost tool for the detection of HCV infection in haemodialysed patients

Sir, Dialysis patients (DP) are at high risk of acquiring hepatitis C virus (HCV) and prevalence of HCV infection is high (up to 50%) in dialysis units. Diagnosis of HCV infection is based on the detection of anti-HCV antibodies (ELISA tests). However, even second generation tests have only 70–90% sensitivity in DP and underestimate real prevalence of HCV infection [1,2]. When compared to aminotransfer-
as, usefulness of GGT activity for the detection of HCV infection has rarely been investigated. To this end, we studied the influence of both chronic renal failure and haemodialysis on liver enzymes activities (AST, ALT, GGT) and compared, in a case-controlled study, these activities for the diagnosis of HCV infection in DP. Serum HCV-RNA detection by PCR (Amplior, Roche) was utilized for the diagnosis of HCV infection. Four categories of patients (total of 80 patients) were included in this study: A, 16 HCV positive DP (9M/7F; 55 ± 4 years); B, 32 HCV negative DP; C, 16 HCV negative patients with moderate to severe renal chronic failure (10–60 ml/min creatinine clearance as estimated by Cockroft formulae); and D, 16 HCV negative patients with normal renal function for their age (>80 ml/min). Patients of categories B, C, D were all matched with category A for age and sex. The number of diabetics was equivalent in groups A and B (3/16). Among DP, duration of haemodia-
lysis was significantly higher in group A (123 ± 31 vs 54 ± 12 months, P < 0.01). History of blood transfusion was known in 80% of HCV-positive DP. Hepatitis B or HIV coinfection, hepatotoxoc drugs or alcohol consumption were excluded. GGT activities were assessed by measurement of 5-amino-2-nitrobenzoate by spectrophotometry at 405 nm with an autoanalyser Chemone (Bayer Technicon) and expressed in IU/l (N < 45 IU/l). Unpaired t test was used for compar-
isons. Results of liver enzymes are shown in Table 1. When compared to C and D groups, AST and GGT activities were lower in B group (P < 0.005). ALT and AST activities were similar in DP patients. GGT activities were higher in HCV-
positive DP than in HCV-negative patients (P < 0.0005). At a cut-off of 25 IU/l, sensitivity of GGT and ALT activities were respectively 62.5 and 23%; specificity were rather similar, respectively 94 and 100%.

Several studies clearly demonstrated the low sensitivity of serum ALT activity to detect HCV infection and diagnosis of HCV infection in DP needs both the search of anti-HCV antibodies and HCV-RNA by PCR. However, PCR is a very high-cost procedure. In this study, we first clearly demon-
strated that, contrary to ALT, normal range values of GGT activities in DP is lower than in healthy subject. Secondly, when compared to HCV-negative DP, GGT activities are significantly higher in HCV-positive patients. Caramelo et al. [2] also found that GGT activities are higher in HCV-RNA-
positive DP. In a long-term follow-up study, Simon et al. [3] found constantly "abnormal" GGT activities in 60.2% of HCV-positive DP. We postulate that GGT activities could represent an useful, low-cost tool, for screening HCV infection in DP, keeping in mind that normal range values of GGT activities in DP are lower than in healthy subjects.

<table>
<thead>
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<th>Categories of patients</th>
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<th>B</th>
<th>C</th>
<th>D</th>
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<td>13 ± 1</td>
<td>19 ± 2</td>
<td>17 ± 2</td>
</tr>
<tr>
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<td>15 ± 2</td>
<td>12 ± 1</td>
<td>16 ± 1</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>GGT</td>
<td>38 ± 9</td>
<td>13 ± 2</td>
<td>30 ± 7</td>
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</table>

A, HCV positive dialysis patients; B, HCV negative dialysis patients; C, HCV negative patients with chronic renal failure; and D, HCV negative patients with normal renal function.

**P < 0.005: B vs C and D.
**P < 0.0005: A vs B.

1Département de Médecine Interne
2Laboratoire d’immunologie
3Laboratoire de Biochimie
4Centre Hospitalier Laennec
5Laboratoire de Biochimie
6Laboratoire de Biochimie
7Laboratoire de Biochimie
8Laboratoire de Biochimie
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23Laboratoire de Biochimie
Improvement of liver function in a paediatric patient with biliary cirrhosis after triple immunosuppression with Mycophenolate following renal transplantation

Sir.

Studies in adult renal transplant recipients have demonstrated that the use of Mycophenolate mofetil (MMF; CellCept®) — compared with placebo or azathioprine — as maintenance immunosuppressive therapy with cyclosporine A (CSA) and prednisone (PRED) can significantly reduce the incidence of acute rejection episodes [1–3]. Recently, the immunosuppressant azathioprine has been replaced by MMF for renal transplantation in paediatric patients. A rare side effect of azathioprine is hepatotoxicity consisting of liver cell necrosis and cholestasis. Actually, data concerning effectiveness and toxicity on the use of MMF in paediatric renal graft recipients are limited [4]. We report about the use of the new triple immunosuppressive regimen in a 9-year-old renal transplant recipient with a complex congenital uropathy, hepatoblastoma in the first year of life and a secondary biliary cirrhosis.

Case

An 8-month-old boy (CMV-IgG negative) was born after an uneventful pregnancy at 34 weeks of gestation with a birth weight of 2130 g and a length of 45 cm. Postnatal renal ultrasound and voiding cystourethrography confirmed the diagnosis of bilateral hydronephrosis and revealed further anomalies like megaureters, a posterior urethral valve with a megacystis and a bilateral vesicoureteral reflux. Numerous surgical interventions could not prevent repeated bacterial or fungal pyelonephritis and chronic renal failure. At 7 months of age, a hepatoblastoma of the predominant epithelial type was diagnosed. By hemi-hepatectomy of the right lobe and cholecystectomy, the tumour could be resected in toto followed by chemotherapy consisting of ifosfamid, cisplatin and doxorubicin over 3 months. As therapeutical complication, the patient developed a biliary pseudocyst, which was surgically treated by pseudocystojejunostomy. A simultaneous liver biopsy showed a secondary biliary cirrhosis without any signs of recurrent hepatoblastoma. The clinically and laboratory findings were portal hypertension with splenomegaly and esophageal varices grade 1, pruritus and pathologic liver function tests (SGPT 157, SGOT 86, γ-GT 284, cholinesterase 2876 U/l). Eight months ago, the 9-year-old boy (CMV-IgG negative) has been transplanted pre-emptively (CMV-IgG positive donor) and shows a good primary function of the renal graft with a creatinine clearance of 81 ml/min/1.73 m². By immunosuppression with MMF at a dosage of 600 mg/m² twice daily combined with CSA (150 mg/m² twice daily, trough level 150–250 ng/ml) and PRED (initial dosage 150 mg/m² twice daily, weekly halving of the dosage to a dosage of 4 mg/m²) the laboratory parameters of the liver function improved significantly (SGPT 58, SGOT 40, γ-GT 134, cholinesterase 3594 U/l) within few months after transplantation. The alphafetoprotein is still in the normal range (1.09 ng/ml). Specific side effects of MMF like gastrointestinal symptoms, CMV-infections, or bone marrow depression were not observed.

Comment

Because of an impaired liver function initially a combined liver and kidney transplantation was discussed. Therefore, the improvement of liver function under the new triple immunosuppressive regimen after renal transplantation is in view of the underlying secondary biliary cirrhosis is remarkable. This finding might be due to renal improvement post-transplant or a result of an anti-inflammatory/proliferative effect of the immunosuppressants on the secondary biliary cirrhosis. Lack of hepatic or renal toxicity of MMF is supported by data originating from adult transplant recipients [1–3]. The lack of hepatotoxicity of MMF might be a favourable advantage compared to the precursor azathioprine.

Departments of Paediatrics and Surgery Albert-Ludwigs-Universität Freiburg Germany L. B. Zimmerhackl


Captopril renal scintigraphy before and after revascularization in a kidney transplanted patient

Sir.

Renal artery stenosis is an important complication in kidney transplanted patients, and an early diagnosis is necessary in order to preserve renal function, reduce morbidity, mortality and prevent graft loss. Captopril renography (CR) has shown to be an useful tool in the diagnosis of renovascular hypertension (RH) with reported sensitivity and specificity above 90% and 85%, respectively [1,2], similar to that of Doppler-ultrasound (US), and incidence of false negative and positive results are low [3]. Some studies have stressed the usefulness of this procedure in the follow-up and in the assessment of response to treatment [4–6]. Nevertheless, only a few studies have been performed in kidney transplanted patients.

We report the case of a 50-year-old transplanted male that developed progressive hypertension (average 170/100 mmHg) despite medical treatment. In order to rule out a possible RH, the patient underwent a CR after an oral dose of 50 mg of captopril administered 1 h before radiotracer injection (100 MBq of 99mTc-mercaptoacetyltriglycerine-MAG3). Subsequently, a second renography was performed in basal conditions according to current diagnostic criteria [7,8]. The combined study was suggestive of RH, being later supported by a positive arteriographic study (Figure 1) and US. A polytetrafluoroethylene (goretex) graft of 6 mm long was then implanted. Only 2 weeks after re-vascularization, the US parameters returned back to normal, along with a reduction in blood pressure values (150 mmHg) without taking any antihypertensive drugs. Nevertheless, a routine
more related to physiology than to anatomy, CR is more prone to detect most cases of physiologically significant RH, not always in agreement with US or arteriography findings. That could justify that sometimes CR is able to identify RH before US is positive or clinical symptoms become very prominent, as seen in the present case. CR has shown to be a reliable tool for the diagnosis and follow-up of RH and can be safely used as an indicator of the persistence of RH or re-stenosis [5]. In fact, it has been suggested that CR can play an important role in predicting the therapeutic outcome in transplanted and non-transplanted patients [4,9]. Although US shows accuracy in the diagnosis of RH, it often presents high technical failure rates, being very dependent on the experience and training of the specialist [10]. In addition, CR has a similar cost efficacy than arteriography in the screening for RH, but is less invasive and does not use contrast agents that could damage the kidney [10]. Nevertheless, arteriography continues to be the ‘gold-standard’.

CR still showed the dramatic changes observed in the pre-treatment study, suggesting persistence of the disease. This finding was initially considered as a possible false positive result of the CR and careful follow-up was decided, instead of performing any further intervention. During the following year the patient presented with progressive hypertension which was difficult to control requiring up to three different antihypertensive medications (atenolol 100 mg/day, hydralazine 150 mg/day and amlodipine 10 mg/day or nitroglycerine). He had occasional headaches and vomiting and was hospitalized during an episode of pulmonary oedema. A third CR was performed, supporting the diagnosis made 1 year earlier, with very severe captopril-induced changes in renography. The diagnosis of re-stenosis was later confirmed by a positive US and arteriography. After the surgical implantation of a stent both the blood pressure and the captopril scintigraphy findings returned to normal during the following days (Figure 2).

Scintigraphic assessment of RH is based in the fall of filtration pressure and glomerular filtration rate secondary to the blockade of renin system by captopril. Because it is

Successful use of oral valacyclovir in post-transplant cytomegalovirus infection in renal allograft recipients

Sir,

Cytomegalovirus (CMV) infection is a frequent complication after renal allograft transplantation, occurring in up to 60%
of seronegative patients (R−) receiving a transplant from a seropositive (D+) donor [1]. There have been considerable efforts to establish effective strategies to prevent and treat CMV infection and disease in these risk patients. Regular post-transplant screening for CMV with sensitive techniques such as PCR or immunofluorescence detection of the pp65 antigen and subsequent pre-emptive treatment of incipient CMV infection have been advocated as a valid management strategy instead of prophylactic regimens for all patients at risk for CMV disease [2].

At our centre we have successfully used the pp65 immunofluorescence staining procedure on a weekly basis to detect the occurrence of the CMV antigen in peripheral blood leukocytes (PBL) in patients at risk (D+ R−). This technique allows early diagnosis and monitoring of response to therapy [2,3]. Thus far we have been treating patients that became pp65-positive with intravenous ganciclovir. This treatment is costly and generally requires the inconvenience of a rehospitalization.

Valacyclovir is an amino acid ester prodrug of the purine nucleoside acyclovir which is rapidly metabolized to acyclovir and valin prior to systemic exposure. Valacyclovir is used in the treatment of herpes simplex and herpes zoster virus infections. Compared to acyclovir, valacyclovir is well absorbed and its bioavailability is 54% compared to only 20% for oral acyclovir [4]. Valacyclovir could prove useful in the pre-emptive treatment of CMV in kidney transplant patients at risk for CMV disease. Here we report the successful treatment of CMV infection with oral valacyclovir in two recipients of renal transplants.

The first patient is a 37-year-old female with type I diabetes. She suffered from diabetic nephropathy with chronic renal failure and received combined kidney and pancreas transplantation. The patient was seronegative for CMV prior to transplantation and received allografts from a seropositive donor. Immunosuppressive therapy consisted of cyclosporine, azathioprine and glucocorticoids. After 6 months she complained about malaise and dyspnea on exertion. Primary CMV infection was detected with 96 positive cells/250 000 PBL. To avoid hospitalization oral treatment with valacyclovir 1000 mg three times daily was started. The treatment was well tolerated and the patient's condition improved within 2 days. In the first control examination 5 days later the CMV positive cells had dropped to 11/250 000 PBL. Eighteen days after starting therapy with valacyclovir the pp65 antigen testing became negative. Antiviral treatment was stopped after 21 days. During the treatment, the patient developed transient mild leukopenia (2590/μl). Azathioprin was given at half the dose and the leukocytes recovered completely.

The second patient is a 49-year-old female with epimembranous glomerulonephritis. She was seropositive for CMV prior to transplantation and subsequently received a seropositive kidney. Immunosuppression consisted of cyclosporine, mycophenolate mofetil and glucocorticoids. Seven weeks after transplantation she presented with fever and malaise. A first episode of CMV infection was diagnosed by detecting 329 positive cells/250 000 PBL. She was then hospitalized and treated with intravenous ganciclovir (5 mg/kg twice daily) for 18 days. With this treatment the pp65 antigen testing became negative. Anti-CMV IgM antibody was detectable in low amounts. The patient was then followed twice weekly in the nephrology outpatient clinic. Six weeks later she presented again with fever. A second episode of CMV infection was found with 184 positive cells/250 000 PBL. To avoid another hospitalization treatment with oral valacyclovir 1000 mg three times daily was then started. Immunosuppressive therapy with mycophenolate mofetil was reduced from 2000 mg to 500 mg daily. Three days afterwards the patient was feeling well and had a normal temperature. After 6 weeks of treatment the antigen test became negative again and the anti-CMV IgM antibody was significantly positive. The patient has been followed for the last 4 months and has remained well.

In a landmark controlled clinical trial Balfour et al. found that the administration of high dose oral acyclovir before renal transplantation and 2 weeks afterwards significantly reduced the rate of CMV infection [5]. Because of the necessity to use high doses and concerns of toxicity a new generation of drugs like valacyclovir and famciclovir with better bioavailability have become attractive alternatives in the management of post-transplant CMV infection and disease. Our initial experience with valacyclovir in two patients with evidence of CMV infection after renal transplantation has been favourable and made it possible to avoid rehospitalization in both patients. We conclude that the possibility of outpatient treatment of CMV infection with oral valacyclovir as opposed to parenteral ganciclovir for 2–3 weeks can improve the quality of the patients' life and greatly reduces costs of treatment of CMV infection.

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