Letters and Replies

Continuous ambulatory dialysis in Poland

Sir,

With great interest I read through the article written by B. Rutkowski and co-workers, entitled: ‘Renal replacement therapy in an era of socioeconomic changes—report from the Polish registry’ and published in Nephrology Dialysis Transplantation 1997; 12: 1105–1108.

As a co-ordinator of the Ministry of Health and Social Welfare responsible in the 1980s for the development of renal replacement therapy in Poland, I have to deny the untrue information published in this article and expressed by the following statement: ‘Until 1992 CAPD did not exist in Poland, with the exception of a cohort comprising 20–25 children’.

It is well known in Poland, that CAPD in adults was brought into practice by Professor Zofia Wankowicz in November 1979 in the Postgraduate Military Centre in Warsaw. Because of very limited funds for equipment from abroad at that time, Prof. Wankowicz and her co-workers worked up and introduced into clinical practice CAPD using their own method of preparation of sterile dialysis solutions in plastic bags of domestic production. Clinical experiences in the cohort of over 50 patients treated in the 1980s in this system in the Military Centre in Warsaw were presented and published in Polish as well as foreign literature (a few titles are enclosed).

At the time of economical and political transformation in Poland in the years 1989 and 1990, Prof. Wankowicz estabhlished in her department, in co-operation with the Renal Division of Baxter Company, the first Polish Reference Centre for CAPD. Then, in the years 1990–1996 together with co-workers, she trained in CAPD up to 400 members of medical teams (physicians and nurses) from all over the country.

Therefore, the information enclosed in the above mentioned article limits the knowledge about CAPD development in Poland exclusively to the activity of the National Committee for Promotion of Nephrology—promoting CAPD development only since 1992—and neglects activity of Prof. Wankowicz’s group in this field, initiated 13 years before and continued through the 1980s.

I hope, that my comment will be published in your excellent journal.

Polish Academy of Sciences

T. Orłowski

Warszawa

Seattle

Poland


5. Panusiuk E, Górna W, Szczyluk C, Wankowicz Z. Cellular immunity in patients on CAPD. IX Congress of Nephrology, Los Angeles, 1984; 225 (abstract)


Reply by author

Sir,


In my opinion the statement limits the knowledge about CAPD development in Poland exclusively to the activity of the National Committee for Promotion of Nephrology—the committee promoting CAPD development only since 1992—and neglects activity of Prof. Wankowicz’s group in this field, initiated 13 years before and continued through the 1980s.

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Polish Academy of Sciences

T. Orłowski

Warszawa

1998 European Renal Association–European Dialysis and Transplant Association
Taking into account all above explanations one has to conclude that the real truth usually is always somewhere in the middle.

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Relationships between volume status and blood pressure in haemodialysis patients—the long and the short of it?

Sir,

Savage et al. [1] examine the relationships between changes in interdialytic blood pressure and weight, trying critically to examine a nephrological ‘chestnut’ that raised blood pressure, so common in this setting [2] and so important to survival on dialysis [3], is a consequence of excessive fluid intake in the interdialytic period. They chose to study a racially heterogeneous group of stable haemodialysis patients all of whom underwent interdialytic ABPM and pre-dialysis echocardiography for LVM estimation. Their conclusion is that hypertension in typical dialysis patients is not completely attributable to volume expansion, in line with recent opinion [4].

This area is bedevilled by methodological difficulties; the authors rightly point out the problems of reliance on clinical weight assessments, and of reliance on interdialytic weight gain as a surrogate for changes in total body water, or, even more relevant, in patients’ plasma volume. Which BP values to use, and how to use them, to represent what is happening, is also far from straightforward.

Their findings are that about 60% of their patients show a clear association between low (sh) BP at the end of dialysis, the interdialytic weight gain, and the (higher) BP just before the next dialysis. So far, so good. The remaining 40% of their patients show an interesting blood pressure response, in that at the end of dialysis session one, as their ABPM session is started (from which the first and last three readings were used to derive an average value for post- and pre-next dialysis BP) the BP was considerably higher at the beginning of the interdialytic period than at its end just before dialysis session two—in other words, despite a comparable (statistically similar but numerically smaller) interdialytic weight gain, the interdialytic BP for group two fell by 10/9 mmHg (cf. group 1 with a RISE of 19/13 mmHg). It is not surprising that merging these two opposite responses leads to the conclusion that there is no (consistent) relationship between interdialytic weight gain and BP. It would be very interesting to know how the BP values for patients in groups 1 and 2 were affected by the haemodialysis session that immediately preceded the start of the 48-h interdialytic ABPM recording—in other words, whether the dialysis session had affected BP values differently for these two cohorts. A BP rise towards the end of dialysis through profound stimulation of the renin-angiotensin and sympathetic nervous systems (not always completely blocked by ACE inhibitors) as the patients ‘hit’ their dry weight before the end of the dialysis session may be one explanation for the behaviour of BP in group 2.

In the earliest published study using ABPM in haemodialysis patients, Battle et al. [5] showed that post-dialysis BP is often low, falling even lower in the next few hours, recovering later on. Similar profound effects of a dialysis session on the BP in the immediate few hours after dialysis were shown in a later study by Leunissen’s group [6]. The reasons for this are alluded to in the present paper, and are likely to be related to different rates of plasma refilling [7].

Little is known of the consistency of response of BP to dialysis in the same patient, let alone the effect of medication. I do not find any difficulty reconciling the two observations, (first) that virtually all patients put onto long-hours haemodialysis (a la Tassin [8] and Withington [9]) will show a marked fall in BP over a short period of time, obviating the need for anti-hypertensives for BP control, and (second) that in individual groups of patients mostly taking anti-hypertensives on short-hours haemodialysis such a relationship between interdialytic weight gain and BP is weak or absent. In elegant intra-institutional cross-over experiments the Tassin group have shown the remarkable difference between 5- and 8-h haemodialysis sessions in the same patients [10]. Long-hours haemodialysis has certainly acquired a mystique similar to that of Burgundian red wine, where ‘terroir’ (the soil, the grape, the climate and elusive elixirs such as supreme confidence in viticultural superiority) produces sublime if exorbitantly expensive results. In fact Chateaux Tassin et Withington produce astonishingly similar output [10,11] using very similar approaches with respect to salt and water restriction. I believe that long-hours haemodialysis works because of two main effects, first, reduction in ‘total body sodium’ (reducing vessel stiffness [12] and diminishing patients’ thirst) and second by causing a persistent state of vasodilatation (possible reasons for which include augmented removal of ADMA [13], prolonged use of acetate dialysate and the generation of more nitric oxide by prolonged exposure of blood to cuprophan [14]); this vasodilatation has been demonstrated by comparing les Tassinites and more conventional Dutch dialysis patients [15]. Even in Tassin they do not appear to believe in the ‘volume’ explanation for their BP results, as shown by recent publications in which there was no relationship even in their patients between interdialytic weight gain and ABPM-derived analysis of interdialytic BP changes [16].

The fact that 60% of the patients in this study show some volume-sensitivity for BP only serves to confirm that this factor is of great significance to the majority of dialysis patients; it is axiomatic though that there are many different and complementary reasons for raised BP in renal failure and that it would be an over-simplification to expect that the same factor would have pre-eminence for all patients all of the time (analogous to ‘essential hypertension’ where salt-sensitivity, insulin-resistance, activity of the sympathetic nervous system and other underlying mechanisms for pressor effects predominate in different patients).

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7. Koomans HA, Geers AB, Dorhout Mees EJ. Plasma volume pressure changes. Our study has several deficiencies, as expected to have minimal impact on circulating volume. Sodium balance should be a far more important determinant of changes in extracellular volume, but is more difficult to assess. In fact, studies have shown that most interdialytic weight gain in dialysis patients is confined to the extracellular space [1], although the explanation for this finding is obscure.


Reply by author

Sir,

We thank Dr Goldsmith for his interest in our article and comments. We are pleased to see that we are in agreement in many areas. While neither London nor Bristol are famed for their vineyards, both are major importers of wine, and we have imported many ideas from elsewhere. There is no doubt, for instance, that long, slow dialysis as practised in Tassin, and, although less well publicised, in South Manchester, allows drug-free control of blood pressure in the vast majority of patients, and that this regimen is associated with unsurpassed survival and freedom from left ventricular hypertrophy. The question for most nephrologists and their patients is whether similar results can be achieved with ‘standard’ dialysis hours—as long hours are unpopular with most patients and have major financial and practical implications for cost-limited dialysis units.

We do not know, as Dr Goldsmith admits in his long and entertaining letter, whether the results obtained by long, slow dialysis are due solely to better control of salt and water balance, to removal of inhibitors of nitric oxide synthesis or other vasoactive substances, or to other unidentified factors. These questions led us to perform our study comparing weight changes during and after haemodialysis with blood pressure changes. Our study has several deficiencies, as indicated in the discussion; some of these are also alluded to by Dr Goldsmith. These include the fact that we only studied one interdialytic interval, and cannot be sure that the division of patients into two groups reflects real and sustained differences between the two groups. If blood pressure falls during dialysis, then it is likely to rise after dialysis, and vice versa; this is the phenomenon of regression to the mean (think what would happen to a patient in whom a fall in blood pressure during dialysis was regularly followed by a fall in blood pressure during the interdialytic period!). In addition, weight gain is a poor surrogate for changes in intravascular volume. Weight gain is the result of the accumulation of water, which, if distributed across total body water, would be expected to have minimal impact on circulating volume. Sodium balance should be a far more important determinant of changes in extracellular volume, but is more difficult to assess. In fact, studies have shown that most interdialytic weight gain in dialysis patients is confined to the extracellular space [1], although the explanation for this finding is obscure.

Dr Goldsmith suggests that sympathetic activation as a result of patients achieving dry weight may have resulted in a rise in blood pressure in those patients whose blood pressure fell between the end of one dialysis session and the start of the next. We think this is an unlikely and dangerous suggestion. ‘Reflex’ hypertension is often cited by dialysis nurses as a reason to abandon further attempts to control hypertension by fluid removal but the evidence suggests that at least some hypertensive haemodialysis patients whose hypertension worsens during fluid removal respond to repeated ultrafiltration, with eventual good blood pressure control [2]; and that pre-dialysis ANP levels, as a marker of subclinical volume overload, are higher in patients whose blood pressure does not respond to volume removal than in those whose blood pressure falls during dialysis [3].

The suggestion that long, slow dialysis improves conduit artery compliance via an effect on total body sodium is intriguing, but not fully supported by studies of vascular compliance in patients on long, slow dialysis, although unfortunately no comparison with patients on shorter-hour dialysis was performed [4]. Increased sodium content of resistance vessels, in contrast, has long been thought to be a factor in increased peripheral vascular resistance [5]. Gradual removal of this vascular wall sodium might well explain the ‘lag phase’ of several weeks between attainment of dry weight and attainment of normotension described by the Tassin group, as well as the inconstancy of the relationship between volume removal and blood pressure change observed in our study and others’.

Finally, Dr Goldsmith suggests that long slow dialysis allows blood pressure control at least in part by increasing nitric oxide generation as a result of prolonged exposure to bio-incompatible membranes and better removal of ADMA and of prolonged exposure to acetic dialysis. These hypotheses are testable, but neither our study nor those he cites contain information to allow us to decide either way. Clearly, further research is required to allow us to identify within the

Letters

Positive skin reaction test in haemodialysis patients allergic to nafamostat mesilate

Sir,
Heparinization during renal replacement therapy is often dangerous when the patient has a bleeding lesion or a haemorrhagic diathesis. For the past 8 years, nafamostat mesilate (Torii Pharmaceutical Co. Ltd, Japan), a serine proteinase inhibitor, has been used as an anticoagulant during renal replacement therapy for such patients because of its short-acting regional activity [1]. Major adverse effects related to nafamostat mesilate have never been reported [1] except for anaphylactoid reaction [2,3]. We report here one haemodialysis (HD) patient who had past history of anaphylactoid reaction to nafamostat mesilate, and showed positive skin reaction test but negative drug lymphocyte stimulation test [4] for nafamostat mesilate.

Case
A 28-year-old Japanese female was admitted to our hospital for parathyroidectomy. She had been on HD for 14 years because of chronic renal failure due to chronic glomerulonephritis. Nafamostat mesilate was used instead of heparin for HD on 12 November 1997 after the operation. She developed chest oppression, abdominal pain, and pruritic eruptions immediately after starting HD using nafamostat mesilate (30 mg/h). Discontinuing HD, hypotension, tachycardia and other symptoms were treated with saline, dopamine, and hydrocortisone injection, and gradually subsided. Prior to the next HD session, skin reaction test by subcutaneous injection of 50 μl of 10 mg/ml nafamostat mesilate was carried out. Skin reaction test was positive with pale urtica (Figure 1). Saline injection was applied for negative control. Simultaneously, peripheral lymphocytes were collected for drug lymphocyte stimulation test, resulting in negative for nafamostat mesilate. She was then switched to dalteparin sodium (low-molecular heparin) (Kissei Pharmaceutical Co. Ltd, Japan), and further HD sessions continued without complications. From these observations, it is most likely that nafamostat mesilate is the source of anaphylactoid reaction in this patient.

In this case, skin reaction test indicated her allergic state to nafamostat mesilate more sensitively than drug lymphocyte stimulation test, avoiding dangerous anaphylactoid reaction. We had another case who had had an episode of chest oppression while HD using nafamostat mesilate, showing positive skin reaction test but negative drug lymphocyte stimulation test for nafamostat mesilate. The skin reaction test for nafamostat mesilate was negative in 10 other HD patients who had no clinical evidence of allergy to nafamostat mesilate. The test was performed after informed consent had been obtained. The drug lymphocyte stimulation test has several disadvantages compared to the skin reaction test. It usually takes several days to obtain the results of the drug lymphocyte stimulation test. In addition, results of drug lymphocyte stimulation test may be false negative because of impaired T lymphocyte function in HD patients [3,5]. We have experienced more than 200 cases with renal failure undergoing renal replacement therapy using nafamostat mesilate, and found only a few cases with clinical evidence of allergy to nafamostat mesilate. However, anaphylactoid reaction to nafamostat mesilate may cause serious complications in critically-ill patients who need nafamostat mesilate. Furthermore, it is not always possible to distinguish anaphylactoid reaction to nafamostat mesilate from other pathologies in such patients. Thus, we believe the skin reaction test for
nafamostat mesilate is a clinically useful test for detection of allergy to nafamostat mesilate. We suggest that it is performed routinely, especially in critically ill patients prior to renal replacement therapy.


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**Table 1. Summary of cytologies (mm³) with and without cutaneous purpura.**

<table>
<thead>
<tr>
<th>Date</th>
<th>With purpura</th>
<th>Without purpura</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCB</td>
<td>WBC</td>
</tr>
<tr>
<td>16.09.92</td>
<td>1200</td>
<td>3</td>
</tr>
<tr>
<td>31.03.93</td>
<td>490</td>
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</tr>
<tr>
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<tr>
<td>06.08.93</td>
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<tr>
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<td>2570</td>
<td>5</td>
</tr>
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</table>

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**Discussion**

We describe a case of recurrent haemoperitoneum in a patient affected by mixed essential cryoglobulinaemia. Haemoperitoneum was strictly related to cutaneous purpura. The observation of discrete roseé stain in one of the exchanges in temporal relation to the purpura in the complete absence of any symptoms, raised our suspicion that the two phenomena were interrelated. Alerted to this possibility we proceeded to cytological examination of the effluent. Simultaneously we tried to exclude other potential causes. We found asymptomatic bilateral renal lithiasis as a chance finding and noted complete absence of coagulatory abnormalities, trauma, intestinal instrumentation etc. The review of literature showed that establishing the correct diagnosis of haemoperitoneum is a complex exercise of differential diagnosis and occasional the cause remains unknown despite all diagnostic efforts [1]. Abundant drainage of blood with clots associated with altered vital signs draw attention to problems involving solid organs, viscera or blood vessels [5–7] implying that prompt diagnosis and rapid and aggressive treatment are necessary.

In the majority of cases the condition is benign. In most females it is strictly related to the cyclical function of genital organs [3]. Consequently, it is self-limited and recurrent. Frequent other causes include heavy exercise, a history of endoscopy of the GI tract, abnormalities of the coagulation system, infusion of hypertonic or hot fluids [8], haematomata of the retroperitoneum, the abdominal wall, or the psoas muscle [9], as well as pathology of intra-abdominal organs, e.g. colitis membranosa, appendicitis, cholecystitis, intestinal infarction, rupture of the spleen or rupture of a graft [8,9]. Although it is rare, haemorrhage secondary to systemic disease, e.g. IgA nephropathy/Schoenlein–Henoch’s purpura deserves mentioning. Here peritoneal capillaries are potential target organs of the disease process, comparable to skin capillaries. They show the same anatopathological lesion, i.e. immunocomplex mediated leukocytoclastic vasculitis. We feel that the present case belongs into the same category. Arguments for this assumption include that negative results in the meticulous search for alternative aetiologies and the strict relation on several occasions between sanguinolent effluence and cutaneous purpura. The possibility of a simple coincidence can reasonably be rejected because the observation was repeatedly made during four episodes. For ethical reasons we could not directly demonstrate the presence of peritoneal purpura, which would have been easy to establish by laparoscopy.
Hemoperitoneum occurs in over half of menstruating women. In the past 5 years we were able to observe five cases (2 women and 3 men) with sanguinolent peritoneal drainage, all of a benign nature. This represents 8% of our CAPD patients. Based on systematic observations of the fluid drained in these cases and based on addition of different quantities of blood to erythrocyte-free drainage bags, we conclude that in the presence of more than 300–400 erythrocytes/mm$^3$ a rosé taint becomes noticeable on inspection, thus permitting easy diagnosis.

**Acknowledgements.** We thank Professor E. Ritz for translating the text from Spanish into English.