Assessment of severity of illness in end-stage renal disease patients: need for multi-disciplinary effort

Sir,

Dr Weisbord and colleagues [1] ought to be congratulated in their attempt to validate the severity of illness in patients with end-stage renal disease (ESRD). A perusal of the symptoms listed in table 2 [1] depicts a range of complaints which may be easily overlooked, if not actively sought for, by the medical personnel. The usual guidelines for adequacy for dialysis and reliance on surrogate markers (creatinine, albumin, haemoglobin, etc.), may fall short in their attempt to validate the severity of illness in patients awaiting renal transplantation. *Am J Gastroenterol* 1983; 78: 328–331


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Risks related to catheter locking solutions containing concentrated citrate

Sir,

We are concerned that risks of using concentrated sodium citrate for a catheter lock solution (CIT) are not well understood. Routine haemodialysis is safe, partly as a result of a sum total of both qualitative and quantitative analysis of the number of symptoms, indicates that in an evidence-based management of assessing the effectiveness of intervention, the number of symptoms, indicates that in an evidence-based management of assessing the effectiveness of intervention, a sum total of both qualitative and quantitative analysis is indicated. Over-reliance only on quantitative measures would tend to ignore the complex non-linear trends of symptoms which accompany chronic medical disease [4]. The current article challenges us to continuously revisit our current treatment strategies when it comes to taking care of patients with ESRD.

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of European Standards requiring medical devices to be safe even under fault conditions [1]. Risk analysis taking foreseeable user errors (FUE) into account is part of the process of obtaining approval to market a new medical product. Medical practitioners are not bound to this process and may neglect the effects of user errors.

During development of a low concentration citrate-containing lock solution we carried out a risk analysis [2]. We concluded that use of CIT is unsafe under certain conditions involving FUE. The risk evaluation is shown below.

Risk analysis. Citrate chelates with the calcium ions in blood and tissue. Serious symptoms have been reported when the ionized calcium level decreases to 0.6 mmol/l [3]. In vitro tests in which a double lumen central venous catheter is filled with a locking solution equal to the filling volume show that ~15% of the locking solution is immediately injected into the patient [4]. The injection is normally done within 1–2 s and the overspill distributes in a volume equal to 1–2 heart beats (~100 ml). Examples of FUE resulting in spillage of more locking solution into the patient include simple mistakes in the lock volume, two instillations of solution into the same lumen and deliberate overinjection of solution to clear a blocked catheter. In the risk analysis we selected an overinjection of 1 and 5 ml.

Effects of overinjection. Assuming that the injected solution is distributed in 100 ml plasma water, 1 ml of 1.8 mol/l (i.e. 47% sodium citrate injected results in a citrate concentration of 18 mmol/l. The solution will be diluted in lung water to ~40% [5]. The effect of sodium citrate infusion on free ionized calcium in whole blood was derived from previous work (K. Sodemann, unpublished data). In this work, total citrate vs. ionized calcium concentration was measured in vivo during lipid apheresis using citrate anticoagulation. The data were fitted with an exponential function: 

$$\text{[Ca}^{2+}\text{]} = \exp(a - b \cdot \text{[citrate]}),$$

where $a = 0.1834$ and $b = 0.265$ ($r^2 = 0.98$).

With a normal blood value for the ionized calcium of 1.3 mmol/l, citrate concentrations of >6 mmol/l result in ionized calcium concentrations of <0.25 mmol/l. This level is unsafe.

Animal tests (done by Biolink Corp., Mansfield, MA, USA; used with permission) corroborate the risks of bolus injection: 5-ml boli of sodium citrate with concentrations between 4% and 47% were injected into healthy animals (dogs and rabbits). Even at the lowest concentrations (equivalent to 0.03 mmol/kgbw citrate) a brief depression of the blood pressure was recorded. The highest concentrations (equivalent to 0.35 mmol/kgbw citrate) resulted in immediate cardiac arrest. For comparison, 1 ml 47% CIT injected into a 70 kg patient is equivalent to a dose of 0.028 mmol/kgbw calcium.

Risk evaluation. The acceptable limit for a potential fatal event due to a machine malfunction has been defined at $10^{-8}$ per treatment. Small patients with cardiac problems are the most at risk population as the consequence of FUE. Assuming that this high-risk group represents 10% of the patient population and estimating the likelihood of user errors at $10^{-3}$–$10^{-2}$, the resulting probability of a hazardous event is $10^{-3}$–$10^{-5}$, which is a factor 1000–100 000 greater than the accepted risk level.

Discussion. The US Food and Drug Administration issued a warning [6] regarding CIT in 2000 after a fatal accident and the product was withdrawn from the market. The citrate concentration in a bolus passing through the heart may be lethal if it persists for some time. To our knowledge, the effects of such a bolus have not been measured in a controlled study (animal tests done by Biolink are anecdotal). It is unclear whether normalization of the dose with body weight is applicable for the bolus application, because the effects occur before equilibrium with plasma water takes place.

If an overinjection is not suspected immediately, cardiac arrest during dialysis may be regarded as a normal event not linked to CIT. Purchase and Gault [7] reported a home patient who injected 47% concentrated sodium citrate lock daily at home and died 24 h after the last dialysis from cardiac arrest. A possible relationship with the locking solution was not discussed, although the patient died about the time when the next injection might have occurred. Stas et al. [8] described the use of 30% sodium citrate locking solution and mentioned the potential risk. Ash et al. [9] reported that 10% of patients had a ‘metallic’ taste shortly after injection of the exact fill volume of 47% sodium citrate. Hendrickx et al. [10] reported the use of a 5% sodium citrate locking solution, which is one-tenth of the strength of the standard 47% CIT. Using the approach above, an overinjection of 1 ml of 5% sodium citrate solution would result in an ionized calcium concentration of ~0.7 mmol/l and can be regarded as safe without further investigations.

Conclusion. Risk analysis and animal test data raise sufficient concern about the safety of concentrated CIT. We are aware that this analysis is limited. It is, however, up to manufacturers (or users if manufactured on request) to prove safety, which includes the risk related to overinjection and the likelihood of such an event.

Conflict of interest statement. H.-D. Polaschegg worked as a consultant for Biolink Corp. until August 2002. K. Sodemann was principal investigator of the German Dialock (Biolink Corp.) study, which ended in 2001.

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8. Stas KJ, Vanwalleghem J, Moor BD, Keuleers H. Trisodium citrate 30% vs. heparin 5% as catheter lock in the interdialytic
Hydrophobic PF5070: dialysis repair and sudden death in dialysis patients

Sir,

We read with interest the letter of Dr Canaud, published by NDT in July 2003 [1], replying to a letter by Drs Slavicek and Jerin [2] about the responsibility for the epidemic of sudden deaths on dialysis, which occurred in Croatia in October 2001. In their letter, Drs Slavicek and Jerin complain about the suggestion in the original expert report of Dr Canaud [3] that there was an element of responsibility for these deaths at the level of the end-user and that his subsequent apology published in September 2002 [4] was inadequate. In his most recent letter [1], Dr Canaud still appears to believe that PF5070 (the toxic substance that caused the deaths of 23 patients in Croatia) might have been removed by more adequate dialyser rinsing. In support of this belief, he states ‘At this stage of the discussion, it is also interesting to remember that several years ago, some capillary filters were extruded and filled with a glycerol solution to keep the fibres open (e.g. Amicon™, haemodiafilter). Interestingly, glycerol, a hydrophobic and insoluble compound, was completely removed by conventional rinsing procedure of the dialysers with 21 saline.’ This statement confirms, in our opinion, his persistent bias or suspicion that end-user responsibility might have been involved in the tragic accidents in Spain and Croatia in August and October 2001, as in fact glycerol, in contrast to PF5070, is a strongly hydrophilic compound [5] that rapidly dissolves in water and consequently is completely removed by a standard 21 saline rinse.

Finally, given the new policy of NDT on the mandatory requirement of authors to sign a ‘Conflict of Interest Declaration’, we find the absence of such a declaration curious, given that he was appointed by Baxter International, Inc. as the head of their expert panel to investigate the deaths following exposure to PF5070 in October 2001 [6]. This omission is even more surprising in view of ongoing litigation against the company concerning deaths associated with PF5070 and an outstanding FDA subpoena related to these deaths [7].

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Peritonitis due to Lactococcus cremoris in an automated peritoneal dialysis patient

Sir,

Peritonitis is the leading cause of drop-out from peritoneal dialysis (PD) therapy. More than 60% of peritonitis is due to Gram-positive cocci [1]. Potential risk factors for the development of peritonitis have been well identified and include: exit-site infection and nasal carriage of Staphylococcus aureus. As far as we could ascertain, no case of PD peritonitis caused by Lactococcus lactis subsp. cremoris has been reported. It has occasionally caused opportunistic infections in immunodeficient people [2,3] but never in PD.

Case. A 67-year-old male PD patient, of Caucasian origin, was referred to our unit in September 2002 because of abdominal discomfort, fever (37.5°C) and cloudy peritoneal effluent. He had a previous history of arterial hypertension, coronary heart disease, partial thyroidectomy and appendectomy. He experienced APD for 16 months because of nephroangiosclerosis. His usual APD regimen consisted of four 2000 ml exchanges nightly with Dianeal 1.36%. The patient had one episode of bacterial peritonitis in March 2002 due to Gemella morbillorum, which was treated successfully with i.p. cefazolin.

On admission, the clinical picture was dominated by mild diffuse abdominal pain, rebound and normal blood pressure (140/80 mmHg). No tunnel or exit-site infection was present. The laboratory data showed an elevated white blood cell count (13 500/µl with 88.5% neutrophils), normocytic anaemia (haemoglobin 13.0 g/dl), increased inflammatory index (C-reactive protein 88 mg/l); normal liver and pancreatic enzymes.

PD samples were collected either in blood culture bottles (BACTEC) or centrifuged large volume sterile bottles without transport medium. Analysis of peritoneal effluent demonstrated a WBC count of 1340/µl with 77% neutro-