Recalibration of population-based GFR formulae by pharmacokinetic methods

Sirs,
In the interesting article ‘Estimating glomerular filtration in the general population: the second Health Survey of Nord-Trondelag (HUNT II)’ by Hallan et al. [1], attention is drawn to the increasing documentation of ‘large underestimation of glomerular filtration rate (GFR) in older subjects using the Cockcroft-Gault formula’. The authors present a new population-based GFR formula and postulate recalibration of such formulae. Unfortunately, they do not discuss explicitly the experimental and mathematical procedures necessary for correct determination of GFR.

As we have shown elsewhere [2,3], underestimation of GFR stems from constant-infusion experiments, theoretically requiring the achievement of steady states, but practically not fulfilling this requirement because of experimental protocols which are generally too short. Despite this obvious weakness, constant-infusion techniques are celebrated as ‘gold standards’.

It appears to us that the only mathematically correct, and at the same time clinically practicable solution, for the GFR standardization problem consists in the use of pharmacokinetic models that are adapted to dynamic concentration courses of physiologically suitable markers. This appears to be all the more valid, since the theoretically correct technique of GFR determination by constant-infusion experiments using infinitely long experimental protocols can be shown with mathematical rigor to be a special case within the wider concept of kinetic techniques.

Kinetic methods are already successfully applied in many fields of biomedicine and biotechnology [4], and a renewed discussion of the GFR-standardization problem as stimulated by the intriguing biometric study by Hallan et al. [1] could pave the way to recalibrated population-based formulae for future nephrological studies.

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Impact of enalapril on renal function in patients with severe chronic kidney disease

Sirs,
Although ACE-inhibitors are nowadays considered drugs of choice in treating hypertension in patients with chronic kidney disease (CKD) [1], the possible occurrences of acute renal failure and hyperkalemia, already described in elderly and diabetic populations [2,3], limit their use in patients with severe CKD.

Hou FF et al. [4] have recently published a paper which led me to evaluate the impact of ACE inhibition on measured creatinine clearance (CrCl) in hypertensives with stages III–IV CKD who were referred to our Hypertension Unit, between 1 January 2004 and 31 December 2005. The analysis was focused on hypertensives with CrCl values ranging between 15 and 60 ml/min/1.73 m², with or without proteinuria. Patients with renal artery stenosis or those already taking antihypertensives were not considered.

In our practice, in nephropathic hypertensives, after assessing ICED score [5], main lab and instrumental parameters, furosemide (25 mg p.o. daily titrated up to 50 mg) + enalapril (10 mg p.o. daily titrated up to 20 mg) are started as a first approach in order to attain the blood pressure (BP) goal (<130/70 mmHg). Other antihypertensives are added in resistant patients. This letter reports data regarding a 8.4±2.0 months (mean±SD) follow-up in 25 caucasian patients (44% males, 15% diabetics, 64% on stage III CKD) who met the inclusion criteria. At the time of first visit, they were 60.7±12.9 years old. All of them reached the BP goal, taking furosemide + enalapril at full titrations. In the entire cohort, enalapril did not influence renal function (baseline: 33.1±5.1 ml/min/1.73 m²; after enalapril: 31.8±6.0 ml/min/1.73 m²; paired Student’s t-test: P=0.43), even after adjusting the analysis by the stage of CKD and the ICED score. Proteinuria (g/day) significantly dropped during the follow-up (baseline: 2.6±1.1; after enalapril: 1.9±0.8; P=0.03). Hyperkalaemia occurred in two patients with stage III CKD (8% of the cohort), but they recovered suddenly after withdrawing the therapy.

Even keeping in mind all the differences in terms of design, follow-up, medications, outcomes and populations between this analysis and Hou’s study [4], it is possible to conclude...
that, in my experience also, ACE-inhibition, independently from the severity of renal involvement and the global clinical picture, can control hypertension in patients with severe CKD with no effects on renal function. However, the possible occurrence of hyperkalaemia suggests a regular checking for serum potassium in this clinical setting. In conclusion, this analysis confirms that patients with severe CKD may also safely experience the renoprotective effects of ACE-inhibition.

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Urokinase for restoration of patency of occluded permanent central venous access in haemodialysis patients—a new protocol

Sir,
Tunneled central vein catheters (TCVCs) are widely used for haemodialysis either as permanent dialysis access in elderly patients with severe peripheral vascular disease or transiently during the maturation period of an arteriovenous fistula. Their use is associated with a relatively high incidence of complications including infection and dysfunction. The most frequently occurring complication is catheter dysfunction or poor flow. Catheter dysfunction may be classified as early, which occurs immediately after insertion and is related to malposition or technical problems with placement, and late, usually induced by partial or complete thrombosis. Catheter thrombosis frequently results in catheter loss and should be addressed immediately. Local instillation or infusion of lytic enzymes such as urokinase or tissue plasminogen activator (tPa) is widely used for clot dissolution and to restore catheter patency. Both have good success rates and safety profiles. In 1998, Twardowski [1] used intradialytic infusion of high dose urokinase (total dose of 250 000 units) for late catheter dysfunction with an 81% restoration of patency and 13% improvement in flow. Urokinase was infused over 3 h. Since dialysis treatment runs on a strict schedule, it is imperative that occluded catheters be restored in a timely, convenient and cost effective manner. After review of the literature, we developed a new shortened protocol: high dose (250 000 units) urokinase infused simultaneously through both lumens over 90 min in patients who developed complete (no blood flow) catheter occlusion.

We prospectively collected data on 15 chronic haemodialysis patients, who had received urokinase for complete catheter thrombosis during the period June 2004 to June 2006. Patients were eligible for inclusion in this study if blood could no longer be withdrawn from the catheter after a prior period of normal function of at least 7 days. We determined the average time from catheter placement to first clot event (primary patency PP), recurrent clot event after urokinase treatment (secondary patency SP), catheter salvage rate, overall catheter life, catheter related infections and cause for removal. All patients received 125 000 units urokinase in 50 cc of 0.9% saline infused simultaneously through each catheter lumen (total dose of 250 000 units urokinase) over 90 min. Haemodialysis was performed immediately after urokinase administration. Blood flow was initially set at a pump speed of 250 ml/min and was increased during the session to a maximum of 300 ml/min. A technical success of urokinase was defined as restoring catheter blood flow rate in both ports to at least 250 ml/min.

From June 2004 to June 2006, 88 TCVCs were inserted for our haemodialysis service. All these catheters were placed in our angiographic unit by the same radiologists. 19 of these catheters (in 15 patients) developed total thrombosis during this time and urokinase was used to restore patency one or more times—total 27 treatments. A high percentage of our patients suffered from diabetes, hypercholesterolaemia (53% each) and hypertension (70%). Of the total patients, 53% were receiving aspirin and 27% were on chronic anti-coagulation with warfarin or low molecular weight heparin (LMWH). The average time of PP was 141 ± 43 days (7–784 days). Eight patients (57%) developed recurrent occlusion and were treated with urokinase more than once: six patients received urokinase twice and three patients received urokinase three times. The average time of SP was 90 ± 33 days (7–364 days). Catheter salvage rate was 100%. Nine catheters were removed over this period of time, but no catheters were removed because of dysfunction due to thrombosis. Catheters were removed due to infection (21%), fistula maturation (19%) or fell out spontaneously (10%). Regular haemodialysis was performed immediately after treatment with blood flow rates of 250 ml/min or more in all patients maximal blood flow rate was 300 ml/min. Overall catheter life (determined as the period of time from catheter placement to removal or to the time of writing) was 508 ± 327 days. No complications were reported during or after urokinase administration even with its recurrent use, except for one patient who developed gastrointestinal bleeding and required a blood transfusion. This patient was on long-term therapy with aspirin and warfarin for chronic atrial fibrillation and required urokinase administrations on three repeated occasions over the 67 days period. This low complication rate is comparable with that reported by Twardowski [1] using high dose urokinase to restore the patency of occluded haemodialysis catheters. Indeed, the total dose of urokinase infused is similar in our protocol, thus bleeding complications are very rare and likely to occur only in high-risk patients requiring recurrent intervention.

In contrast to previous protocols, our study demonstrated 100% efficacy and it is of interest to consider why. The experience gained with the use of thrombolytic agents