Improvements in the use of plasma creatine as a marker of the glomerular filtration rate
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General Discussion
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Prediction of GFR from the Cockcroft-Gault formula

The formula of Cockcroft and Gault [1] after inhibition of tubular creatinine secretion by administration of cimetidine (CG<sub>cim</sub>) has been demonstrated to approximate the glomerular filtration rate (GFR), provided that an enzymatic plasma creatinine assay is used. This has been shown for patients with type 2 diabetes mellitus, for follow-up of these patients and for renal transplant recipients. The accuracy or bias, that is the mean difference between CG<sub>cim</sub> and the GFR of the patients, was good. There was a non-significant bias for the diabetic patients, -3.4 ml/min/1.73m<sup>2</sup> and -0.2 ml/min/1.73m<sup>2</sup> at follow-up. The bias for allograft recipients was 4.9 ml/min/1.73m<sup>2</sup>, far less than the bias of the endogenous creatinine clearance based on 24-hour urine collections (23.8 ml/min/1.73m<sup>2</sup>). The precision, that is the standard deviation of the difference between CG<sub>cim</sub> and GFR or the inter-individual variability around the mean difference, was moderate but definitely better than the precision of the endogenous creatinine clearance. For the type 2 diabetic patients the precision of CG<sub>cim</sub> was 14.8 ml/min/1.73m<sup>2</sup> versus 23.1 ml/min/1.73m<sup>2</sup> for the creatinine clearance. In the renal transplant patients, with a lower GFR, the precision was 9.0 ml/min/1.73m<sup>2</sup> for CG<sub>cim</sub> and 14.5 ml/min/1.73m<sup>2</sup> for the creatinine clearance.

In diabetic patients there was zero bias (chapter 2), but the precision was less good than in patients with renal disease [2]. We hypothesized that this might be due to a larger variability in the relationship between body weight and muscle mass than in non-diabetic patients, due to the frequent presence of a varying degree of obesity. However, this relationship might be fairly constant in an individual patient. During follow-up of individual patients this would give to a certain extent a systematic error. Therefore, we studied after an interval of two years, whether the intra-individual variability of CG<sub>cim</sub> was smaller than the inter-individual variability in the diabetic patients (Chapter 3). The study showed that this was the case. Also, the changes of CG<sub>cim</sub> were similar to the changes in GFR, although not identical. In renal transplant recipients GFR was lower than in the type 2 diabetic patients. Therefore a relatively higher amount of tubular creatinine secretion could be expected [3,4], which in turn might not have been inhibited completely by the same dose of cimetidine [5]. There was a small positive bias of CG<sub>cim</sub> in these patients, especially in patients with a GFR below 40 ml/min/1.73m<sup>2</sup>, but the bias of the endogenous creatinine clearance without cimetidine was five times larger.
Other GFR-prediction formulas

Only the formula of Cockcroft and Gault has been used in this thesis. No attempt was undertaken to construct a new formula from our results, because the study population was relatively small. Other formulas, incorporating plasma creatinine and other variables, have been described for GFR-estimation. Large patient groups are necessary to derive a formula from multiple regression analysis. Preferably a second population is studied to assess the reproducibility of the formula, before it can be advocated in clinical practice. Three formulas have been described in the literature in studies for patients with advanced renal failure (n = 85), for african americans (n = 193) and for elderly patients (n = 41) [6-8]. These formulas have not been validated in a test population and have not been used often in clinical practice.

The Modification of Diet in Renal Disease (MDRD) study was a large scale clinical trial to assess the effect of protein restriction on the deterioration of renal function. A formula was derived in 1070 patients and tested in 558 other patients of the same population [9]. It incorporated, besides gender, age and plasma creatinine, also ethnicity, serum albumin and urea, but not body weight. There is no sound reason to incorporate serum albumin in a GFR-prediction formula and urea is dependent on many other factors than GFR, but these parameters emerged from the multiple regression analysis. This formula was more precise for GFR-estimation than the Cockcroft-Gault formula in that study, but no enzymatic assay nor cimetidine had been used. The precision of the MDRD formula was about the same as the precision of the Cockcroft-Gault formula after cimetidine in patients with renal disease [2]. The variability of serum albumin assays [10] argues against the widespread use of the MDRD formula. Protein restriction itself has an influence on serum urea concentration.

The formula of Cockcroft and Gault has a logical theoretical foundation, that is estimation of the urinary creatinine output, which in steady state equals the creatinine production, by age, gender and body weight. This estimation is divided by plasma creatinine to obtain a clearance value. It was performed in 226 males and only 10 females [1]. Not a GFR-measurement, but the endogenous creatinine clearance based on two 24-hour urine collections served as reference value. No cimetidine was used to inhibit tubular secretion. And no enzymatic plasma creatinine assay, but the less accurate alkaline picate (or Jaffé) method was used. Nevertheless and surprisingly, by applying modifications to the procedure, consisting of the use of an enzymatic creatinine assay and the administration of cimetidine, GFR-estimation from the Cockcroft-Gault
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formula appeared appropriate in both males and females, compared to a ‘gold standard’ GFR-measurement. In fact, we did not test but rather improve the procedure using the Cockcroft-Gault formula by the two modifications [11].

The relevance of the plasma creatinine assay

The plasma creatinine assay is important for accurate GFR-estimation from CG\textsubscript{Gm}. It has been shown that the alkaline picrate reaction, based on the formation of an orange-red Janovsky complex between creatinine and picrate under alkaline conditions, was not suitable for GFR-estimation (chapter 5). This was due to the interference of non-creatinine chromogens which elevated measured plasma creatinine values, especially in the low to normal range. This is because the positive error was a constant and not a percentual error of approximately 20 $\mu$mol/l in this plasma creatinine range [12,13]. For example, a plasma creatinine of 80 $\mu$mol/l measured with the alkaline picrate assay was 60 $\mu$mol/l when measured with the high performance liquid chromatography (HPLC) method, so the positive error was 33%. This in turn led to a similar percentual underestimation of GFR by CG\textsubscript{Gm} in the normal to high GFR range, as plasma creatinine is in the denominator of the Cockcroft-Gault formula. In the higher creatinine range, or lower GFR range, this underestimation decreased in terms of percentage. The enzymatic plasma creatinine assay used in this thesis, creatininas PAP and later PAP+, consists of three enzymatic steps - creatininas, creatininas and sarcosine oxidase - and a final chromogen coupling reaction using peroxidase [14]. We have found no relevant differences between this assay and the HPLC method, because of a reduction in interfering substances [14-16]. As a result, GFR-estimation from CG\textsubscript{Gm} was accurate at all levels of GFR in patients with a plasma creatinine up to 180 $\mu$mol/l.

A plasma creatinine concentration below 180 $\mu$mol/l was used as an inclusion criterium for two reasons. First, in this plasma creatinine range renal function can be either normal, slightly decreased or markedly reduced. A more accurate GFR-estimation can guide timely interventions to preserve or improve renal function. Above a plasma creatinine concentration of 180 $\mu$mol/l GFR is almost always below 40 ml/min/1.73m$^2$ [3], renal function can be easily followed by plasma creatinine [17] and therapeutic interventions are usually less successful in improving renal function. A second reason is that a new steady state of plasma creatinine will develop after inhibition of tubular creatinine secretion by cimetidine. The time period needed to attain a new
steady state is dependent on the biological half-life of a substance, i.e. in this case renal function. A previous study showed that the new steady state was reached within 24 hours after cimetidine administration, if plasma creatinine was below 180 μmol/l [2]. A more prolonged administration for patients with a higher plasma creatinine level is not practical in the outpatient setting.

**Limitations of the Cockcroft-Gault formula**

The limitations of $\text{CG}_{\text{Cm}}$ as a measure of GFR should be realized. First, while the accuracy was good, the precision was only moderate especially in type 2 diabetic patients. This means that in a group of patients mean $\text{CG}_{\text{Cm}}$ is equal to mean GFR, but for the individual patient $\text{CG}_{\text{Cm}}$ can be 20 ml/min/1.73m² above or below GFR. This holds true for the GFR range above 40 ml/min/1.73m² and no correction of this over- or underestimation is possible on clinical grounds. Still, $\text{CG}_{\text{Cm}}$ can be used to classify patients in normal, mildly or moderately reduced renal function, which is not possible with the endogenous creatinine clearance due to a low precision. If the exact GFR or its change after an acute intervention has to be known in an individual patient, as in research settings, then $\text{CG}_{\text{Cm}}$ is not sufficient and measurement of GFR with inulin or radiotracers is necessary.

The patient groups studied were drawn from regular outpatient clinics, but the inclusion criteria should be realized. A plasma creatinine concentration below 180 μmol/l as explained above. A body mass index between 15 and 30 kg/m² and in type 2 diabetic patients up to 35 kg/m² free of edema is not present in all patients, especially in renal or cardiac patients with fluid overload. Furthermore, the patients should not take interfering drugs, in practice only trimethoprim because it also inhibits tubular creatinine secretion. Another limitation is the compliance of patients using cimetidine for 24 hours previously to blood sampling in the outpatient setting. In the diabetic patients we checked the consumption of cimetidine by qualitative urinalysis. As a consequence, we knew whether the patients had taken cimetidine, but not how many doses they had used. In an outpatient setting it is laborious to perform urinalysis and perhaps this can be restricted to occasions when there is doubt about the patients' compliance.
Toxicity of cimetidine

No toxicity was found in these studies with rather small patient groups, but it is unclear whether toxicity would occur if this approach would be put into clinical practice. Interstitial nephritis due to cimetidine has been reported but is extremely rare, around 1 in 100,000 treated patients, and has always been reversed on cessation of therapy [18]. Other adverse effects are generally infrequent and usually reversible following a reduction of dosage or withdrawal of therapy [19].

As tubular creatinine secretion was not inhibited completely in all patients, it is speculative whether a higher cimetidine dose above the maximum allowed daily dose of 2400 mg will cause complete inhibition. Van Acker et al. obtained complete inhibition of tubular secretion 3 to 6 hours after a dose of 1200 mg measured by the simultaneous creatinine and inulin clearance, in patients who did not have complete inhibition with a dose of 200 mg every 3 hours [5]. This approach is not feasible when the Cockcroft-Gault formula is used, since administration over 24 hours is required to attain a new steady state of plasma creatinine, and a dose above 2400 mg will be necessary in the patients. Overdosage with cimetidine 5.2 to 20 g, including a patient who took about 12 g daily for five days, has not produced serious toxic effects. Cimetidine can increase serum levels of ciclosporin, theophylline, acenocoumarol, phenytoin and nifedipine through an interaction with cytochrome P450 the liver, but it is unlikely that this will be relevant with a single day administration [19]. Another way to inhibit tubular creatinine secretion more completely might be the co-administration of trimethoprim, because it uses the same proximal tubular organic ion transporter system [20]. Both a moderate and a high dose of trimethoprim reduce tubular creatinine secretion to the same extent [21]. The only occasion where combination of cimetidine and trimethoprim has been studied was in an animal study to investigate the reduction of dapsone-mediated methemoglobinemia [22]. Cimetidine increased the area under the curve of trimethoprim threefold, but no influence on the tubular creatinine secretion was mentioned.

The cost-effectiveness of the enzymatic plasma creatinine assay has not been studied. A blinded randomized approach with long-term follow-up would be necessary to assess this subject. At the start of this thesis the enzymatic assay was ten times more expensive than the alkaline picrate assay, but four years later when it was introduced in one of the study hospitals only three times more expensive. This was due to a more widespread use of the enzymatic assay and a reduction in the volume of reagents. A further reduction of the cost may be possible.
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Direction for future study

The major advantage of $CG_{Gm}$ is that it is more accurate than $CG$ without cimetidine or the endogenous creatinine clearance and that it can be applied more easily and more often than cumbersome GFR-measurements. In type 2 diabetic patients, early changes in renal function can be detected by clinicians and early interventions can be performed to preserve or improve renal function. A long-term follow-up study in a large group of renal patients is needed to determine the accuracy and particularly the precision of the change in $CG_{Gm}$ using the enzymatic plasma creatinine assay.

References


