Improvements in the use of plasma creatine as a marker of the glomerular filtration rate
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Introduction

Aim and outline of the thesis

Improvements in the use of plasma creatinine as a marker of the glomerular filtration rate: the importance of tubular creatinine secretion and plasma creatinine assay.
Introduction

The plasma creatinine concentration is commonly used for the assessment of renal function, i.e. the glomerular filtration rate (GFR). However, there are some drawbacks that prohibit accurate GFR-prediction from plasma creatinine. First, plasma creatinine is not only dependent on GFR, but also on muscle mass, age and gender [1]. Second, the power relationship between plasma creatinine and GFR causes a much faster decrease of GFR than an increase of plasma creatinine. Therefore, an important loss of GFR has already occurred in many patients, when plasma creatinine increases above the upper limit of normal [2]. Third, the alkaline picrate or Jaffé assay of plasma creatinine, based on a colour reaction, gives rise to falsely high values due to non-creatinine chromogens [3]. And finally, creatinine is not only filtered by the glomeruli, but also secreted by the tubules [4]. Therefore, the endogenous creatinine clearance overestimates GFR by the tubular creatinine secretion. The reference values for GFR are 90-170 ml/min/1.73m² for males and 90-150 ml/min/1.73m² for females [5]. In a large group of renal patients the overestimation of GFR by the creatinine clearance is higher when GFR is lower. The overestimation is 10-20 % in the normal range and 70-80 % at a GFR of 20 ml/min, below which the overestimation is lower again [6]. Furthermore, the amount of creatinine secreted by the tubules in an individual can be variable during the course of the disease and therefore creatinine clearance can change discordantly from GFR during follow-up [7]. Consequently, no standard formula can convert creatinine clearance to GFR.

It is notoriously difficult to obtain a correct urine sample without bladder catheterization. Urine collections can be obviated when formulas and nomograms are used to assess creatinine clearance. These formulas are derived from plasma creatinine and from variables such as age, weight and gender, that are related to muscle mass, i.e. creatinine production. The formula of Cockcroft and Gault, described in 1976 [1], is used most often, in the past mostly for drug dosing but more recently also for prediction of GFR. Newer formulas for GFR-prediction have been described later, comparing 'gold standard' GFR-measurements with formulas derived from multiple regression analysis [8-11].

Tubular creatinine secretion can be inhibited competitively by cimetidine. In this way the overestimation of GFR by the endogenous creatinine clearance can be prevented or at least reduced. A previous study has shown that the creatinine clearance during cimetidine administration became equal to GFR, when a sufficient dose of cimetidine was administered [12].
Because of the allowed maximal daily dose of cimetidine some patients needed a single high dose of cimetidine and a 3-hour clearance period, which is inconvenient. The creatinine clearance, assessed by the formula of Cockcroft and Gault, also approached GFR in patients with renal disease, when cimetidine was administered for one day in order to obtain a new steady state of plasma creatinine [13].

**Aim and outline**

The aim of this thesis was to investigate whether plasma creatinine could be improved as a marker of GFR after inhibition of tubular secretion by cimetidine. This was studied in other patient groups at risk for deterioration of renal function, such as patients with type 2 diabetes mellitus and renal transplant recipients. Furthermore, the contribution of the accuracy of different plasma creatinine assays on the estimation of renal function was studied.

In chapter 1 the literature on the prediction of GFR from the plasma creatinine concentration as applied in different formulas is reviewed. The accuracy and precision of the predicted GFR in various patient groups is analyzed. In chapter 2 GFR-estimation by the endogenous creatinine clearance or the formula of Cockcroft and Gault before and during cimetidine administration is studied in patients with non-insulin dependent or type 2 diabetes mellitus. Patients are divided in subgroups without albuminuria, with microalbuminuria or with overt nephropathy. Chapter 3 contains a follow-up study on the accuracy of GFR, estimated from the Cockcroft-Gault formula after cimetidine in the type 2 diabetic population. The hypothesis is tested that the over- or underestimation of a weight-based formula for GFR is due to the inappropriate reflection of muscle mass by body weight in diabetic patients and that the over- or underestimation is for a large part consistent in time. In chapter 4 the Cockcroft-Gault formula with cimetidine is compared to the endogenous creatinine clearance without cimetidine for the prediction of GFR in renal transplant patients. In this patient group tubular creatinine secretion is especially important, because of a relatively low GFR (see above). Subgroups of patients with a GFR below and above 40 ml/min/1.73m² are analyzed separately.

In chapter 5 the importance of the plasma creatinine assay for GFR-estimation is studied in patients with type 2 diabetes. The alkaline picrate or Jaffé assay is compared to an automated enzymatic assay and to the reference high performance liquid chromatography method. Chapter 6 describes the influence of ketoacidosis on the plasma creatinine assay. The metabolic
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disturbances and their severity is studied during and after episodes of ketoacidosis in patients with diabetes mellitus. In the appendix a survey is given of the various methods and their limitations to measure GFR. A refinement of the GFR-measurement by $^{125}$I-iothalamate and $^{131}$I-hippuran, using correction for inaccurate urine collections and for varying plasma tracer concentrations is described. This GFR-measurement is used as the reference method in chapters 2 to 5. In the general discussion the improvement of the plasma creatinine concentration after inhibition of tubular creatinine secretion as a marker of GFR is debated. The relevance of an accurate plasma creatinine assay is discussed. Practical guidelines when to use plasma creatinine and especially when not to use it and directions for future study are presented.

References


