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Cystatin C vs creatinine as markers of renal function in patients on digoxin treatment

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ABSTRACT

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Background: The kidney function is a major determinant of the serum concentration of digoxin as this drug is mainly eliminated unchanged through the kidneys. Since digoxin is widely prescribed among the elderly, and the glomerular filtration rate (GFR) declines with age, it is important that the clinician takes the patient's GFR into account when prescribing digoxin. Serum cystatin C has been suggested to be superior to creatinine for estimation of GFR, which may have relevance for the optimization of treatment with digoxin. **Methods:** To evaluate which of the two GFR markers serum creatinine and serum cystatin C that best correlates with serum digoxin, we compared the serum levels of digoxin with the serum levels of creatinine and cystatin C in 149 patients on therapeutic drug monitoring of digoxin at our hospital. **Results:** Overall, there was a stronger correlation between serum digoxin concentrations and cystatin C (p=0.00001) as compared to creatinine (p= 0.00003). Interestingly, of the patients with a serum digoxin concentration Bl.5 nmol/L, 29% had a serum creatinine level within normal limits, as compared to 20% with normal cystatin C levels. **Conclusions:** In this study, serum cystatin C correlated better to serum digoxin than did serum creatinine. With improved GFR monitoring, digoxin concentrations should be better controlled.

INTRODUCTION

Digoxin is commonly used in the treatment of congestive heart failure and atrial fibrillation. The drug has become a subject of discussion after recent publications that showed a gender-related difference in mortality [1], a gender-related difference in serum (s) digoxin [2], and subsequently an increased mortality for men with s-

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digoxin Bl.5 nmol/L[3]. This has led to a revised recommendation at our hospital to target s-digoxin to <1.5 nmol/L. In this context, an heightened attention to the patient's s-digoxin level is warranted.

Adverse drug events affect millions of patients each year and was responsible for up to 14% of acute hospital admissions at a Swedish internal medicine clinic in 2001 [4]. In the elderly, adverse drug events occur in 14.6% to 35%, depending on the population setting and measures employed for their identification [5, 7]. Toxic concentrations of digoxin may require hospital treatment and digoxin intoxication is one of the most frequent causes of hospital care due to toxic drug effects[8]. Among individuals aged 75 and older, almost 20% were on medication with digoxin in 1996 [9]. Despite declining use in the last few years, digoxin is still one of the most frequently prescribed drugs; it was listed twice among the top 200 prescriptions in 2000 [10]. In 1995, it was the drug most often monitored therapeutically [11] because of its narrow therapeutic window and potentially serious side effects.

Digoxin has a half-life of approximately 1.5 days and the drug is mainly eliminated unchanged in the urine [12]. Glomerular filtration rate (GFR) has a major impact on s-digoxin [12]. As geriatric patients often have reduced GFR, monitoring kidney function during digoxin treatment is important.

In the last decades, creatinine has become the most commonly used marker of GFR [13, 14]. Despite its common use, creatinine has limitations as a renal function marker. Creatinine is influenced by factors such as age, gender, muscle mass, physical activity and diet [15]. It is also insensitive for detection of small decreases in GFR, in the so-called creatinine-blind GFR area, due to the non-linear relationship between serum concentration and GFR [16]. Thus, there is a need for better GFR markers. Several markers such as β-trace protein, cystatin C and β_2-microglobulin have been suggested as alternatives to creatinine [17–19]. The normal serum level of cystatin C is <1.20 mg/L for patients less than 50 years of age and <1.55 mg/L for patients over 50 years of age, while increasing levels is detected in serum from patients with reduced GFR. Cystatin C is a polypeptide with a molecular mass of 13 kDa and an ellipsoid molecular shape with axes of about 30 and 45 Å [20]. Studies on the handling of human cystatin C in the rat have shown that the serum clearance of cystatin C is 94% of that of the generally used GFR-marker ^{51}Cr-EDTA [21]. A recent meta-analysis has indicated that s-cystatin C is superior to s-creatinine as a renal function marker [22].

We have studied the correlation between s-digoxin and the GFR markers s-creatinine and s-cystatin C. The study was performed to evaluate which of the two GFR markers s-creatinine and s-cystatin C that best correlated with s-digoxin. One earlier study of 18 healthy elderly individuals found no correlation between either s-cystatin C or s-creatinine and digoxin clearance, and thus concluded that s-cystatin C did not offer any advantages over s-creatinine in this respect [23]. However, the small number of study subjects may have been insufficient to detect a correlation, and also, actual digoxin treated patients have not been studied.

MATERIALS AND METHODS

Patient samples and assays

Consecutive routine requests (n=163) for therapeutic drug monitoring of s-digoxin were also analyzed for s-cystatin C and s-creatinine. The material consisted of samples from 98 females and 65 males, both in- and out-patients treated with digoxin for any medical condition. The mean age was 80 years (range 55–106 years), and the mean dose of digoxin was 0.18 mg/day (range 0.07–0.3 mg/day).

S-digoxin was determined on the Advia 1650 (Bayer Corp., Tarrytown, NY, USA). S-digoxin values below 0.6 nmol/L were reported as <0.6 nmol/L. S-cystatin C measurements were performed by a latex-enhanced reagent (N Latex Cystatin C, Dade Behring, Deerfield, IL, USA) using a Behring BN ProSpec analyzer (Dade Behring). The total analytical imprecision (coeficient of variation, CV) of the method was 4.8% at 0.56 mg/L and 3.7% at 2.85 mg/L. S-creatinine measurements were performed by means of the modified kinetic Jaffe reaction on the Advia 1650 analyzer (Bayer Corp) and reported as S.I. units (µmol/L). The total analytical imprecision (CV) of the method was 2.6% at 170 µmol/L and 2.4% at 740 µmol/L. All assays were performed independently and without prior knowledge of other test results at the Department of Clinical Chemistry and Pharmacology at our hospital. The study was approved by the local ethical board at Uppsala University (1–167).

Statistical calculations

Data on s-cystatin C, s-creatinine and s-digoxin were normally distributed, and statistical correlation analysis was performed with the Pearson product-moment correlation test using Statistica 5.1 (StatSoft Inc., Tulsa, OK, USA). Digoxin values <0.6 (n=14) were excluded from the statistical analyses, giving a total number of patients of 149. P-values <0.05 were taken as statistically significant throughout the study.

RESULTS

Digoxin concentrations

When analyzing only those patients who had reached steady-state concentrations of digoxin and in whom serum levels had been measured at through were analyzed (n=94), mean s-digoxin was 1.5 nmol/L (range 0.6-4.0 nmol/L), with higher concentrations among females (1.6 nmol/L) than males (1.4 nmol/L). This difference did not reach statistical significance (p=0.24, unpaired t-test). Among these patients, 33% of the digoxin concentrations were Bl.5 nmol/L and 9% >2.5 nmol/L. There was no correlation between age and s-digoxin (p=0.86, r=-0.02, n=94).

Correlation between s-digoxin and s-cystatin C vs s-creatinine

Overall, s-digoxin correlated stronger to s-cystatin C (p=0.00001, R=0.35, n=149) as compared to s-creatinine (p=0.00003, r=0.34, n=149). The difference was more marked (fig 1 and 2) when only patients who had reached steady-state of digoxin

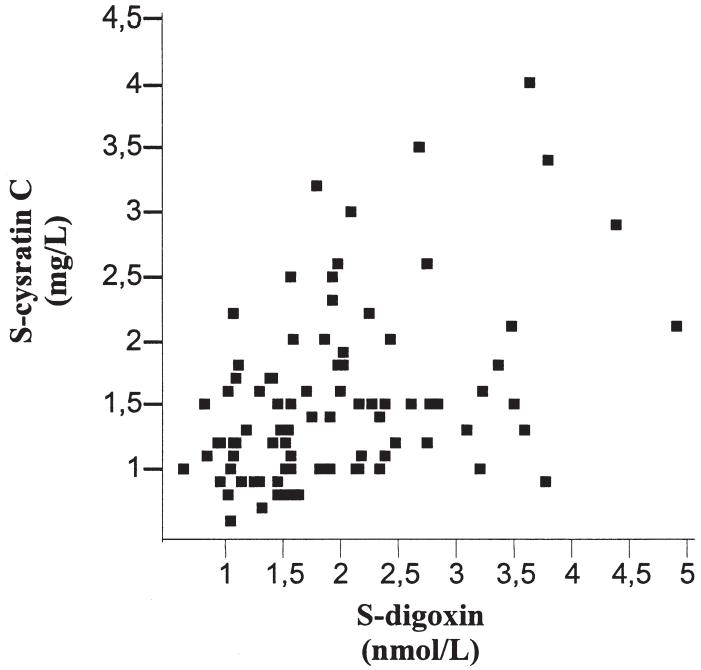

Fig. 1. Correlation between S-digoxin and S-cystatin C for individual patients.

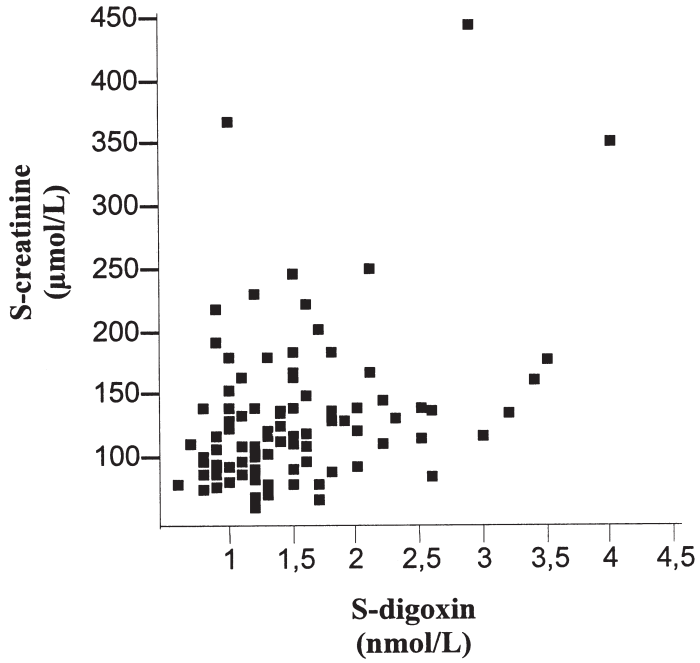

Fig. 2. Correlation between S-digoxin and S-creatinine for individual patients.

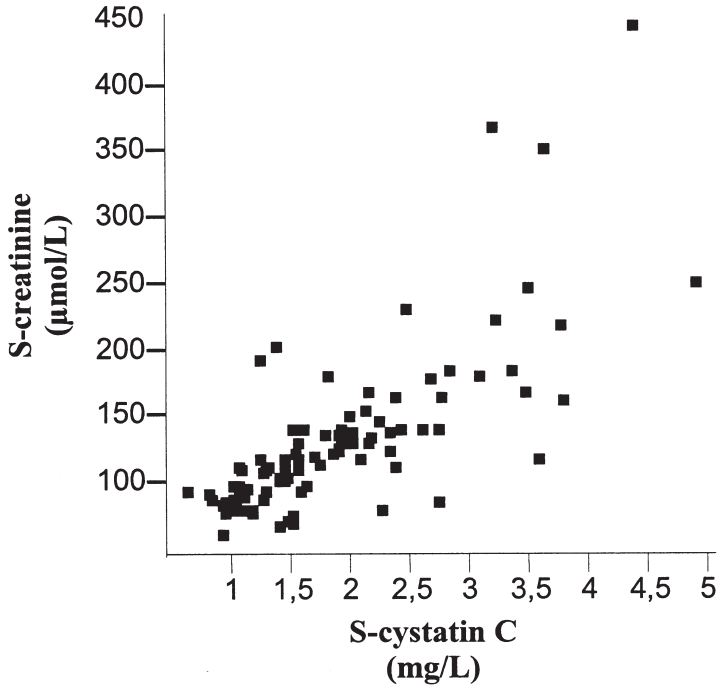

Fig 3. Correlation between s-creatinine and s-cystatin C for individual patients.

and in whom serum levels had been measured at through (n=94) were analyzed (s-digoxin vs s-cystatin C, p=0.000001, r=0.45, n=94 s-digoxin vs s-creatinine, p= 0.0003, p=0.37, n=94). The difference was similar in both genders. Also, of the patients with a s-digoxin concentration Bl,5 nmol/L, 29% had a s-creatinine level within normal limits (69–113 µmol/L), as compared to 20% with normal s-cystatin C levels. There were also inverse correlations between digoxin dose and s-cystatin C (p=0.007, r=–0.28, N=94), and digoxin dose and s-creatinine (p=0.04, r=–0.22, n=94). The correlation between s-cystatin C and s-creatinine is illustrated in fig 3.

DISCUSSION

GFR is generally accepted as the best overall index of renal function. GFR decreases with age and reduced GFR is the most important complication of renal disease. Reduced GFR affects the clearance of many drugs used today, including digoxin, so that in many cases the recommended dose has to be adjusted depending on the patient's GFR. There is thus a need for robust GFR markers. Inulin, iohexol and ^{51}Cr-EDTA clearances are considered the golden standards for GFR measurements [22, 24]. The disadvantage with these assays is that they are cumbersome, costly and slow which may delay the start of treatment. Assays such as s-creatinine and s-cystatin C can provide rapid test results. Creatinine in combination with the Cock-

croft-Gault equation is often used to estimate GFR [25]. Using actual body weight in the Cockcroft-Gault equation overestimates the GFR for obese patients [26]. An alternative could be to use lean body mass, but this is not usually available. Creatinine often overestimates GFR in patients with slight reductions in GFR [27]. This may cause the prescribing physician to treat the patient with unnecessary high drug doses, which will increase the cost and possibly cause side effects.

The inverse correlation between digoxin dose and s-cystatin C and s-creatinine in this study indicates that the kidney function should be considered when digoxin is prescribed. However, the high prevalence of patients with uncontrolled s-digoxin Bl.5 nmol/L, and the strong correlations between s-digoxin and s-cystatin C and s-creatinine indicate that even greater consideration should be taken to GFR function. S-digoxin correlated stronger to s-cystatin C as compared to s-creatinine, which is in agreement with previous studies showing s-cystatin C to be superior to s-creatinine as a marker of renal function [22]. The use of cystatin C has been hampered by the limited availability of the test and the problem of relating cystatin C to an estimated GFR. The introduction of new cystatin C tests that can be applied on widely available chemical analyzers will increase the availability of the test. Our hospital has for the last year offered measurements of s-cystatin C as a STAT request and also reported cystatin C in mg/L as well as converted to GFR (mL/min). This has improved the clinical usefulness of the assay and we have noticed a rapid increase in the number of requests for cystatin C.

We conclude that greater consideration should be taken to GFR when prescribing digoxin, and that s-cystatin C correlates better to s-digoxin than does s-creatinine among patients on digoxin treatment.

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