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Urinary β_2-microglobulin, Antimicrobial Chemotherapy and Infectious Diseases

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ABSTRACT

A review of the literature concerning β_2-microglobulinuria during treatment with antibiotics and during febrile conditions is presented. Aminoglycoside treatment in normally used therapeutic doses causes an impairment of the tubular reabsorptive capacity as evidenced by β_2-microglobulinuria in the majority of patients. Increases in urinary β_2-microglobulin can, however, not be used to predict clinical nephrotoxicity in the individual patient since the urinary concentration is dependent on several factors. The main indication for measuring urinary concentrations of this protein during aminoglycoside treatment is to compare the nephrotoxic potential of different aminoglycosides and possibly of other antimicrobial agents, e.g. cephalosporins. Fever causes a temporary impairment of the proximal tubular reabsorptive capacity with increases in the urine of several low molecular weight proteins, e.g. β_2-microglobulin. It is therefore highly likely that this is the explanation of the β_2-microglobulinuria seen in patients with pyelonephritis. The suggestion that measurements of urinary β_2-microglobulin could be of value to determine renal involvement of urinary tract infections is therefore doubtful.

INTRODUCTION

The renal proximal tubuli are the primary target for aminoglycosides and for cephalosporins with nephrotoxic side effects. The proximal tubuli are also the site where filtered β_2-microglobulin is normally absorbed and metabolized. Damage of the tubuli will result in a reduced absorption and concomitant excess loss of β_2-microglobulin in final urine. Measurement of urinary β_2-microglobulin has, therefore, been advocated as an early test of renal damage from antimicrobial therapy before clinical nephrotoxicity becomes apparent. However, several issues complicate the interpretation of urinary β_2-microglobulin values in such patients. Firstly, a clear-cut association between proximal tubular damage and clinical nephrotoxicity - as revealed by

an increased serum creatinine value - has not been established. Secondly, the increased loss of β_2-microglobulin in urine in patients with infectious diseases may have other causes than antimicrobial toxicity. Thus, β_2-microglobulinuria has been described to occur in patients with fever and in patients with an impaired glomerular filtration rate.

The following review is an effort to position the value of measurement of urinary β_2-microglobulin in patients with infectious diseases receiving treatment with nephrotoxic antimicrobial agents.

AMINOGLYCOSIDE-ASSOCIATED NEPHROTOXICITY AND β_2-MICROGLOBULINURIA

Aminoglycoside treatment results in tubular and glomerular changes in virtually all patients receiving these drugs in normally used therapeutic doses. The glomerular impairment is detectable after less than one week of treatment by measurement of ^{51}Chrome-EDTA clearance (18). The effects on the proximal tubuli are detected immediately after initiation of therapy by the increased activity in the urine of enzymes originating from proximal tubular cells, e.g. alanine aminopeptidase and N-acetyl-β-D-glucosaminidase (9, 16, 19,).

In many patients there is also an increase in the urinary loss of β_2-microglobulin indicating an impairment of the proximal tubular reabsorptive capacity (14, 16, 19). Intraindividual changes are, however, sometimes difficult to interpret, since increases in urinary β_2-microglobulin can also be the result of changes in tubular function due to underlying infections, fever, trauma or operations (6, 25). Many patients, therefore have high urinary β_2-microglobulin levels before start of aminoglycoside treatment which make it difficult to evaluate the reasons for changes during treatment. In addition, patients with reduced glomerular filtration rate and subsequently high serum β_2-microglobulin levels may lose excess β_2-microglobulin in the urine due to saturation of the tubular reabsorptive capacity (24). Due to the unique antibacterial spectrum of the aminoglocysides it has until recently not been possible to perform comparative studies on urinary β_2-microglobulin in patients receiving aminoglycosides and non-aminoglycoside antibiotics. With the introduction of new broad-spectrum β-lactam antibiotics this is now possible. We have, in a comparative study shown a significant increase in urinary β_2-microglobulin in gentamicintreated patients as compared to patients receiving the β-lactam cefotetan (20).

Increases in urinary β_2-microglobulin during aminoglycoside treatment are subjected to major intraindividual variations and all patients do not develop increases (14, 16, 18, 19). The percentage of patients who develop increases in urinary levels of the protein varies between different studies, as does the

size of peak level achieved. In some patients an initial rise in urinary β_2-microglobulin levels is followed by a decline during the same treatment course (15, 19). It is not known if this fall is due to regeneration of tubular ephithelium, as suggested by an animal study (8) or has other causes.

It has been suggested that urinary β_2-microglobulin can be used to predict clinical nephrotoxicity and thus to monitor aminoglycoside treatment (14, 16). This suggestion has, however, been contradicted by two studies, in which it was found that the levels in the urine of the protein could not be correlated to subsequent serum creatinine increases (4, 19,). It is therefore my opinion that β_2-microglobulin measurements currently have no place in the routine clinical management of aminoglycoside treated patients. When, however, new aminoglycosides are studied or when old compounds are compared urinary β_2-microglobulin should be determined in combination with other sensitive tests for detection of renal side effects, e.g. urinary enzymes and ^{51}Chrome-EDTA clearance.

ARE CEPHALOSPORINS TUBULOTOXIC IN MAN ?

It has been clearly shown in experimental animals that all cephalosporins have a nephrotoxic potential when given in sufficiently high doses (11). It has also been clearly shown in patients that cephaloridine, one of the oldest compounds of the cephalosporin family, was responsible for nephrotoxic reactions (3). The nephrotoxic reactions of cephalosporins in experimental animals are localised to the proximal tubuli (7, 11, 17). Similar to aminoglycoside nephrotoxicity cephalosporin nehprotoxicity is related to high concentrations of the drug in the proximal tubular cells (21, 22). It is hypothesized that cephalosporins which enter the tubular cells and thereafter are actively secreted have a very low nephrotoxic potential, while compounds like cephaloridine, which enter the tubular cells without being secreted, accumulate there and have a higher nephrotoxic potential (10, 21, 22). At the time when cephaloridine was much used, determinations of β_2-microglobulin or other low molecular weight proteins in the urine were not performed for the evaluation of antibiotic induced tubulotoxicity and no data are, therefore available to what extent the proximal tubular reabsorptive capacity was impaired by the drug. The localisation of the histopathologic lesions in cephaloridine treated animals and similarities between cephaloridine and aminoglycoside accumulation in proximal tubular cells strongly suggest, however, that cephaloridine might impair the tubular reabsorptive capacity of low molecular weight proteins. Most of the currently available cephalosporins, with the possible exception of ceftazidime, are not nephrotoxic at serum concentrations used in clinical practive. Ceftazidime causes a small decrese of the glomerular filtration rate

(1, 10) and is, like cephaloridine, excreted through the glomeruli (5). In two studies no effects of the drug on urinary β_2-microglobulin levels could be demonstrated (1, 10). Due to wide variation of pretreatment β_2-microglobulin levels, larger comperative studies are, however, necessary to exclude any drug-induced tubular inpairment.

In summary, there is insufficient knowledge on the mechanism of cephalosporin induced renal changes. In view of the large number of cephalosporins and related compounds which are currently entering the market it is extremely important that any signs of nephrotoxicity are discovered at an early stage and related to possible benefits before a new drug is allowed to be registered for use. One of the several tests suitable for evaluation of renal side effects is in my opinion the indirect measurement of proximal tubular reabsorptive capacity by urinary β_2-microglobulin.

UPPER URINARY TRACT INFECTIONS, FEVER AND β_2-MICROGOLBULINURIA

"Febrile proteinuria" is a well-known phenomenon described several decades ago (2, 23), but the composition of the proteins excreted in elevated amounts in patients with fever has not until recently been studied. In a study from Denmark (6) patients with febrile infections not involving the urinary tract showed a tubular pattern of proteinuria characterized by the increase of 4 low molecular weight proteins (free lambda and kappa light chains from immunoglobulins, lysozyme and β_2-microglobulin). Patients with temperature above 38.5^{o}C had significantly higher levels of these proteins than patients with temperature between 38.0^{o}and 38.5^{o}C. Three days after normalisation of the temperature the urinary concentration of the low molecular weight proteins had normalised. Some of the febrile patients also showed a "glomerular proteinuria" with elevated urinary levels of high molecular weight proteins, e.g albumin, concurrently with the tubular proteinuria. The "glomerular proteinuria" persisted for longer time than the "tubular proteinuria". The authors suggest that the fever per se caused an impairment of the proximal tubular reabsorptive capacity of low molecular weight proteins while other factors in the infectious process caused the glomerular leakage of high molecular weight proteins.

A retrospective analysis of pooled data from studies on antibiotic nephrotoxicity conducted by the reviewer and co-workers (1, 10, 18, 19 and others) supports the Danish results. The studies include 208 patients with infections not involving the kidneys. Before start of antibiotic treatment, 71 of 96 febrile patients (74%) had urinary β_2-microglobulin concentrations above 60 mg/mol creatinine compared to 53 of 112 afebrile patients (47%). If only patients with serum β_2-microglobulin levels below 4.5 mg/l were considered 46

of 69 febrile patients (67%) and 27 of 84 afebrile patients (32%) had urinary β_2-microglobulin levels above 60 mg/mol creatinine. Both comparisons yield significant differences between the febrile and afebrile groups ($p<0.001$, Fisher's exact test). Many of the patients with high fever and severe infections had urinary β_2-microglobulin levels of similar magnitude as patients with pyelonephritis. With exception of aminoglycoside treated patients the urinary β_2-microglobulin levels decreased towards normal when the temperature normalised.

In view of the relationship between fever and β_2-microglobulinuria it is unlikely that urinary β_2-microglobulin would be a valuable tool in level diagnosis of a urinary tract infection or in the monitoring of treatment response in patients with pyelonephritis, even though this has been suggested (12, 13). Measurement of a patient's body temperature should give comparable information.

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