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More on Cephalosporin Interference with Creatinine Determinations

To the Editor:

Several cephalosporin antibiotics—cephalothin, cephaloglycine, cephalexin, cephalexin, cefazolin, and cefoxitin—reportedly interfere positively with measurement of creatinine by the Jaffe reaction. Others such as cefazolin, ceftaxine, cefadroxil, and cefalpin give negative or only very slight responses under the same in vitro conditions (1, 2). Rankin et al. (3) showed in vivo interference with assays for both plasma and urinary creatinine after cephalothin administration, but found that the creatinine clearance calculated from these erroneous creatinine values was unaltered. They concluded that creatinine clearance is a valid indicator of renal function in the presence of concomitant cephalosporin administration. Durham et al. (4) also showed that values for serum and urinary creatinine were falsely increased after cefoxitin administration, especially at peak cefoxitin concentration, but they concluded that values for creatinine clearance, depending on the timing of the serum creatinine sample, could be falsely increased also. Thus, creatinine clearance, measured under these conditions, reportedly was clinically unreliable.

Clinically, increases in apparent creatinine owing to cephalosporin interference could lead to inappropriate alteration of therapy. The magnitude of this interference could be appreciable in patients with compromised renal function, where large quantities of cephalosporins are allowed to accumulate due to the relatively large therapeutic index of cephalosporins. Additionally, interference with urinary creatinine assay may cause spurious creatinine clearance calculations and consequently the calculation of excessive doses of drugs excreted renally.

We designed in vitro and in vivo studies to investigate the interference with creatinine determinations of the four cephalosporins currently used in our hospital: cefoxitin, cephalothin, cefazolin, and cefamandole.

Cephalothin (Ceporacine®; Glaxo Laboratories, Toronto, Ontario), cefazolin (Ancef®, Smith, Kline & French, Montreal, Quebec), cefamandole (Mando®; Eli Lilly Co., Toronto, Ontario), and cefoxitin (Mefoxin®, Charles E. Frost & Co., Dorval, Quebec), and desacetylccephalothin, a major metabolite of cephalothin, were reconstituted and aliquots were added to pooled plasma to give final concentrations of 0, 200, 1000, and 2000 mg of drug per liter. Creatinine was measured in each sample six times with the Greiner Selective Analyzer II (5).

Results of the in vitro experiments (Figure 1) demonstrated a linear relation between the increase in apparent creatinine and the cephalosporin concentration in plasma. Cefoxitin demonstrated the most marked effect, followed closely by cephalothin and desacetylccephalothin. Cefazolin and cefamandole caused only negligible interference. Similar results were observed when the four cephalosporins were added to urine specimens to give respective concentrations up to 5000 mg/L.

The in vivo study was performed on four patients who were receiving cephalothin and four receiving cefoxitin, with doses every 4 to 6 h of between 1 and 2 g of cephalosporin, administered by infusion during 20-60 min. After steady state was attained (24 h), blood samples were obtained before the next dose infusion, immediately after the infusion, and 1 and 2 h after the end of the infusion. Creatinine was determined, and cephalosporin concentrations were measured by a microbiological diffusion-in-agar method (6).

Figure 2 shows the in vivo increases in apparent plasma creatinine in patients receiving cephalothin and cefoxitin. Increases were calculated from the difference between the apparent plasma creatinine concentration while the patient was receiving cephalosporin and the baseline value obtained when cephalosporin concentrations were negligible.

The in vivo study confirmed that cephalothin and cefoxitin interfere with both plasma and urinary creatinine assay. The highest cefoxitin concentrations obtained, 50 and 25 mg/L after a 2-g and 1-g infusion, respectively, showed the greatest interference. Specimens sent at times later than immediately post-infusion gave low cefoxitin concentrations and showed only slight interferences. The concentrations
of cefoxitin immediately post-infusion were 250 mg/L and 100 mg/L after a 1-g infusion. The increase in apparent plasma creatinine declined more slowly with time than did cefoxitin. This is likely due to the higher concentrations of creatinine in plasma and to the additional interference by desacetylcephalothin. Cefoxitin is essentially unmetabolized.

Two 24-h urine specimens, one collected during steady state and the other at least five biological half-lives after the drug was discontinued, were collected from each of two patients receiving cefoxitin and two receiving cefalothin. Urinary creatinine concentrations and their differences were calculated, as well as the creatinine clearances and their differences (Table 1). We calculated creatinine clearances when the patients were on cefoxitin, using plasma creatinine values obtained when cephalosporin concentrations were lowest.

In three patients, there were increases in apparent urinary creatinine, and the average increase in clearance was 18 mL/min. Because cefalothin and cefoxitin are eliminated primarily by renal tubular secretion, whereas creatinine is lost mainly by glomerular filtration, the status of a patient's glomerular function relative to tubular function may affect the degree of interference with respect to urine. This may explain the failure of one patient to demonstrate such interference. Other factors could be an incomplete 24-h urine collection or a change in renal function on the collection day.

Overall, creatinine clearance is not a clinically reliable index of glomerular filtration for patients being treated with cephalosporins, because the values for apparent plasma creatinine vary during a dosing interval as cephalosporin concentrations fluctuate. If the clearance is calculated with the plasma creatinine value obtained when cephalosporin values are minimal, false increases in creatinine clearance are observed. This confirms the results of Durham et al. with cefoxitin (4), but contradicts those of Rankin et al. with cephalothin (3). The latter authors may have minimized increases in the creatinine clearance by fortuitously using plasma creatinine values at the highest cephalosporin concentrations.

In summary, cephalosporins falsely increase apparent creatinine in plasma and in urine, both in vitro and in vivo when a direct Jaffé reaction is used. The significance of the in vivo interference depends on the clinician's interpretation of results; therefore, to promote awareness and management of potential interferences, we developed the following guidelines for interpretation of plasma creatinine and creatinine clearance results:

1. In patients receiving cefalothin and cefoxitin, use caution in interpreting creatinine values from patients on maximal doses or patients with renal dysfunction.
2. Draw blood for the measurement of creatinine values when cephalosporin concentrations are low, to minimize interference.
3. Verify creatinine clearance calculations with an estimate from a nomogram such as that of Siersbæk-Nielsen. The plasma creatinine concentration measured when cephalosporin is lowest should be used.
4. When doses of drugs are calculated on the basis of a creatinine clearance value obtained during concomitant cephalosporin administration, monitor the serum drug concentrations where possible.

References

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Use of Azide to Enhance the Sensitivity of Colorimetric Immobilized-Glucose-Oxidase Methods for Glucose

To the Editor:

Use of glucose oxidase (EC 1.1.3.4) immobilized on nylon tubing for the colorimetric continuous-flow determination of glucose is well established (1–3). Typically, buffered samples are pumped through the immobilized enzyme reactor, and the color-forming reagents are added downstream from the enzyme loop. The "analytical" and "indicator" reactions are separated because the wash of the continuous-flow system is poor when the indicator reagent is pumped through the immobilized enzyme reactor, presumably because the organic chromophore tends to adsorb to the walls of the nylon coil.

We have used the immobilized glucose oxidase-Trinder method (4, 5) to study the fundamentals of enzyme reactors in continuous-flow systems. One of our studies involved an investigation of assay sensitivity as a function of immobilized enzyme (IME) reactor length. We were surprised by the results shown in Figure 1, curve A; little or no change in sensitivity was achieved when the length of the IME reactor was increased beyond ~25 cm. The maximum proportion of glucose converted was known to be <5%, and so the bend-off in the curve could not be explained by a large extent of reaction.

All commercially available glucose oxidase preparations are contaminated with catalase (EC 1.11.1.6), which decomposes hydrogen peroxide into oxygen and water. If some catalase were co-immobilized with glucose oxidase,