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Gamma-Glutamyltransferase Is a Reliable Marker for Tubular Effects of Contrast Media

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ABSTRACT

The aim of this study was to evaluate the usefulness of the measurement of urinary excretion of the brush-border enzyme gamma glutamyltransferase (GGT), in comparison with that of alanine aminopeptidase (AAP), as a marker for tubular toxicity due to contrast media (CM).

Urinary activities of AAP and GGT were measured prior to the administration of CM and 1, 3 and 5 days after in forty-nine adult renal patients undergoing a radiological examination with intravascular administration of CM.

The behavior of GGT was similar to that of AAP. In fact, urinary activities of both AAP and GGT increased greatly after CM. This effect was maximal on the 1st day and statistically significant for both enzymes. Furthermore, on the 1st day a relevant increase of enzyme activity (at least +50% over the basal value) was observed in the same number of patients (67%) for AAP and GGT. The concordance between GGT and AAP variations was high and statistically significant. Finally, different variables (osmolarity, dose of CM, and baseline renal function of the patients) had a similar effect on urinary excretion of AAP and GGT.

The repeatability of duplicated determinations of GGT resulted better than that of AAP. In conclusion, the good concordance of the results of

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GGT with those of AAP justifies the use of GGT as a marker for tubular effects due to CM. Furthermore, the measurement of GGT has a better repeatability than that of AAP.

Key Words: Contrast media; Nephrotoxicity; Kidney tubule; Urinary enzymes; Brush border enzymes; Alanine aminopeptidase; Gamma-glutamyltransferase.

INTRODUCTION

The urinary excretion of alanine aminopeptidase (AAP), a brush border enzyme of the proximal tubular cells (1), is a sensitive marker for tubular toxicity due to contrast media (CM) (2–11). Gamma glutamyl-transferase (GGT) is another brush border enzyme (1); its urinary excretion is less frequently employed to evaluate the nephrotoxicity due to CM (2,4,5,7–13).

The aim of this study was to assess the usefulness of urinary excretion of GGT, in comparison with AAP, as a marker for tubular toxicity due to CM.

PATIENTS AND METHODS

Patients

Forty-nine renal patients (24 females and 25 males; age 21–76 years, mean 52; body weight 45–103 kg, mean 71) with different degrees of renal impairment: plasma creatinine between 0.6 and 10.8 mg/dL, mean 1.25 (< 1.4 mg/dL in 39 patients and from 1.4 to 10.8 mg/dL in 10 patients).

All patients underwent a radiological examination with intravascular administration of CM: urography in 41 patients, computed tomography in 6 and angiography in 2. High- or low-osmolar CM were employed: diatrizoate, ionic high-osmolar, in 17 patients; iohexol or iopamidol, non ionic low-osmolar, in 32 patients. The administered dose of CM ranged between 0.2 and 3.3 g of CM/kg of body weight (mean 0.97): the dose was 0.2–1.8 g/kg BW (mean 0.83) for high-osmolar CM, and 0.2–3.3 g/kg BW (mean 1.04) for low-osmolar CM. No other potentially nephrotoxic drug was administered during the study period.

Urinary Enzymes and Conventional Tests of Renal Function

AAP was determined with a non automated spectrophotometer by incubating a sample of fresh non-dialyzed urine with L-alanine-β-naphthylamide (as substrate) for 120 min. From the reaction of β-naphtylamide with p-dimethylaminobenzaldehyde originates a yellow color, read at 450 nm (14).

GGT was determined on fresh non dialyzed urine with an automated method (Boehringer Mannheim, autoanalyzer Hitachi 911), the same method that is routinely employed for the plasma determination of GGT (15).

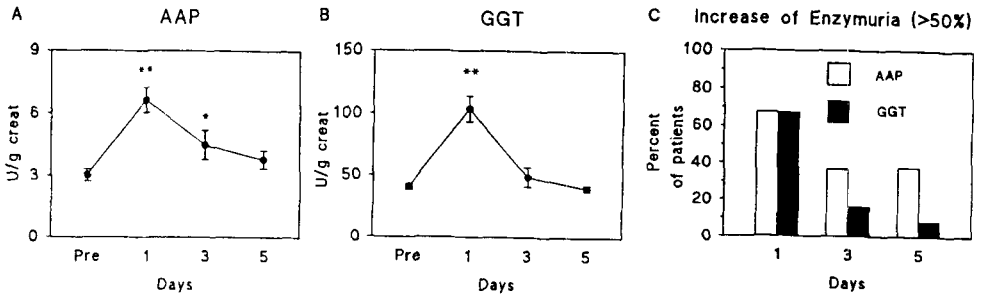

Figure 1. A,B) Urinary activities of alanine aminopeptidase (AAP) and gamma glutamyl- transferase (GGT) before and after contrast media (CM) (mean values ± SEM ; $*p < 0.05$ $**p < 0.001$); C) Percent of patients with increase of enzymuria (at least +50% over the basal value after CM (□ AAP, ■ GGT).

Urinary enzyme activities of AAP and GGT were measured twice in the week preceding the radiological examination and 1, 3 and 5 days after the administration of CM. Both urinary enzymes were determined on the same sample of morning urine and were expressed as enzyme activity adjusted per g of urinary creatinine (measured by autoanalyzer).

The renal effects of CM were also evaluated by means of conventional tests of renal function: urinary concentration of proteins (dipstick) in 44 patients, plasma creatinine (autoanalyzer) in 46 patients creatinine clearance (measured over 12 hours) in 41 patients. The glomerular filtration rate (GFR) was measured in 38 patients, before and 3 days after CM administration, as the renal clearance of ^{99m}Tc-DT PA, by means of the bladder cumulative method (16).

Statistical Analysis

Paired or unpaired Student's t test and Chi-square test were employed. A p value <0.05 was considered significant. The repeatability of duplicate measurements of AAP and GGT was evaluated (17).

RESULTS

CM induced only mild effects on the conventional tests of renal function. In fact, the only significant effect was a very slight increase in plasma creatinine on the third day after CM (from 1.26 ± 1.50 mg/dL to 1.33 ± 1.49; $p < 0.01$, paired Student's t test) accompanied by a non significant decrease in creatinine clearance and in GFR. Urinary excretion of proteins was unmodified.

The urinary excretion of both AAP and GGT increased greatly after the administration of CM, with a similar time-course (Fig.la,b). The increase in was maximal on the first day, and was statistically significant for both enzymes ($p < 0.001$). On the first day the mean values of the two urinary enzymes were more than doubled: the mean ratio 1st

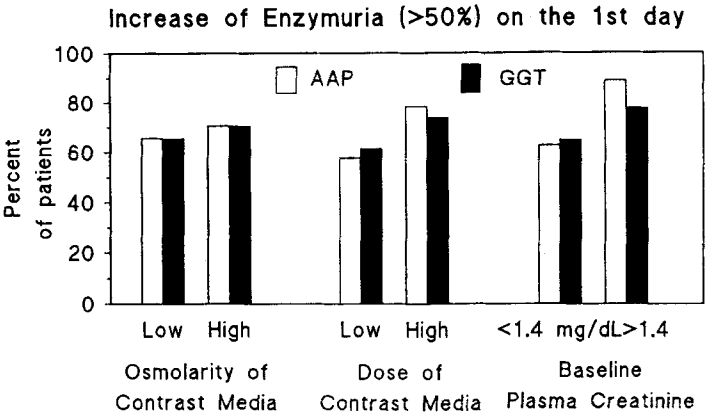

Figure 2. Effects of osmolarity dose of CM, and baseline renal function of the patients on the increase of enzymuria on the 1St day after CM (□ AAP, ■ *GGT*)..

day/basal values was 2.9 ± 2.6 SD for AAP and 2.6 ± 1.6 SD for GGT. AAP returned to baseline values on the 5th day, while GGT returned to baseline earlier, that is on the 3rd day after CM administration.

The behavior of urinary excretion of AAP and GGT in individual patients after the administration of CM was similar (Fig. 1 c). In fact, on the first day after CM administration, a relevant increase in enzyme activity (at least +50% over the basal value) was seen in the same number of patients (67%) for AAP and GGT. On the following days, in a lower number of patients, urinary enzyme activities remained elevated, especially AAP.

The concordance between GGT and AAP variations was tested on the first day after CM administration. GGT and AAP variations were considered concordant when both enzymes increased (at least +50% over the basal values) or when both remained unmodified. Both AAP and GGT increased in 28 patients and both enzymes remained unmodified in 11 patients. Therefore, the behavior of AAP and GGT was concordant in 39/49 patients ($p < 0.001$ Chi-square test).

The effect of different variables on the behavior of AAP and GGT was evaluated on the first day after administration (peak-time of tubular effects due to CM). At this time, osmolarity of CM, dose of CM, and baseline renal function of the patients had similar effects on the urinary activities of AAP and GGT (Fig. 2). In fact, AAP and GGT increased in a similar percentage of patients, without difference between those administered with low- or high-osmolar CM. Furthermore, both enzymes increased in a higher number of patients who were administered high doses of CM (> 0.9 g/kg BW) with respect to those who were administered low doses (< 0.9 g/kg BW). Finally, both enzymes, especially AAP, increased in more patients who had baseline renal impairment (plasma creatinine >1.4 mg/dL) than in those with normal plasma creatinine.

The repeatability of the determinations of AAP and GGT was evaluated on duplicate measures of the two enzymes, performed in the week preceding the administration of CM. The differences between the two repeated measurements were expressed as percent

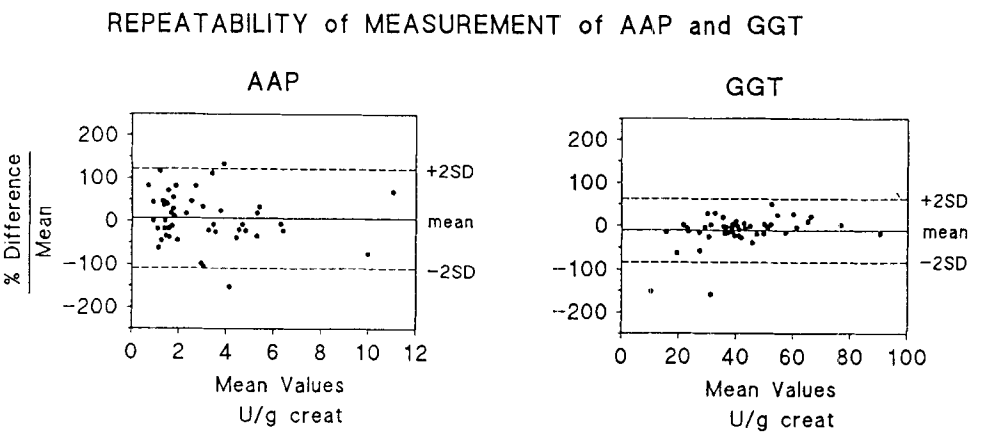

Figure 3. Responsibility of duplicate measurements of AAP and GGT. The solid lines represent the mean difference between the two measurements, which are expressed as percent of their mean value; the dashed lines are plus and minus 2 SD from the mean difference.

of their mean value (Fig. 3). The repeatability of GGT resulted better than that of AAP, as indicated by the lower standard deviation of the differences between the repeated measurements.

DISCUSSION

The results of this study confirm that the renal effects of CM are often not detected by means of conventional tests of renal function (12,13). On the contrary, urinary excretion of both brush border enzymes, AAP and GGT, appear to be very sensitive to CM. The close contact between tubular urine, containing filtered CM (18), and the brush border of the tubular cells, where AAP and GGT are located, may explain the high sensitivity of these enzymes to the administration of CM.

Some studies suggest that CM have a similar effect on urinary excretion of AAP and GGT (2,4,5,7,9,10), while others seem to indicate a greater effect on AAP (8). The results of our study indicate that the behavior of GGT is similar to that of AAP, in particular on the first day after the administration of CM. At this time, AAP and GGT increase to a similar extent (2.9 and 2.6 times the basal values), and in the same percentage of patients (67% of patients). All the examined variables (osmolarity and dose of CM, and baseline renal function of patients) affect urinary excretion of AAP and GGT in a similar manner.

Finally, it is important to note that the method for the determination of urinary activity of GGT has a better repeatability and is simpler than that of AAP.

In conclusion, the good concordance of the results of GGT with those of AAP justifies the use of GGT as a marker for tubular effects due to CM. Furthermore, the measurement of GGT has a better repeatability and is suitable for a wide clinical use thanks to the advantages of the automated determination.

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