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URINARY ENZYMES EXCRETION AFTER ACUTE ADMINISTRATION OF PARACETAMOL IN PATIENTS WITH KIDNEY DISEASE

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Summary. *The effect of paracetamol, commonly used as analgesic drug, upon excretion of some enzymes, markers of kidney damage, was investigated. Patients with Balkan endemic nephropathy and glomerulonephritis, having kidney vulnerable to toxic drugs, were enrolled in the study. Timed urine specimens were collected: before drug administration, and in 3h periods for 24 h after an oral dose of 2 g of paracetamol.*
Excretion of APN activity related to mmol creatinine before paracetamol treatment was significantly higher in patients with glomerulonephritis than in healthy persons from the city or village, and from BEN patients. Urinary excretion of DPP IV and GGT was significantly increased in patients with glomerulonephritis, BEN, and in clinically healthy inhabitants of the endemic villages compared to healthy adults from the city. After paracetamol administration urinary excretion of APN, DPP IV and GGT did not change significantly in any group studied.
This study has shown that urinary excretion of APN, DPP IV and GGT, as markers of kidney brush border damage, did not change after 2 g of paracetamol taken orally.

Key words: *Paracetamol, Balkan endemic nephropathy, glomerulonephritis, aminopeptidase N, dipeptidylpeptidase IV, γ-glutamyltranspeptidase*

Introduction

People taking analgesic drugs are at increased risk of end-stage renal disease (ESRD). In 1953 Spuler and Zollinger (1) have found that prolonged use of analgesic drugs could cause tubulointerstitial nephritis. Phenacetin was subsequently identified as the responsible agent, and was withdrawn from the marked. Paracetamol (acetaminophen) is the main metabolite of phenacetin. Three case control studies have found association between chronic paracetamol intake and ESRD (2-4).

Paracetamol is the most common drug overdose in the United States with 80,000 cases in 1992. In toxic doses, paracetamol can cause acute tubular necrosis and hepatic necrosis (5). Acute renal failure secondary to paracetamol poisoning occurs alone or in combination with hepatic necrosis. In humans the mechanisms of acute renal failure after toxic dose of paracetamol have not been well defined.

We have studied the possible nephrotoxic effect of a single oral dose of 2 g of paracetamol in patients with Balkan endemic nephropathy (BEN) and glomerulonephritis, as well as, in healthy controls. Kidney brush border enzymes were used as markers of nephrotoxicity.

Patients and methods

Patients

This study was performed on 12 patients with BEN, 8 patients with glomerulonephritis, 16 clinically healthy inhabitants of endemic settlements and 10 healthy volunteers from the city of Niš.

Serum creatinine was 168 ± 15 mmol in patients with BEN, and 174 ± 15 mmol in patients with primary glomerulonephritis. Glomerular filtration rate was reduced in both groups- to 55 ± 8.1 ml/min in BEN patients, and to 49 ± 7.9 ml/min in glomerulonephritis patients. Serum creatinine and glomerular filtration rate in healthy controls were in the limits of normal.

Patients and controls were not taking alcohol on a chronic basis, or drugs that stimulate P-450 microsomal oxidase enzymes (anticonvulsants).

Paracetamol administration

Timed urine specimens were collected: before drug administration, in the morning from 7-10 h (sample 0), paracetamol 2 g per os was taken, and the 3 h samples were collected, from 10-13 h (sample 1), 16-19 h (sample 2), and from 7-10 h on the next day (sample 3).

Methods

Urine was centrifuged for 15 min at 3000 rpm, and kept at +4^{o}C until analyzed. Urinary creatinine was determined by an autoanalyser procedure of Astra 4 (Beckman, USA). Enzyme activities of aminopeptidase N (APN), dipeptidylpeptidase IV (DPP IV), and γ-glutamyltranspeptidase (GGT) were determined by spectrophotometric methods using as substrates alanine p-nitroanilide, glycylprolin p-nitroanilide and γ-glutamyl-p-nitroanilide, respectively (6-8).

Statistical analysis

Mean values±SD, when appropriate, are given. Enzyme activities are expressed as medians with ranges in parenthesis. Statistical significance was estimated by Mann-Whitney U-test.

Results

Urinary excretion of enzymes before paracetamol ingestion is presented in table 1. In patients with primary glomerulonephritis, BEN, and in healthy inhabitants of endemic villages a significantly increased urinary excretion of DPP IV ($p<0.05$) and GGT ($p<0.01$) over the activity in city controls was observed.

Urinary excretion of APN in BEN patients was not different from the city and village controls. In patients with glomerulonephritis excretion of APN was significantly increased compared to the excretion in city and village controls ($p<0.05$), and to BEN patients ($p<0.01$).

Paracetamol treatment did not produced any significant increase of enzymes excretion in patients with BEN and glomerulonephritis, as well as, in city and village controls (Figs. 1-3). A small increase of DPP IV and GGT after paracetamol ingestion was observed in BEN patients, however, it did not reached the level of significance.

Discussion

Toxic effects of paracetamol on kidney and liver have not prevented its widespread use, even in children. Paracetamol was estimated safer than other analgesic drugs. Alternative analgesic drugs, such as salycilates and pyrazolones, probably induce fewer cases of ESRD, but these medications must be carefully evaluated for other risks (6).

Acute renal failure occurs in less than 2% of all paracetamol poisonings. Toxic effects of paracetamol at therapeutic dosages were observed in alcoholics, and patients who take drugs that stimulate P-450 microsomal oxidase enzymes.

The mechanisms of acute toxic effects to the human kidney have not been well defined. Studies of Mitchell et al. on Fischer rats has suggested that a renal toxic metabolite of paracetamol was formed by in situ metabolic activation (9). The kidney is thought to form a toxic metabolite only when it is glutathione depleted. These animal studies indicate that when the kidney is overwhelmed with paracetamol, its oxidation via the P-450 system results in tubular damage.

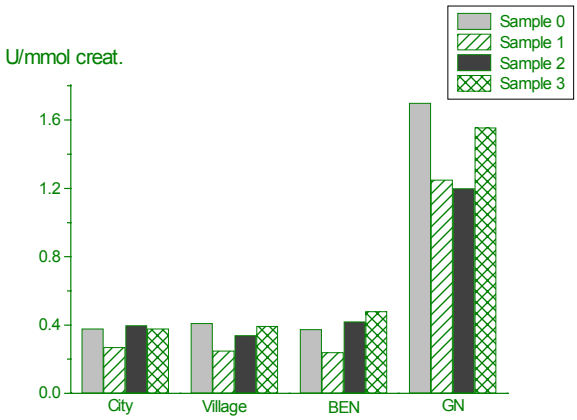

Fig. 1. Urinary excretion of APN after paracetamol administration.

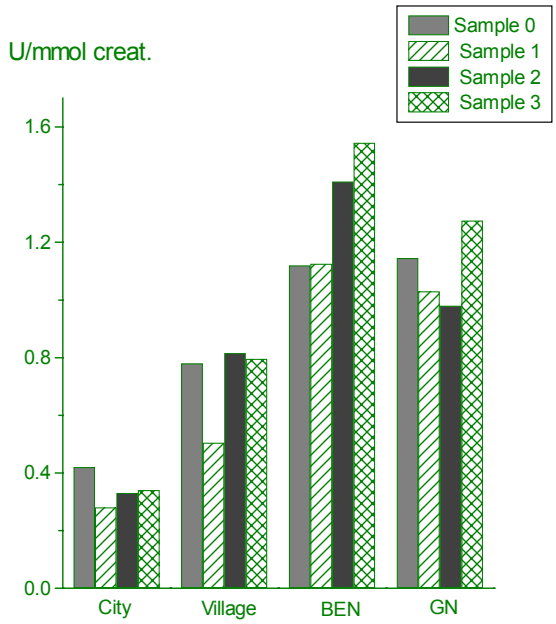

Fig. 2. Urinary excretion of DPP IV after paracetamol administration.

A single toxic dose of paracetamol that will result in adverse effects usually exceeds 15 g, although much less can be enough to poison some.

Chronic kidney disease predisposes to the toxic effects of paracetamol. Alcoholics have a predisposition to the toxic effects of paracetamol, and ingestion of 4 g only can result in toxicity (5).

This study has shown that paracetamol given in a dose of 2 g to the adult persons, and also to the patients with kidney disease does not produce kidney damage, as estimated by the urinary excretion of kidney brush

border enzymes.

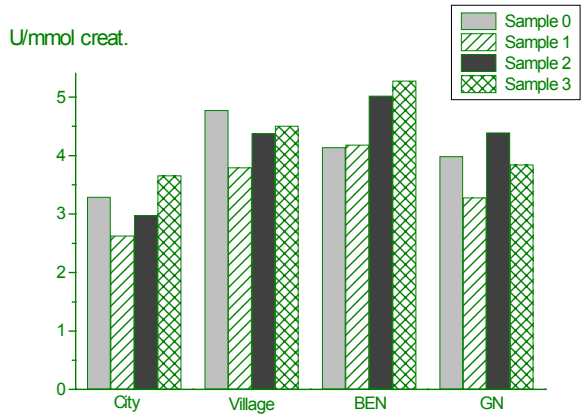

Fig. 3. Urinary excretion of GGT after paracetamol administration.

This study has also shown that the pattern of an increased excretion of kidney brush border enzymes in BEN and primary glomerulonephritis is different. In patients with glomerulonephritis urinary excretion of APN was significantly increased, however, in BEN patients it is not different from controls. Urinary excretion of the other two enzymes studied, DPP IV and GGT, was increased in both, BEN and primary glomerulonephritis.

Chronic paracetamol ingestion is associated with increased risk of ESRD (2-4). The study of Perneger et al. deserves a special attention due to the carefully selected control subjects from general population (4). Heavy average use of paracetamol (more than 1 pill per day) and medium-to-high cumulative paracetamol intake (more than 1000 pills in a life-time) each doubled the odds of ESRD. Perneger et al. calculate that reduced consumption of paracetamol could lower the incidence of ESRD by 8 to 10 percent. Although this percentage may be an overestimate, it does not seem unreasonable and worthy of an effort. However, in a recent editorial it was suggested that caution is needed in recommending restrictive measures, because such a recommendation might induce habitual paracetamol user to revert to other medications whose safety may also be questionable (10).

References

1. Spuler O, Zollinger HU. Die chronisch-interstitielle Nephritis. Z Klin Med 1953; 151: 1-50.
2. Pommer W, Bronder E, Greisser E, et al. Regular analgesic intake and the risk of end-stage renal failure. Am J Nephrol 1989; 9: 403-412.
3. Sandler DP, Smith JC, Weinberg CR, et al. Analgesic use and chronic renal disease. N Engl J Med 1989; 320: 1238-1243.
4. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflamatory drugs. N Engl J Med 1994; 331: 1675-1679.
5. Blackely P, McDonald BR. Acute renal failure due to acetaminophen ingestion: a case report and review of the literature. J Am Soc Nephrol 1995; 6: 48-53.
6. Diener U, Knoll E, Langer B, Rautenstrauch N, Ratge D, Wisser N. Urinary excretion of N-acetyl-b-D glucosaminidase and alanine aminopeptidase in patients receiving amikacin or cis-platinum. Clin Chim Acta 1981; 112: 149-157.
7. Wolf GB, Scherberich JE, Fischer P, Schoeppe W. Isolation and characterization of dipeptidyl aminopeptidase IV from human kidney cortex. Clin Chim Acta 1989; 179: 61-72.
8. Rosalki SB, Tarlow D. Optimized determination of gama-glutamyltransferase by reaction-rate analysis. Clin Chem 1974; 20: 1121-1124.
9. Mitchell JR, McMurtry RJ, Statham CM, Nelson SD. Molecular basis for several drug-induced nephropathies. Am J Med 1997; 62: 518-526.
10. Ronco PM, Flahault A. Drug-induced end stage renal disease.N Engl J Med 1994; 331: 1711-1712.

IZLUČIVANJE ENZIMA URINOM NAKON UZIMANJA PARACETAMOLA KOD OSOBA SA BUBREŽNOM BOLEŠĆU

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Kratak sadržaj*: Ispitivan je efekat paracetamola, leka koji se koristi kao analgetik, na izlučivanje nekih enzima, markera oštećenja bubrega. U ovoj studiji obradjeni su bolesnici sa Balkanskom endemskom nefropatijom i glomerulonefritisom čiji su bubrezi osetljivi na toksično dejstvo lekova. Sakupljani su sledeći uzorci urina: pre uzimanja leka, i u intervalima od 3 sata za period od 24 sata nakon oralnog uzimanja 2 grama paracetamola.*
Aktivnost APN u urinu po mmol kreatinina, pre tretiranja paracetamolom je značajno veća u bolesnika sa glomerulonefritisom nego u zdravih osoba iz grada i seoskog područja, kao i obolelih od BEN. Izlučivanje DPP IV i GGT urinom prema mmol kreatinina značajno je povećano u bolesnika sa glomerulonefritisom, BEN i u klinički

zdravih ispitanika iz endemskih sela u odnosu na zdrave osobe iz grada. Tretman paracetamolom ne daje nikakve značajne razlike u izlučivanju enzima APN, DPP IV i GGT kod ispitivanih grupa.
U ovoj studiji je ustanovljeno da nakon uzimanja 2 grama paracetamola ne dolazi do promena aktivnosti enzima APN, DPP IV i GGT, kao markera oštećenja četkastog pokrova bubrega.

Ključne reči: *Paracetamol, Balkanska endemska nefropatija, glomerulonefritis, aminopeptidaza N, dipeptidilpeptidaza IV, gama-glutamiltranspeptidaza*

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