

MONITORING RENAL TOXICITY OF CIS-PLATINUM BY URINARY ENZYMES

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Introduction

Cis-platinum (cis-diaminodichloro-platinum) is a potent anti-neoplastic drug which plays a considerable role in the treatment of ovarian, lung and testicular cancer and sarcomas. Major side effects on renal function, peripheral nerves and gastrointestinal tract limit its use [1]. Before the introduction of intensive pre- and post-treatment hydration with normal saline and osmotic diuresis with mannitol acute oligo-anuric renal failure occurred frequently. With the schedule of hydration and diuresis the frequency of acute renal failure is reduced but not completely eliminated [1-3]. Thus monitoring for renal toxicity is necessary, particularly because additional nephrotoxic drugs, such as aminoglycosides and non-steroidal anti-inflammatory drugs, are often urgently needed.

Patients and methods

Ten patients with different solid cancers entered our study. All had normal renal function (serum creatinine, creatinine clearance, BUN, protein excretion, urinary sediment) and normal urinary enzyme excretion. All patients received cis-platinum; additional drugs were vindesine in three of 10 patients, etoposide in three of 10 patients and ifosfamide in four of 10 patients. During five consecutive days 30mg cis-platinum (total dose 150mg) were given intravenously over 30 minutes. Hydration was maintained with 2000ml normal saline in two hours before and after administration of cis-platinum. One hundred millilitres of mannitol 20% and 20mg frusemide were given before cis-platinum in order to initiate diuresis.

Before, during the five days of treatment, and the four following days and on the fifteenth day after cis-platinum administration, urinary enzyme excretion, BUN, serum creatinine, creatinine clearance and protein excretion were analysed. Urine for enzyme and protein excretion was collected in a three hour morning period from 6 to 9am to avoid any influence of circadian variation

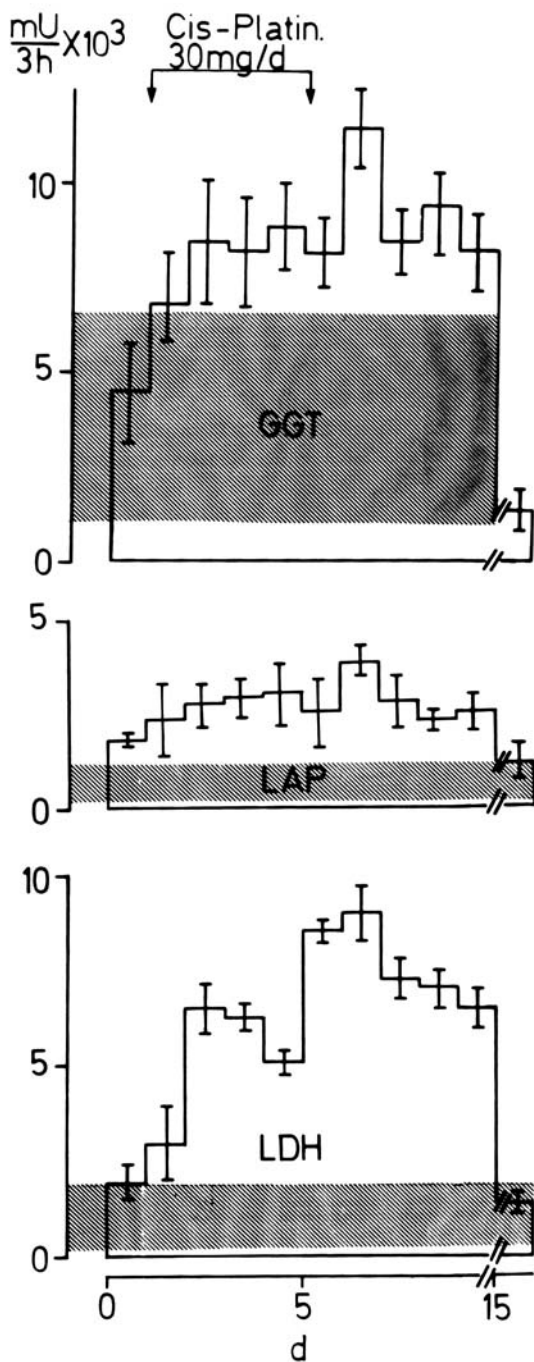


Figure 1. Urinary excretion of lactate dehydrogenase (LDH), leucine arylamidase (LAP) and gamma-glutamyl-transferase (GGT) in nine out of 10 patients receiving cis-platinum. Values expressed as mean \pm SD

on urinary enzyme excretion. Immediately after the collection periods the urine specimens were prepared by gel filtration on Sephadex G50 fine.

Lactate dehydrogenase (LDH), leucine arylamidase (LAP), gamma-glutamyl-transferase (γ GT), N-acetyl- β -glucosaminidase (NAG) and beta-galactosidase (GAL) were determined as described [4].

Protein was measured according to Patrick and Thiers [5]. Urinary enzyme output was calculated as mU/3hr, corrected for the average adult body surface of 1.73m², and protein excretion as mg/3hr, performing the same correction.

Results

None of the 10 patients had significant changes in BUN, serum creatinine, creatinine clearance; urinary sediment remained normal, proteinuria was not noted.

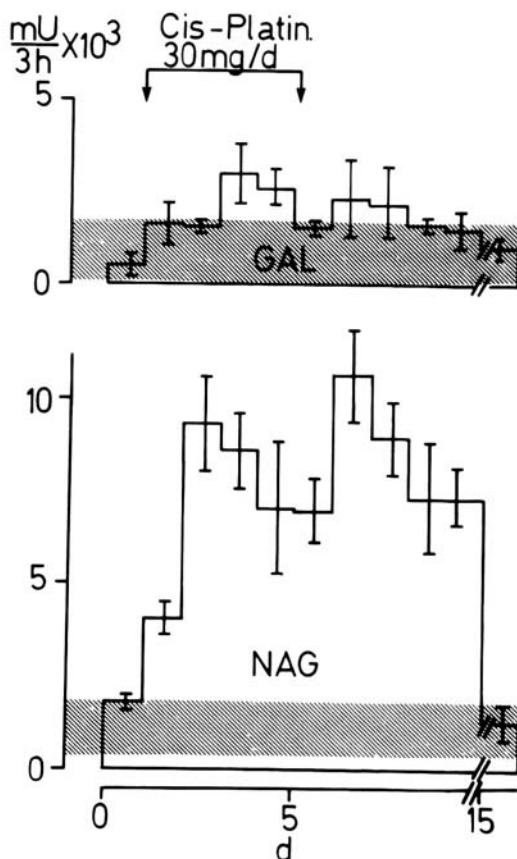


Figure 2. Urinary excretion of beta-galactosidase (GAL) and N-acetyl- β -glucosaminidase (NAG) in nine out of 10 patients receiving cis-platinum. Values expressed as mean \pm SD

All patients showed an increased urinary enzyme excretion of all five enzymes studied. LAP, LDH and γ GT are brush border enzymes of tubular epithelial cells. Urinary output of these three enzymes increased immediately after cis-platinum administration, remained elevated during the whole observation period until day nine, but had returned to normal on day 15 (Figure 1). Maximum levels were determined either on the sixth or seventh day.

Similar to the brush-border enzymes urinary excretion of the lysosomal enzymes NAG and GAL increased directly after cis-platinum and remained in the pathological range until the ninth day; normal values were reached on the fifteenth day (Figure 2).

Discussion

The nephrotoxic action of cis-platinum has been known for many years. Our results confirm the concept that sufficient hydration with normal saline and osmotic diuresis may prevent acute renal failure. However, our findings that nine of 10 patients develop substantially increased enzymuria in response to cis-platinum demonstrate that nephrotoxicity is not completely abolished.

The two-fold increase in γ GT excretion is probably due to tubular cell damage. The overall enzyme pattern suggests that mainly the proximal tubule is affected. However, disturbance of the distal tubule is not excluded by this data. This hypothesis of the local action of cis-platinum is supported by histological findings of cell necrosis in the proximal tubule induced by cis-platinum in animal models [2].

The chronological course of enzymuria demonstrates that the period of renal injury persists at least five days after termination of cis-platinum treatment, and that the damage seems to be reversible.

Our data indicate that monitoring of renal function in patients treated with cis-platinum may be warranted for at least two weeks. During this post-treatment period one should take care to maintain adequate hydration, sufficient sodium intake or saline infusion and avoid additional potential nephrotoxic agents.

References

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