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Urinary β2-microglobulin: early indicator of high dose cisdiamminedichloroplatinum nephrotoxicity? Influence of furosemide

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Summary. To evaluate the efficacy of β2-microglobulin as an indicator of cisplatinum nephrotoxicity, creatinine clearance and urinary β2-microglobulin were measured in 19 patients during 5 h after administration of a single dose of 80 mg/m^2 cisplatinum. Eleven patients received furosemide as a concomitant therapy. Serum creatinine and β2-microglobulin remained unchanged. A decrease of creatinine clearance was observed. Urinary β2-microglobulin increased between 1 and 3 h after administration. This suggests transient tubular damage immediately after the treatment course. The concomitant administration of furosemide does not modify these results. However, patients who developped long-term nephrotoxicity had no early rise of urinary β2-microglobulin excretion; thus, it is not possible to predict cumulative nephrotoxicity by measuring β2-microglobulin immediately after the first course of high-dose cisplatinum.

Introduction

Nephrotoxicity is the dose-limiting factor of cisplatinum therapy; however the mechanism of renal damage remains unclear. The toxicity may be mediated by effects of cisdiamminedichloroplatinum (CDDP) on renal perfusion, tubular function, or both [14]. There is not much information on the influence of interventions to prevent it [6]. It is advisable to induce diuresis by vigorous hydration [2], but the use of loop diuretics such as furosemide remains controversial [6]. Usually blood urea and/or creatinine are used to monitor the toxicity [11], but transient changes in renal function are not always reflected by serum creatinine values [16]. Previous reports have observed elevation of β2-microglobulin excretion several days after cisplatinum administration [8]; it is considered a valid and very sensitive test of the reabsorption capacity of the proximal tubules after some forms of cancer chemotherapy to reflect subclinical renal damage not shown by conventional laboratory tests [3, 4, 8]. Recently we described a reduction of creatinine clearance during the first hours after cisplatin administration [5]. The aim of the present study was to indicate whether patients receiving high-dose CDDP, with or without furosemide, presented early tubular damage exhibited by elevation of β2-microglobulin urinary excretion. If such is the case, this could predict the long-term toxicity of platinum derivatives. Moreover, we investigated the incidence of the diuretic concomitant therapy on nephrotoxicity.

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Material and methods

Nineteen hospitalized patients, with malignant diseases were included in the protocol. Selection conditions were Karnowski performance score >60% [9], normal blood urea and creatinine, hemoglobin >130 g.l^{-1}, white blood cell count >4.10^9·l^{-1}, platelets >180.10^9.l^{-1}. No patients had had prior CDDP treatment. None of them received other nephrotoxic agents such as aminosides. The drug dose was 80 mg/m^2 of body surface area. Six hours before drug administration, patients received 2000 ml 5% glucose. One hour before chemotherapy, 11 patients received intravenous furosemide (20 mg/m^2 body surface area) as in the study by Ostrow et al. [15]. A 20-min constant-rate intravenous infusion of CDDP was followed by a 4-h infusion of 1500 ml 5% glucose. Associated treatments were antiemetic and antispasmodic drugs. Blood samples were drawn and urine samples collected before the start of CDDP infusion, during infusion (10 min), at the end of infusion (20 min) and 30, 40, 60, 75, 105, 120, 150, 180, 210, 240, 270, and 300 min after starting infusion. Blood samples were centrifuged and the serum was removed and stored at −20 °C until creatinine and β2-microglobulin determination. Each urine sample was collected separately, the volume determined, and one aliquot made up to pH 8 with NaOH *N* for β2-microglobulin determination, another for creatinine analysis. Urine samples were stored at −20 °C until analysis. Then the following courses of cisplatinum were preceded by serum creatinine determinations. Administration was stopped if serum creatinine rose more than 40% above the reference value.

Biological analysis. Creatinine concentrations were determined by Jaffé's method with dialysis. β2-microglobulin determinations were effected by immunoenzymatic assay (Phadezym β2 microtest, Pharmacia Diagnostics, Uppsala, Sweden).

Data analysis. All computations were performed on a Tektronix 4050 desk-top computer using the TRIOMPHE software designed at the Département d'Informatique Médicale of the CHUR of Dijon. Blood and urine samples

having been simultanously collected, it was possible to determine renal clearance Cl_r of creatinine and β2-microglobulin for each interval (t, t') using the formula:

$$Cl_r = \frac{\Delta u}{\int_t^{t'} C(h)\, dh},$$

where C(h) is the creatinine or β2-microglobulin serum concentration at time h, Δu the amount of creatinine or β2-microglobulin excreted in urine from t to t' (h varying from t to t'). This allowed, for each patient the drawing of the curve of renal clearance of creatinine and β2-microglobulin vs time. Moreover we calculated the fractional excretion of β2-microglobulin (Cl_r β2-microglobulin/Cl_r-creatinine).

Statistical analysis was performed by two-way analysis of variance.

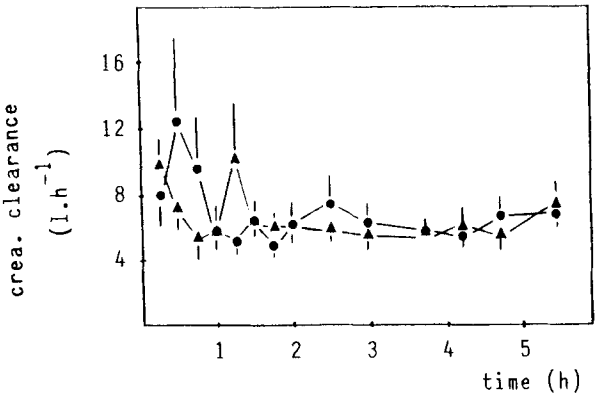

Fig. 1. Creatinine clearance vs time in patients without (▲) and with (●) concomitant furosemide therapy. Each point represents mean ± SE of six to eight determinations in the first group and six to 11 determinations in the second group

Results

Before each treatment patients had normal blood creatinine and β2-microglobulin, urinary β2-microglobulin ($< 400\ \mu g.l^{-1}$), and creatinine and β2-microglobulin clearances. None of them presented an increase of creatinine or β2-microglobulin concentration in serum during the study. The initial value of urinary β2-microglobulin concentration, the highest value of the urinary concentration, the time of the peak and the apparition of ultimate nephrotoxicity after further administrations of cisplatinum are indicated for each patient of both groups in Table 1. The median predose urinary β2-microglobulin is 0.11 g/mol creatinine (range 0.01–0.48) in the group without diuretic and 0.17 g/mol creatinine (range 0.02–1.45) in the second group. The median peak is 0.72 g/mol creatinine (range 0.02–3.01) in the group without furosemide and 0.21 g/mol creatinine (range 0.03–0.90) in the group with furosemide. The urinary β2-microglobulin concentration increases in 12 patients (seven without diuretic and five with furosemide). Most of them had a peak of excretion within 1–3 h after starting infusion. Nephrotoxicity, appearing after several administrations of the drug, was observed in three patients. This side effect did not appear among those who had an abnormal increase of urinary excretion of β2-microglobulin.

The mean creatinine clearance exhibits a decrease from the beginning of infusion ($10\ l.h^{-1}$) to 5 hours later ($7\ l.h^{-1}$) in the group without furosemide. This decrease seems less important than in the diuretic group but the difference between groups is not statistically significant (Fig. 1). In Fig. 2 the comparison of the evolution of the mean urinary β2-microglobulin concentration exhibits an increase between 1 and 3 h after starting infusion with no statistically significant difference between groups. Figure 3 shows the fractional excretion of β2-microglobulin vs time.

Table 1. Early β2-microglobulin urinary data and nephrotoxicity after several administrations of cisplatinum in patients without (group 1) and with (group 2) concomitant furosemide therapy

Group 1: without furosemide								
Patient	JAC	CHAT	DEL	LAR	CHA	BOT	BOU	MAS
Initial urinary β2-microglobulin (g/mol creatinine)	0.03	0.01	0.01	0.07	0.08	0.01	0.19	0.48
Highest urinary β2-microglobulin (g/mol creatinine)	3.01	0.04	0.05	1.39	0.11	0.02	0.69	0.48
Time of the peak (h)	1.5	1.5	5	3	2	2	1.5	/
Nephrotoxicity[a]	0	0	+	0	0	0	UK	+

Group 2: with furosemide											
Patient	MOT	GUN	NAU	PER	COR	BOU	BLE	DUM	GAU	GRA	DOU
Initial urinary β2-microglobulin (g/mol creatinine)	0.03	0.05	0.04	0.07	0.03	0.04	0.03	0.05	1.50	0.02	0.03
Highest urinary β2-microglobulin (g/mol creatinine)	0.3	0.05	0.6	0.07	0.03	0.04	0.03	0.05	0.9	0.06	0.18
Time of the peak (h)	5	/	1	/	/	/	/	/	2	0.25	3
Nephrotoxicity[a]	0	0	UK	0	0	+ + +	0	0	0	0	0

[a] Nephrotoxicity observed after several courses of the drug: UK, unknown; +, serum creatinine concentration > 0.15 mmol. l^{-1}; + + +, serum creatinine concentration > 0.70 mmol. l^{-1}

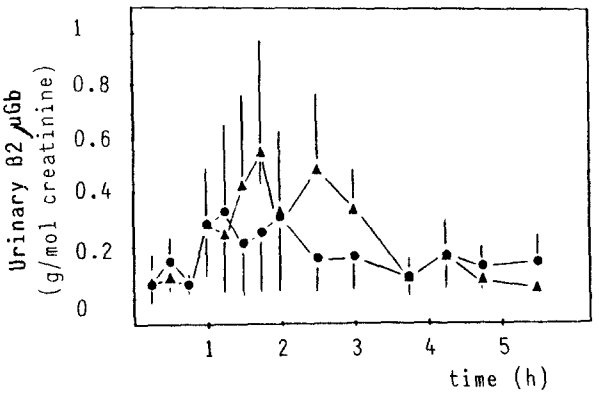

Fig. 2. Urinary β2-microglobulin concentration vs time in patients without (▲) and with (●) concomitant furosemide therapy. Each point represents mean ± SE of six to eight determinations in the first group and seven to 11 determinations in the second group

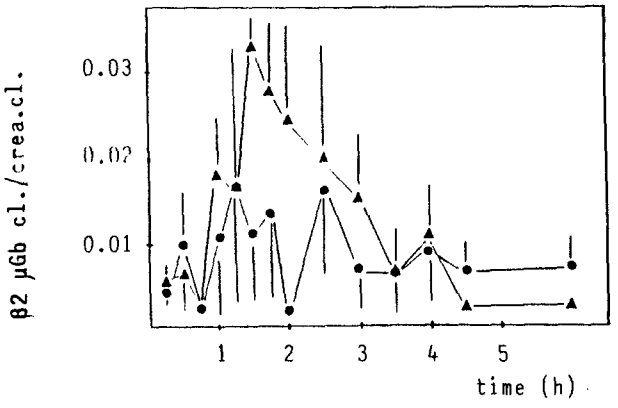

Fig. 3. Fractional excretion of β2-microglobulin vs time in patients without (▲) and with (●) concomitant furosemide therapy. Each point represents mean ± SE of five to eight determinations in the first group and six to 11 determinations in the second group

Despite a higher value in the group without diuretic from 1.5 to 2 h (0.033 vs 0.015 at 1.5 h no significant difference is observed, whether during the first 5 h or during the period 1–3 h after infusion. Moreover, we observed no correlation between the rise of β2-microglobulin excretion and fractional clearance in individual patients.

Discussion

The pathological changes in nephrotoxicity consecutive to platinum administration consist essentially in tubular disease [7, 8]. Thus, β2-microglobulin, which is filtered by the glomerulus and reabsorbed in the proximal tubule, may be used as a good indicator of acute tubular injury and predictor of further renal insufficiency [3]. We chose to study concentrations of urinary β2-microglobulin correlated to urinary creatinine in order to avoid disturbances consectuive to variation of urinary flow [18]. Among the 12 patients who presented an increase of urinary β2-microglobulin, 10 had an elevation of the excretion from 1 to 3 h after administration. This corresponds to the peak of urinary concentration of cisplatinum as shown in a previous report [5]. In a study on administration of low doses of cisplatinum (20 mg/m^2 for 5 consecutive days), Sorensen et al. [17] reported a similar elevation of urinary β2-microglobulin on the 2nd and 3rd days of treatment. Similarly we found no modification of serum β2-microglobulin. The elevation of urinary β2-microglobulin concentrations cannot be the consequence either of a rise of β2-microglobulin production or of tumor destruction (none of our patients had cancer pathology known to raise β2-microglobulin [4]. The study of the fractional excretion of β2-microglobulin (β2-microglobulin clearance/creatinine clearance) exhibits an elevation of 700% and 150% in the first and the second group respectively 1.5 h after administration of cisplatinum. This is probably the consequence not of glomerular lesions, but of tubular injury. These findings are to be compared to the acute renal failure observed with administration of metals, such as mercury, where the lesions occur immediately after administration [10]. The absence of correlation between creatinine clearance and β2-microglobulin excretion may be explained by a delay of the maximum intensity of both phenomena. The fall of creatinine clearance could be the consequence of vascular changes, as described in a previous report [14], this possibly causing tubular dysfunction by alteration of platinum transports.

Despite a smaller increase of urinary β2-microglobulin excretion in patients with furosemide we observed no statistically significant difference between groups. In fact, the effect of furosemide in preventing nephrotoxicity is controversial. Kidney disease is supposed to be the consequence of high intratubular concentrations of cisplatinum [13], so furosemide could protect the kidney by diluting platinum in tubules [16]. According to other studies, furosemide may potentiate platinum nephrotoxicity [12]; this could be analogous to its potentiation of aminoside nephrotoxicity [1]. However, if we study the evolution of renal function in each patient we can see that the patients who present tubular impairments exhibited by alteration of β2-microglobulin excretion are not those who develop a nephrotoxicity with elevation of serum creatinine after several administrations of cisplatinum.

In conclusion, cisplatinum treatment seems responsible for early tubular damage, but our study showed no relation between acute and chronic toxicity. The comparison of toxicity of platinum with and without furosemide has not demonstrated any significant potentiation or diminution of the acute tubular injury or further nephrotoxicity by the diuretic agent.

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