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Review

Cisplatin nephrotoxicity

A review

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Introduction

The introduction of platinum compounds as antitumor agents has revived the significant clinical problem of nephrotoxicity caused by heavy metals. Cisplatin-induced nephrotoxicity has been shown to be dose-related in both animals and humans [57]; proximal renal tubular necrosis has been demonstrated in most animal species [72]. The major damage in humans has been observed in more distal parts of the proximal tubule or in the distal nephron segments [33]. Prolonged weekly injections in rats cause tubular atrophy of cortical nephrons, cystic dilatation of inner cortical or medullary tubules, and chronic renal failure due to tubulointerstitial nephritis [92]. Dobyan et al. [25] have located the lesion in the rat to the S_3 segment of the proximal tubule in the outer stribe of the medulla. In rats, renal failure may be nonoliguric due to a renal concentrating defect [74]; the inhibition of vasopressin synthesis or release has also been proposed [12].

In early clinical trials with cisplatin, serious toxicity was encountered, mainly severe nausea, vomiting, neurotoxicity, ototoxicity and nephrotoxicity. Initial experience revealed that approximately 25% of the patients who received a single dose of cisplatin suffered reversible azotemia for 1–2 weeks following treatment [49]. Irreversible renal failure requiring dialysis has also been experienced, especially with large doses or multiple courses of treatment [39]. Single courses of 2 mg/kg or 75 mg/m^2 cisplatin are associated with nephrotoxicity in one-third of the patients treated [49].

The cellular mechanism of platinum nephrotoxicity is unknown. Levi et al. [54] have reported a decrease in protein-bound sulfhydryl groups in the renal tissue in rats prior to the development of frank renal failure. In vitro studies showed no direct interaction of platinum with sulfhydryl groups of cysteine or renal homogenates. The decrease in sulfhydryl groups was similar in magnitude in the outer medulla and cortex, whereas platinum concentrations were higher in the medulla. Cysteamine, penicillamine and *N*-acetylcystein offered no protection against experimental platinum nephrotoxicity [83].

There is evidence that the therapeutic efficacy of cisplatin increases with increasing dose [14, 38, 50, 66]. Higher doses of cisplatin also increase the vulnerability of the kidney as the primary excretory organ for platinum. This problem is especially important in patients with germ-cell tumors, because this group consists of young patients with a high cure rate and normal renal function prior to treatment.

To reduce cisplatin-induced nephrotoxicity, an insight into the pathophysiological mechanism is of great importance. The main purpose of the present review was to summarize current knowledge about these mechanisms and discuss proper means of assessment of kidney function during treatment with cisplatin.

Pathophysiology

In most forms of acute renal failure (ARF), both vascular and tubular factors contribute to the pathogenesis. Until recently the vascular component was regarded as being more important during the initiation phase of ARF, with the tubular component contributing primarily to its maintenance. In accordance with this, Offerman et al. [64] reported that effective renal plasma flow was reduced prior to change in glomerular filtration rate (GFR) in patients treated with cisplatin. These authors suggested that altered renal hemodynamics play an important role in cisplatin-induced nephrotoxicity; however they estimated renal plasma flow based on the clearance of iodohippuric acid.

Data reported by Miura et al. [63] and results obtained in the dog (Daugaard and Abildgaard, unpublished data) indicate that the renal clearance and perfusate disappearance of *p*-amminohippuric acid is markedly depressed by cisplatin, suggesting impaired proximal tubular transport of organic ions. Moreover, in a study by Groth et al. [36], acute inhibition of the active tubular transport of ^{125}I-orthoiodohippurate was observed after cisplatin administration, without acute changes in GFR. In the study by Miura et al. [63], glomerular and tubular functions were concomitantly impaired following perfusion with cisplatin, making it difficult to identify either the glomerulus or the proximal tubule as the primary target of cisplatin.

Recent studies have made it clear that cisplatin-induced nephrotoxicity is not initiated by hemodynamic changes [15, 16]. Just after the administration of cisplatin, renal blood flow (RBF, measured by electromagnetic flowmeter) and the GFR did not change significantly (Fig. 1); however, the lithium clearance method [86] showed that fluid delivery out of the proximal, straight segment of the nephron increased significantly (Fig. 1) [16, 19]. These ob-

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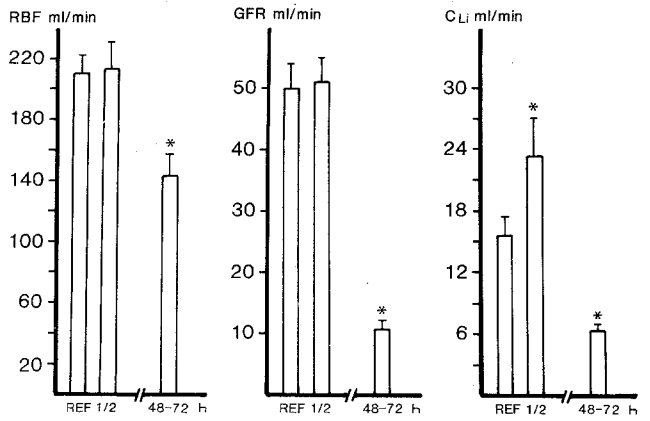

Fig. 1. Changes in renal blood flow (*RBF*), *glomerular filtration rate* (*GFR*) and lithium clearance (C_{Li}) immediately and 48–72 h after the i.v. administration of 5 mg/kg cisplatin in dogs. * $P < 0.05$ compared with reference (*REF*) value

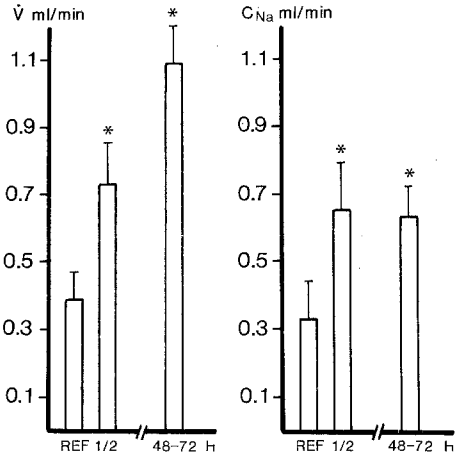

Fig. 3. Changes in urinary flow (*V*) *and sodium clearance* (C_{Na}) with time after cisplatin administration. * $P < 0.05$ compared with reference (*REF*) value

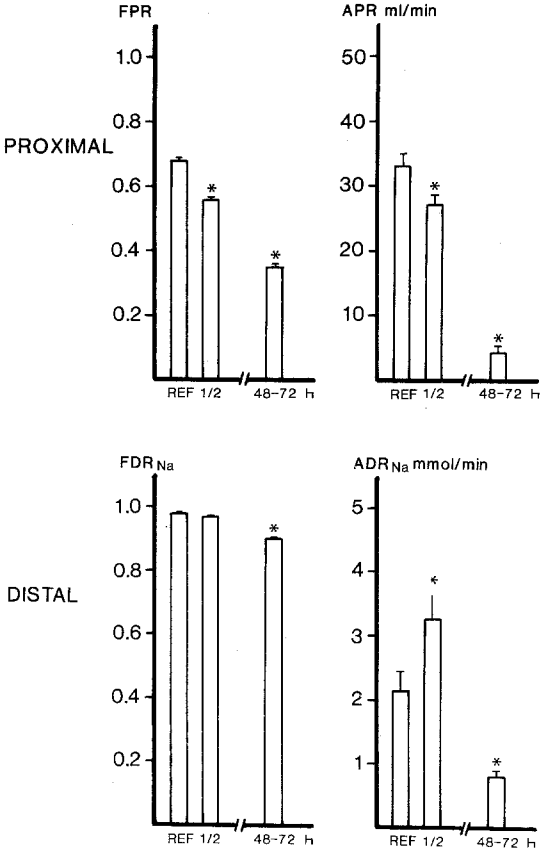

Fig. 2. Changes in proximal and distal reabsorption rates with time after the i.v. administration of 5 mg/kg cisplatin in dogs. Reference value (*REF*) and 0.5-h (*1/2*) value from Daugaard et al. [16]; value for 48–72 h from Daugaard et al. [17]. *FPR* and *APR*, fractional and absolute proximal reabsorption rates of sodium and water; FDR_{Na} and ADR_{Na}, fractional and absolute distal reabsorption rates of sodium. * $P < 0.05$ compared with *REF*

servations suggest that cisplatin-induced nephrotoxicity is initiated by a proximal tubular impairment [16, 19]. The increase in fluid delivery from the proximal tubules to the thin, descending limb of Henle's loop resulted in a rise in sodium and water reabsorption at nephron sites beyond the proximal tubules (Fig. 2). This finding is consistent with the data on rats reported by Schnermann [80], suggesting that an increase in proximal fluid delivery was accompanied by an increase in sodium reabsorption in more distal segments of the nephron.

In dogs, the rise in reabsorption rates in the distal nephron segments did not completely counteract the increase in delivery from the proximal tubules, and this may account for the observed changes in sodium and water excretion (Fig. 3). These observations are in agreement with findings in the rat [19]. At 2–3 days after cisplatin administration in dogs, RBF was reduced by 33% and GFR by 78% [17] (Fig. 1). Since the lithium clearance (C_{Li}) only decreased by 38%, absolute and fractional proximal reabsorption rates were further reduced (Fig. 2). The severe reduction seen in GFR, together with only a moderate reduction in C_{Li}, strongly suggests that either the filtration pressure or the filtration coefficient (K_f) was reduced. The present data cannot distinguish between these two possibilities, but the concomitant decrease in RBF speaks in favour of the former.

A decrease in RBF due to increased vascular resistance has also been observed in the rat [93]. The decreased rate of fluid flow from the end of the proximal, straight segment into the thin, descending limb of Henle's loop (C_{Li}) was associated with a marked fall in not only absolute but also fractional sodium and water reabsorption rates in more distal nephron segments, leading to increased urinary flow and sodium excretion (Figs. 2, 3). These findings indicate that cisplatin also induces a late distal tubular impairment. The histological changes in the dog kidney 48–72 h after the administration of cisplatin [17] were fairly similar to those observed in the human kidney, with patchy necrosis in proximal and distal tubules [33].

In contrast to the results obtained in dogs, Safirstein et al. [74] observed no changes in urinary flow or osmolality or in sodium or potassium excretion in rats until 3 days after intraperitoneal cisplatin administration. When renal failure had become manifest (≥3 days), proximal fractional reabsorption was normal in the rats [74]. The discrepancy between these results is most likely due to differences in the route of administration or the choice of anaesthetics. The thiobarbiturate inactin, used in the rat stud-

ies by Safirstein et al. [74, 93], has been shown to inhibit proximal fractional and absolute reabsorption to the same extent as cisplatin in our study [27, 42]. Thus, the inhibitory effect of inactin may have attenuated the initial effect of cisplatin.

Four main pathophysiological mechanisms have been proposed to explain the decrease in GFR noted with nephrotoxic and ischemic ARF: hemodynamic alterations, alterations in glomerular capillary permeability, tubular obstruction and tubular back-leak. The influence of the first two mechanisms on cisplatin-induced nephrotoxicity has been outlined above. At present there is no evidence that tubular obstruction should play a primary role in cisplatin-induced ARF [17, 19, 93]. The increase in intratubular pressure observed in rats shortly after cisplatin administration can readily be explained by the depression of salt and water reabsorption in the proximal tubules [19].

Tubular fluid back-leak has also been mentioned in connection with the decrease in GFR observed after cisplatin administration. Chopra et al. [11] found a 38% reduction in superficial nephron GFR with no evidence of tubular fluid back-leak before the puncture site; however, the overall kidney GFR was depressed by 88%, suggesting a more severely reduced GFR in deep nephrons – perhaps together with a tubular fluid back-lead in more distal nephron segments. These observations were made in rats after the administration of 10 mg/kg cisplatin, which resulted in severe necrosis of the S_3 segment of the proximal tubule. In dogs, only single-cell necrosis was observed after the administration of 5 mg/kg cisplatin, but in this model a severe decrease in GFR was also observed [17].

Neither the angiotensin I-converting enzyme inhibitor captopril nor the calcium channel blocker verapamil has reversed cisplatin-induced ARF [76]. Moreover, these studies suggest that the renin-angiotensin system does not play a significant role in cisplatin-induced reduction in GFR. It seems unlikely that cisplatin-induced vasoconstriction in the kidney is initiated by increased activity of the renal sympathetic nerve, since α-adrenoreceptor blockade does not change the renal vascular conductance (Daugaard and Abildgaard, unpublished data).

Cellular toxicity

Although the cellular abnormalities occuring during ischemic or nephrotoxic ARF have been investigated for many years, progress in understanding the pathogenesis of cell injury in ARF has been complicated by the morphological heterogeneity of the kidney and by the different susceptibilities of the various nephron segments to injury.

One current theory to explain cisplatin nephrotoxicity has invoked an interaction between cisplatin and Na^+/K^+-ATPase enzymes. In a rabbit renal cortical slice model, Phelps et al. [72] observed a rapid decline in both ATP and K^+, which could support this hypothesis. Another theory involves the uncoupling of oxidative phosphorylation in the mitochondria [2]; the data of Phelps et al. [72] support this hypothesis. An initial effect of mitochondrial uncoupling would lead to a decrease in ATP production such as that seen by Phelps et al. [72]. Since ATP production is necessary for the activity of Na^+/K^+-ATPase, the flux of Na^+ and K^+ ions would be disrupted, thereby explaining the decline of intracellular K^+.

On the other hand, Safirstein et al. [75] found that when isolated tubule suspensions were used, neither membrane-associated Na^+/K^+-ATPase nor the mitochondria seemed to be important, early pathogenetic targets for cisplatin. Likewise, Uozumi and Litterst [87] found that the inhibition of ATPase activity is unlikely to be the course of nephrotoxicity, although cisplatin can affect ATPase activity [87]. Studies relating DNA turnover in renal tissue to cisplatin nephrotoxicity are being evaluated [76], but further investigations are needed before any conclusions can be drawn.

Methods for measuring cisplatin-induced nephrotoxicity

S-creatinine and creatinine clearance

In >90% of the clinical studies concerning cisplatin-induced nephrotoxicity, plasma creatinine and/or creatinine clearance has been used as the only measure of GFR. This fact may contribute to the discrepancies in the severity of cisplatin-induced nephrotoxicity reported in the literature.

Several studies have reported no changes in serum creatinine or creatinine clearance, despite the administration of high-dose cisplatin [9, 53, 65]. In contrast, a significant decrease in GFR has consistently been observed in studies using ^{51}Cr-EDTA clearance [20, 29, 36]. Therefore, the correlation between the decrease in GFR as measured by ^{51}Cr-EDTA clearance and the changes in serum creatinine values during treatment with cisplatin was investigated in a recent study [20]. No correlation was found during treatment. At 3 months after the termination of treatment a significant increase in serum creatinine was observed, but without a concomitant decrease in GFR.

There are several explanations for this discrepancy. It is known that in patients with moderate to severe malnutrition, plasma levels of creatinine and urea nitrogen tend to be low, despite a substantial reduction in GFR, due to decreased production [48]. Furthermore, in patients with muscular atrophy serum creatinine has been shown not to be a good indicator of GFR [26]. Both of these problems are relevant to patients who receive cisplatin. It has also been shown that individuals with particularly low-normal serum levels of creatinine may display a significant reduction in GFR before the upper-normal level is reached and that creatinine is likely to be the least reliable measure of GFR during early impairment of renal function [41].

A comparison between ^{51}Cr-EDTA clearance and creatinine clearance in patients treated with high-dose cisplatin [20] showed a good correlation between these measurements before and during the first treatment cycle, whereas no correlation was observed during the second and third cycles. A good correlation was observed 3 months after the termination of treatment.

Thus, serum creatinine and creatinine clearance have very limited value as an investigative tool in the above-mentioned clinical situations as well as in other groups of patients [67]. Several studies [67, 81] have shown that even in "steady-state" situations, the sensitivity of changes in serum creatinine or creatinine clearance is very low, especially in the range of moderately reduced GFR (40–80 ml/min * 1.73 m^2). Excellent agreement between the clearances of ^{51}Cr-EDTA and inulin has been observed throughout the whole range of GFR in several studies [28,

Table 1. Urinary excretion of enzymes and protein during and after cisplatin treatment

Patients (*n*)	Cisplatin dose (mg/m²)	NAG	AAP	LAP	Total protein	β-2-m	Albumin	Comments	Reference
10	100	+	+		+				[35]
3	50 × 4 days	+	+		+				[35]
23	20 × 5 days	Slight	Slight						[24]
12	90	+	+		+				[34]
12	120	+		+		+		Elevation after 6 weeks	[47]
22	100	+	+			−			[9]
6	20 × 5 days			+	+	+		No elevation after 8 weeks	[37]
19	80					+			[22]
18	20 × 5 days					+	−		[84]
35	27 – 145 mg				−	+			[13]
22	20 – 5 days					−			[29]
15	20 × 5 days				−			Measured 6 – 24 months after treatment	[23]
24	20 × 5 days					−			[62]

AAP, alanine aminopeptidase; LAP, leucine aminopeptidase; NAG, *N*-acetyl-β-D-glucosaminidase; β-2-m, β-2-microglobulin; +, increased values; −, no elevation

31, 52]. Therefore, future studies on cisplatin-induced nephrotoxicity should not use serum creatinine or creatinine clearance as a measure of kidney function.

Excretion of enzymes and proteins

Several different methods have been used to evaluate tubular function in patients undergoing treatment with cisplatin. Proximal tubular function has been evaluated by the excretion rate of small proteins such as β-2-microglobulin (β-2-m) and of amino acids. These are normally filtered freely across the glomerular membrane and nearly completely reabsorbed by the proximal tubule [6, 9, 47]. In addition, the excretion rates of enzymes preferentially located in the proximal tubular cells, such as alanine aminopeptidase (AAP), leucine aminopeptidase (LAP) or *N*-acetyl-β-D-glucosaminidase (NAG), have been used as markers of damage to the tubular cells [9, 47].

Urinary excretion of β-2-m has been found to increase during and after cisplatin treatment in some studies and to remain unchanged in others (Table 1), with no clear correlation to the dose delivered. Urinary excretion of enzymes (AAP, LAP, NAG) has consistently increased in patients receiving higher doses of cisplatin (Table 1). After patients were given 40 mg/m² cisplatin daily for 5 days, we measured the urinary excretion rates of β-2-m, amino acids and NAG. A significant increase was observed in β-2-m and NAG during the 5 days of cisplatin infusion [21]. Both values returned to pretreatment levels before the next cycle was started 3 weeks later. As observed by Sørensen et al. [84], β-2-m could not be used as an indicator of persistent tubular damage measured 3 and 6 months after the termination of treatment; neither could NAG. In contrast to the normalization of β-2-m and NAG excretion rates, proximal and distal tubular reabsorption rates of sodium and water were still significantly depressed 6 months after the end of treatment [21].

Amino acid excretion gradually increased during the treatment period. Increased urinary levels of amino acids have been observed as early as 4.5 h after cisplatin administration in rats [55]. Foulkes and Blanck [30] observed that both maximal tubular capacities and the affinity constant for amino acid reabsorption decreased in rabbits after pretreatment with heavy metals.

Proteinuria has seldom been observed in human studies when smaller doses have been given. All patients treated with 40 mg/m² cisplatin daily for 5 days developed some degree of proteinuria [20]. Peterson et al. [69] have shown that quantitative determinations of urinary β-2-m and urinary albumin may be useful in detecting disorders of the renal handling of plasma proteins [69]. We observed an increase in urinary excretion of β-2-m during cisplatin treatment, whereas that of albumin and IgG increased 3 – 4 days after the last infusion (days 8 – 10) [20]. Peterson et al. [69] observed a high β-2-m/albumin clearance ratio in tubular proteinuria, an intermediate ratio in normal subjects and a low one in glomerular proteinuria. Our data suggest that proteinuria secondary to cisplatin infusion is primarily of tubular origin, whereas that observed between infusions is mainly of glomerular origin. The latter observation is further supported by a simultaneous increase in IgG excretion [70] and the IgG/albumin clearance ratio. A similar mixed type of proteinuria has been reported after prolonged exposure to cadmium [4].

Proteinuria can result from increased permeability of the glomerulus due to either an enlargement of pores or a loss of the negative, fixed charges of the glomerular capillary walls. Restriction by negatively charged glomerular capillary components seems to be important for the reduction in filtration of polyanions such as albumin [7, 8]. Another explanation for increased excretion of high-molecular-weight proteins is incomplete reabsorption by the proximal tubules. A third possible mechanism, which mainly applies to IgG, is release into the urine of proteins synthesized by the kidney [73]; however, the clearance of IgG correlated well with the total protein excretion rate, as did the clearance of albumin. As albumin is not synthesized by the kidney, a similar mechanism is presumably responsible for the increased excretion of IgG and albumin.

Electrolyte disturbances associated with cisplatin treatment

The effect of cisplatin on sodium excretion

Both proximal and distal sodium reabsorption rates are affected by cisplatin administration [16, 17]. In human studies, renal sodium loss has been shown to be dose-dependent and has only been observed in patients treated with high-dose cisplatin (i.e., 40 mg/m^2), in whom the increase in sodium clearance persisted for at least 6 months after the termination of treatment [21]. In the literature, severe hyponatremia secondary to renal tubular sodium wasting has been reported in only one case in association with cisplatin therapy [51].

The effect of cisplatin on potassium excretion

An increase in potassium clearance has been observed both shortly and 48–72 h after the administration of cisplatin to dogs [16, 17]. A tendency towards increasing potassium clearance has likewise been observed in patients [21]. A probable explanation for this observation would be that the decrease in proximal reabsorption causes increased delivery of sodium and water to the more distal segments of the nephron, resulting in a sodium-load-dependent potassium secretion [32].

Hypokalemia has been reported in some cases during cisplatin treatment [40, 79]. In patients treated with high-dose cisplatin [21], a significant decrease in P-potassium was observed during each treatment cycle. This could be due to renal potassium loss, but magnesium deficiency (see below) can also conceivably contribute to a decreased level of P-potassium [82]. In addition, the vomiting induced by cisplatin contributes to hypokalemia.

The effect of cisplatin on magnesium excretion

Hypomagnesemia is a common complication of cisplatin administration in humans [78, 79], and persistent, increased excretion of magnesium in the presence of severe hypomagnesemia suggests that the hypomagnesemia is due to a defect in renal magnesium reabsorption [78]. Recent studies in a rat model suggest that abnormal magnesium excretion might be due to a defect in magnesium transport in juxtamedullary nephrons or collection ducts [60].

In normal humans only 25% of the filtered magnesium is reabsorbed in the proximal tubule, whereas 50%–60% is reabsorbed in the thick, ascending limb of the loop of Henle. In a study by Vogelzang et al. [91], 87% of 30 patients became hypomagnesemic during treatment with 4–6 cycles of cisplatin (20 mg/m^2 for 5 days), vinblastine and bleomycin. The decrease in s-magnesium was sequential, but no acute clinical effects were observed. Similar results were obtained in a study by Buckley et al. [10]. Bell et al. [3] observed clinical symptoms in 10% of subjects tested, and all patients were still hypomagnesemic 3 months after commencing treatment. Most of them showed inappropriately high urinary magnesium excretion. Moreover, Stewart et al. [85] found 5.8% of their patients to be hypocalcemic.

In patients treated with high-dose cisplatin, a significant increase in magnesium clearance together with a significant decrease in plasma magnesium levels was observed [21]. It is likely that cisplatin alters magnesium transport in the ascending limb of Henle's loop as part of the observed distal tubular impairment [17, 21]. By decreasing proximal reabsorption of magnesium [59], saline infusion could also contribute to the decrease in plasma magnesium, as could the use of mannitol, which increases magnesium excretion to 40%–50% of that filtered [94].

Schilsky et al. [79] observed persistent hypomagnesemia following cisplatin-based chemotherapy for testicular cancer: 38% of their patients remained hypomagnesemic for as long as 3 years following the discontinuation of cisplatin treatment. In contrast, we observed a normalization of plasma magnesium levels within 6 months after treatment [21].

Intervention

Infusion of mannitol and saline or furosemide is the clinical intervention most commonly used to prevent cisplatin-induced nephrotoxicity. The exact mechanism by which mannitol- or saline/furosemide-induced diuresis reduces the nephrotoxicity of cisplatin is unknown, but reduction of the time during which the drug and renal tubule are in contact has been implicated as one possible contributing factor. In a recent study carried out in rats [19] saline loading (2% of body weight) apparently either resulted in a less severe inhibition of the absolute, proximal reabsorption rate in the deep as opposed to superficial nephrons or caused a less severe depression of the rate of reabsorption in the straight vs convoluted segment.

A previous study in mice [56] suggests that cisplatin nephrotoxicity is affected by the drug vehicle. An LD_{100} dose of cisplatin in distilled water did not produce any toxic deaths when given in 4% saline. This approach was clinically introduced by Ozols et al. [65], who concluded that when 3% saline was used as a vehicle for cisplatin, no renal toxicity was observed as measured by serum creatinine and creatinine clearance in patients treated with high-dose cisplatin.

When ^{51}Cr-EDTA was used as a measure of GFR, a significant decrease in the latter was observed despite the use of 3% saline [20]. Thus, only a partial protection of the kidney is observed after saline loading. This finding is in agreement with several reports, which have indicated that cisplatin and/or its metabolites may be transported across the basolateral membrane by either an organic anion [75] or a cation [5] transporter. Data reported by Miura et al. [63] showed that organic ion transport was markedly inhibited in not only filtering but also non-filtering kidneys, where access to cisplatin was limited to the basolateral site, thereby indicating that filtration of cisplatin is not a prerequisite for induction of renal damage. This was confirmed in a recent study in rats [89].

The exact mechanism by which mannitol-induced diuresis reduces cisplatin nephrotoxicity is also unknown. Pera et al. [68] investigated the effect of mannitol and furosemide on cisplatin nephrotoxicity. Histological evaluation of rat kidneys indicated that an approximately equivalent degree of proximal tubular necrosis occurred in rodents after the administration of cisplatin alone or with either furosemide or mannitol 1–4 days after drug administration. Thereafter, a trend developed toward less persistent damage in the mannitol groups and progression of tubular injury in the furosemide-treated rats as compared with that seen in rodents treated with cisplatin alone (5–10 days after durg administration). The partial renal protection offered by these diuretics was not attributable to increased urinary excretion, faster plasma clearance or de-

creased renal levels of platinum. Furosemide given at high doses has been demonstrated to result in proximal tubular necrosis [61]. No studies have proven that there is an advantage to the use of furosemide; thus, as yet there is no reason to use this diuretic for the prevention of cisplatin-induced nephrotoxicity.

Since Howell and Taetle [43] and Ishizawa et al. [45] reported that the toxicity of cisplatin could be reduced by sodium thiosulfate (STS), there have been several studies concerning the effect of the latter on cisplatin nephrotoxicity [1, 44, 46]. The mechanism by which STS attenuates the renal toxicity of cisplatin is not yet fully understood. In vitro studies have shown that cellular uptake of platinum was reduced by 60% following STS exposure [90]. This finding suggests that in animals treated with both STS and cisplatin, the concentration of platinum in renal cells or cellular organelles might be different following STS coadministration. This hypothesis could not be confirmed by Uozumi and Litterst [88]; thus, further studies are needed to elucidate the mechanism of this protective effect. The effect of STS on renal toxicity has also been investigated in humans after both intravenous and intracavitary administration of cisplatin [58, 71]. These studies suggest that STS might protect against cisplatin-induced nephrotoxicity; however, serum creatinine and blood urea nitrogen were the only functional variables used for determination of nephrotoxicity.

Conclusion

Cisplatin is currently one of the most used agents in the treatment of cancer, and it is essential in the treatment of germ-cell cancer. The use of this drug is hampered by its side effects, especially renal toxicity, which is dose-limiting. This review presents the pathophysiological mechanisms possibly involved in cisplatin-induced nephrotoxicity.

Immediately after administration of cisplatin in dogs, the renal blood flow (RBF) and glomerular filtration rate (GFR) remained unchanged, whereas a significant decrease was observed in both the fractional and absolute proximal reabsorption rates of sodium and water. Cisplatin-induced nephrotoxicity seems to be initiated by an acute, mainly proximal tubular impairment that precedes alterations in renal hemodynamics. At 48–72 h after cisplatin administration, depressed renal function can be attributed to the impairment of proximal as well as distal tubular reabsorptive capacities, now associated with increased vascular resistance. The polyuria occurring at this time appears to be due to the impaired reabsorption rate in the distal nephron segments, which affects the concentration mechanism.

Human studies have shown that four cycles of 20 mg/m^2 cisplatin can be given daily for 5 days without causing major damage to the kidney. A small decrease in GFR has been observed that has no significant influence on tubular function [18]. During treatment with high-dose cisplatin (40 mg/m^2 cisplatin daily for 5 days) a clearly progressive decrease in GFR is observed, and GFR remains depressed for up to 2 years after the termination of treatment. A marked reduction in the proximal tubular reabsorptive capacities for sodium and water has also been observed in this group, together with a decrease in distal tubular function. These changes persist for at least 6 months after treatment.

The nephrotoxicity of cisplatin is cumulative, but the decrease in GFR is heavily dependent on the amount of the single dose. The development of azotemia does not reflect the deterioration of kidney function after treatment with high-dose cisplatin, whereas the development of hypomagnesemia clearly reflects the cumulative cisplatin dose. Chronic renal tubular damage cannot be predicted by measurements of NAG and β-2-m in urine; these tubular markers are of no value in monitoring progressive nephrotoxicity in this group of patients during therapy. It is also apparent that s-creatinine and creatinine clearance cannot be used for the assessment of kidney function in patients treated with cisplatin.

There is a very good correlation between the data on GFR and tubular function obtained in the dog and those recorded in patients. Thus, lithium clearance and ^{51}Cr-EDTA clearance seem to be suitable variables for the determination of acute and long-term cisplatin toxicity.

After treatment with high-dose cisplatin, proteinuria is observed; it is mainly of tubular origin during cisplatin infusion and of glomerular origin between treatment cycles. Several observations indicate that important active transport systems in the renal tubules are impaired by platinum compounds. To date there is no convincing evidence that either the renal cell mitochondria or membrane-associated Na^+/K^+-ATPase are important early pathogenetic targets of cisplatin.

Observations in both man and experimental animals suggest that the nephrotoxic effect of cisplatin can be modified by saline or mannitol infusion. However, the precise mechanism for these modifications has not been determined. Due to the increasing interest in high-dose cisplatin, an important goal for future studies is to pinpoint the mechanisms of cellular toxicity, thereby hopefully developing a rational protection against cisplatin-induced nephrotoxicity.

Several new platinum derivates have recently been introduced into clinical trials, the most important ones being JM-8 (carboplatin) and JM-9 (iproplatin); apparently, none of these durgs induces renal toxicity. These and other platinum compounds are possible candidates for future alternatives to cisplatin under several conditions. Until then, however, cisplatin remains one of the most potent antineoplastic agents ever developed. Further work should be carried out to reduce its renal toxicity.

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