Renal Complications of Cis-diamminedichloroplatinum*

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ABSTRACT

The use of cis-diamminedichloroplatinum II (DDP), an active agent against special cancer types, is limited by its nephrotoxicity. It damages the proximal tubular epithelium and may cause specific tubular dysfunctions, such as elevation of enzymes and 2 beta microglobulin in the urine or, under special conditions, low calcium and/or magnesium serum concentrations. Cis-diamminedichloroplatinum II produces acute renal failure which can be prevented by hydration. The value of diuretics in preventing renal failure is not determined and needs to be evaluated further.

Introduction

Cisplatin (cis-diamminedichloroplatinum II = DDP) belongs to a new class of potent cancer drugs, the metal coordination complexes. It is the first drug in this group to be used intensively in man, being effective against testicular carcinoma, ovarian and bladder carcinoma, head and neck carcinoma, osteogenic sarcoma, neuroblastoma, and special types of brain tumors. The discovery of this agent was made by Rosenberg and his co-workers in 1965. They found that the discharge of an electric current from a platinum electrode through a nutrition broth inhibited the replication of E. coli. Cisplatin was isolated and shown to be the active principle. Following extensive animal experiments with the drug, it was introduced in man in 1972. Its mechanism of antitumor action appears to be inhibition of deoxyribonucleic acid synthesis most likely owing to the formation of inter- and intrastrand crosslinks.

In man, DDP has to be administered by either I.V. bolus or six to eight hour infusion. In the early studies, the drug was given as a single dose (90 mg per M²) or divided in five equal doses (15(20) mg per M²). The treatment was repeated every four weeks. De Conti has described a biphasic plasma clearance of DDP following bolus
Initially, DDP plasma levels decline rapidly with a half-life between 25 to 45 minutes. Thereafter, the drug concentration levels off and the half-life of this phase is between 53 to 73 hours. The DDP excretion in the urine shows a similar pattern. Twenty-seven percent is excreted in the first six hours after DDP administration with an additional 20 to 25 percent being excreted within the following five days. Manaka explained the biphasic plasma clearance of DDP by developing the following mathematical model. After DDP is administered intravenously, a small "mobile" fraction equilibrates very rapidly with the tissues and a second portion, which makes up about 90 percent of the injected drug, becomes bound slowly in plasma, red cells and tissues to protein and DNA. This fraction is very stable and its metabolism is slow.

The major dose-limiting side effect of DDP is its toxic effect on the kidneys. Platinum, which belongs to the group of heavy metals, produces renal changes similar to the ones seen after mercury administration. It is postulated that DDP binds to the sulphydryl groups of the proximal tubules' brush borders. In animals, a dose at 9 mg per kg results in demonstrable tissue injury. By light microscopy, the tubular epithelial cells show granular and vacuolar degeneration, fragmentation, and necrosis. In addition, lymphocytic interstitial infiltrates are occasionally present. The glomeruli tend to be spared. The earliest changes of toxicity demonstrated by electron microscopy occur in the mitochondria of the tubular epithelia. Their elongated contours become rounded, and the cristae swell. Additionally, the mitochondria migrate from their usual peripheral cytoplasmic position near the tubular basal lamina toward the nucleus. Mitochondrial vacuolization occurs 48 hrs after the administration of DDP. This is followed in 24 hrs by loss of the brush border. In addition, lysosomes increase in size during the first few days after DDP administration. Some subsequently rupture, thus causing cell death.

**Nephrotoxicity**

In man, the few available sporadic observations of the toxic renal effects of DDP are similar to those observed in experimental animals. In addition to the pathological changes, renal dysfunction is observed. Although the main toxic effect of DDP on the kidney is proximal tubular damage, the main clinical concern is oliguric renal failure with elevation of serum urea nitrogen and creatinine, consequent to decreased glomerular filtration. It is postulated that proximal tubular dysfunction leads to decreased reabsorption of sodium chloride. This results in increased delivery of salt to the distal convoluted tubule, stimulation of the juxtaglomerular apparatus and, thereby, activation of angiotensin II, which constricts the glomerular arterioles and dramatically reduces renal blood flow and glomerular filtration rate. Oliguria and elevation of serum creatinine and urea nitrogen ensue.

In the early human studies, DDP produced elevation of serum blood urea nitrogen creatinine in 25 to 30 per cent, 6 to 10 days after the therapy was initiated. Recovery from this renal dysfunction usually occurred after three to four weeks. However, some patients developed persistent renal dysfunction. To prevent DDP-induced nephrotoxicity, the rate of administration was modified, and fractionated doses were given over a period of days. However, only vigorous hydration programs with and without diuretics successfully prevented nephrotoxicity. The protective mechanism of hydration might be either the dilution of sodium chloride in the tubules which may prevent renin release from the juxtaglomerular apparatus and prevent angiotensin
mediated renal vaso-constriction or simply the dilution of DDP in the renal tubule by increased tubular flow. In rats, the 24 hour urine excretion of DDP was increased with hydration. In dogs, however, the amount was similar to that of non-hydrated control animals.

The fact that hydration is effective in preventing nephrotoxicity is best demonstrated by findings that high DDP doses (120 mg per M^2) are tolerated without severe renal problems when hydration is added. So far, it is unclear whether or not mannitol and furosemide given together with high fluids are of additional value. Only in recent years have randomized studies been initiated in order to evaluate the different hydration programs. Taylor and Al-Sarraf hydrated patients before DDP administration, and 24 hours thereafter. One group of patients received mannitol and the other group did not. Taylor stated that mannitol was of no additional value. Al-Sarraf saw less moderate to severe renal toxicity in the patients treated with mannitol. Ostrow et al compared mannitol vs. furosemide in a hydration program. There was no difference in nephrotoxicity in the two groups of patients. The Pediatric Division of the Southwest Oncology Group demonstrated in two consecutive studies that renal dysfunction was similar whether furosemide was given alone with I.V. hydration or in combination with mannitol.

Although renal failure after a single DDP administration can be prevented by hydration, its cumulative effect, if given repeatedly on the glomerular function, is not well described. Because of a pool of tissue-bound DDP and slow urinary elimination of DDP, chronic effects are to be anticipated. Indeed, Bruno et al observed that their patients experienced decreasing creatinine clearances after several DDP administrations.

Tubular dysfunction as an early sign of DDP toxicity has been studied in man only recently. All patients were treated with DDP plus various hydration programs. Urinary beta glucuronidase concentration was increased in 23 of 23 patients and 2-beta microglobulin excretion was elevated in 15 of 15 patients. None of these patients had any other signs of renal dysfunction. In a third report, 15 patients had normal tubular function. In this study the following parameters were measured: total protein, free immunoglobulin light chain, phosphorus, and urine to serum glucose ratio. The first two reports demonstrated tubular dysfunction may occur as an early event without sign of renal failure. This observation concurs with the observation made in animals receiving mercuric chloride that renal failure was prevented by increased normal saline intake, but pathological tubular changes were not.

Calcium and magnesium are reabsorbed in the tubules. Hypomagnesia and hypocalcemia may occur without any other sign of renal dysfunction. In 1978, we reported on two children with childhood tumors with decreased serum magnesium concentration. Since then several reports became available (table I). Twenty-one of 37 adults treated with DDP developed low magnesium levels. Hayes and associates demonstrated that 15 of 16 children with solid tumors treated with the same drug had low serum magnesium concentrations. In addition, all 13 children with neuroblastoma treated with DDP and VM-26* who received magnesium supplement had low serum magnesium concentration. The urinary magnesium excretion was increased in adults and children in whom it was measured. Hypocalcemia occurred in some of these patients. Hypomagnesia was usually seen three to four weeks after the DDP administration. Baum and his co-writers divided hypomagnesia and

* VM-26 = 4'-Dimethylepipodophyllotoxin 9-(4,6-O-2-thenylidene-β-D-glucopyranoside).
hypocalcemia into acute and chronic forms. Acute was defined as occurring 24 hours after DDP and chronic as a gradual decline in serum level from course to course. Those patients who suffered from hypomagnesia and hypocalcemia were prone to be symptomatic.

Conclusion

The use of DDP, an active agent against special cancer types, is limited by its nephrotoxicity. DDP damages the proximal tubular epithelium and may cause specific tubular dysfunctions, such as elevation of enzymes and 2 beta microglobulin in the urine or, under special conditions, low calcium and/or magnesium serum concentrations. DDP produces acute renal failure which can be prevented by hydration. Whether or not diuretics are of further benefit is unknown so far. Because renal failure owing to DDP administration is now preventable with hydration, more patients are being treated for a longer time period with this drug. Therefore, it is possible that in the future more isolated tubular dysfunctions and signs of chronic renal failure will be detected.

References


