cis-Diammineplatinum (II) dichloride

Synonym: cisplatin
CAS: 15663-27-1
MF: $Pt(NH_3)_2Cl_2$
MW 300.1
MW of elemental platinum 195
Solubility: cisplatin is water soluble; insoluble in most common solvents; soluble in dimethylformamide.

Major use
cis-Diammineplatinum (II) dichloride (cisplatin) is a widely used antineoplastic agent. It is administered, usually in combination with other cytostatics (e.g., bleomycin, vinblastine, or cyclophosphamide), or in combination with radiotherapy, for the treatment a variety of tumors, such as colorectal cancer, uterine cancer, bladder cancer, small-cell lung carcinoma, testicular cancer, or recurrent lymphoma [1].

Human toxicity
In cancer therapy, cisplatin is administered by daily intravenous injection of 50-100 mg/m^2, from once every 4 weeks to 5 times per week. Each mg of cisplatin contains 0.65 mg of platinum [2].

Cisplatin is highly nephrotoxic at higher doses; it may cause acute renal failure, acute tubular necrosis, and tubular atrophy of cortical nephrons [3]. Moreover, cisplatin is ototoxic: it causes degeneration of the inner ear, which may lead, in severe intoxication cases, to a total deafness. Cisplatin may also cause visual alterations, both reversible and irreversible (blindness) [4]. Ototoxicity and visual disturbances both occur during the first 48 h after intoxication [5].

Blood changes include hypomagnesemia, leucopenia, and thrombocytopenia. Among nonhematologic toxic properties are nausea, vomiting, and diarrhea.
Other adverse reactions include neurotoxicity (seizures, hallucinations), electrolytic disturbance, and anaphylactic reactions [6].

Intravenous bolus injection of 50 mg/m^2 of cisplatin in 6 patients produced average total platinum plasma concentrations of 4.7 mg/l at 5 min, 1.8 mg/l at 1 hour, and 1.2 mg/l at 6 hours. The corresponding values for a 100 mg/m^2 dose were 6.2, 2.5, and 1.6 mg/l [2].

The minimum lethal toxicity level of platinum was not determined, however, toxicity can occur even at therapeutic plasma level of cisplatin, higher than 5 mg/l.

The threshold limit value for occupational exposure is 1 mg/m^3 for platinum and 0.002 mg/m^3 for its soluble salts in the industrial atmosphere [2].

Carcinogenicity: evidence in humans for carcinogenicity is limited [6].

Kinetic data
Kinetics is biphasic.

Absorption. Cisplatin is not effective when administered orally; therefore it is usually administered intravenously. Cisplatin is totally absorbed after intravenous use; it is widely distributed into body fluids and tissues [1].

Passage of blood brain barrier: limited [1].

Plasma protein binding: about 90%. Cisplatin and any platinum-containing products are rapidly bound to tissue and plasma proteins, including albumin, gamma-globulins and transferring [6].

Plasma initial half-life after administration of usual doses is between 25 and 50 min; concentrations decline subsequently, with a half-life of 58 to 73 h [1]. According another study, the cisplatin half-life averaged 20 min (reviewed in [2]).
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Rapid intravenous injection of cisplatin over 1 to 5 min or infusion over 15 min or one hour, results in *peak plasma concentration* immediately [6].

Metabolism and excretion
The knowledge about metabolism of cisplatin is restricted. There is little evidence that it undergoes enzymatic biotransformation.

Cisplatin appears to enter cells by diffusion. In the cells, cisplatin undergoes hydrolysis, when the chloride atoms may be replaced by water molecules, resulting in positively charged and highly reactive electrophylic products (reviewed in [7]). The platinum and its reactive species may react with DNA, RNA and proteins. For example, in DNA, platinum produces both intrastrand and interstrand cross-links [1].

Excretion: An average of 50% of the administered platinum in an intravenous bolus dose of cisplatin was excreted in the 24 h urine of 3 patients (reviewed in [2]).

Toxicological mechanisms
The toxic effect of cisplatin in tumor cells is mainly due to its capacity to bind to the DNA molecules (especially at the guanine bases, e.g. at N-7 of guanine) and to inhibit DNA synthesis. Cisplatin has biochemical properties similar to those of bifunctional alkylating agents [1, 6].

The kidney accumulates and retains platinum to a greater degree than other organ. There are several theories which try to explain cisplatin nephrotoxicity. One of them is based on an interaction between cisplatin and Na^+/K^+-ATPase enzymes leading to decline in both ATP and K^+. The second theory involves the uncoupling of oxidative phosphorylation in the mitochondria (reviewed in [3]).

Target organs: kidney, liver, intestines.

References
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