PRODUCT MONOGRAPH

PLATINOL
(Cisplatin)

PLATINOL-AQ
(Cisplatin Injection)

Antineoplastic Agent

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DATE OF PREPARATION:

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NAME OF DRUG

PLATINOL
(Cisplatin)

PLATINOL-AQ
(Cisplatin Injection)

CAUTION: PLATINOL (CISPLATIN) AND PLATINOL-AQ (CISPLATIN INJECTION) ARE POTENT DRUGS AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE TAKEN REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW OR ABNORMAL RENAL OR HEPATIC FUNCTION IS SEEN.

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

ACTION AND CLINICAL PHARMACOLOGY

Platinol (cisplatin) and Platinol-AQ (cisplatin injection) has biochemical properties similar to those of bifunctional alkylating agents producing interstrand and intrastrand crosslinks in DNA (1). It is apparently not cell-cycle specific.

After an intravenous bolus dose of radioactive cisplatin to patients, plasma levels decay in a biphasic manner. The initial plasma half-life is 25 to 49 minutes. The post-distribution plasma half-life is 58 to 73 hours. During the post-distribution phase, greater than 90% is protein bound. It is excreted primarily in the urine. However, only 27 to 45% is recovered in the first five days after dosing. Data are insufficient to determine whether biliary or intestinal excretion occurs.

Following a single intravenous dose of radioactive cisplatin to patients, concentrations of cisplatin were found primarily in liver, kidneys and large and small intestines. It has apparently poor penetration into the CNS.

INDICATIONS AND CLINICAL USE

Platinol (cisplatin) and Platinol-AQ (cisplatin injection) are indicated as palliative therapy, to be employed in addition to other modalities, or in established combination therapy with other chemotherapeutic agents in the following:

Metastatic Testicular Tumours - in patients who have already received appropriate surgical and/or radiotherapeutic and/or chemotherapeutic procedures.

Metastatic Ovarian Tumours - as secondary therapy in patients refractory to standard chemotherapy.

Advanced Bladder Cancer - as a single agent for patients with transitional cell bladder cancer.

CONTRAINDICATIONS

Platinol (cisplatin) and Platinol-AQ (cisplatin injection) should not be given to individuals who have demonstrated a previous hypersensitivity to it or other platinum-containing compounds.

When used as indicated, the physician must carefully weigh the therapeutic benefit versus risk of toxicity which may occur.

WARNINGS

Platinol (cisplatin) and Platinol-AQ (cisplatin injection) should be given cautiously to individuals with pre-existing renal impairment, myelosuppression or hearing impairment.

Platinol (cisplatin) and Platinol-AQ (cisplatin injection) produces cumulative nephrotoxicity. The serum creatinine, BUN, and creatinine clearance should be measured prior to initiating therapy, and prior to each subsequent course.

Anaphylactic-like reactions to Platinol have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to Platinol, and have been alleviated by administration of epinephrine, corticosteroids and antihistamines.

Safe use in pregnancy has not been established. Platinol is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. Although carcinogenicity and teratogenicity have not been established, compounds with similar mechanisms of action have been reported to be carcinogenic.

As with any potent antineoplastic drug, the benefit to patient versus risk of toxicity must be carefully weighed.

PRECAUTIONS

Platinol (cisplatin) and Platinol-AQ (cisplatin injection) should be administered by individuals experienced in the use of antineoplastic therapy.

Since renal toxicity is cumulative, measurements of BUN, serum creatinine and creatinine clearance should be performed prior to initiating therapy and prior to each subsequent dose. At the recommended dosage, Platinol or Platinol-AQ should not be given more frequently than once every 3 to 4 weeks. Pretreatment hydration with 1 or 2 litres of fluid infused for 8 to 12 hours prior to a Platinol and Platinol-AQ dose is recommended to minimize nephrotoxicity.

Since ototoxicity of Platinol is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug.

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurological examinations should also be performed regularly.

After reconstitution, Platinol (cisplatin) and Platinol-AQ (cisplatin injection) are physically incompatible with any I.V. set, needle and syringe containing aluminum. An interaction will occur between aluminum and platinum from Cisplatin causing a black precipitate which is visible in the solution. (See PREPARATION OF INTRAVENOUS SOLUTIONS).

ADVERSE REACTIONS

Nephrotoxicity

Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of Platinol (cisplatin) and Platinol-AQ (cisplatin injection). Renal toxicity has been noted in 28 to 36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a

dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of Platinol or Platinol-AQ can be given.

Renal function impairment has been associated with renal tubular damage. The administration of Platinol using a 6 to 8 hour infusion with intravenous hydration, and mannitol diuresis has been used to reduce nephrotoxicity.

Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of Platinol 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz). Decreased ability to hear normal conversational tones may occur occasionally. Ototoxic effects may be more severe in children receiving Platinol or Platinol-AQ. Hearing loss can be unilateral or bilateral, tends to become more frequent and severe with repeated doses and may not be reversible. Careful monitoring of audiometry should be performed prior to initiation of therapy and prior to subsequent doses of Platinol or Platinol-AQ.

Hematologic

Myelosuppression occurs in 25 to 30% of patients treated with Platinol. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses ($\geq$50 mg/m^2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia.

Gastrointestinal

Marked nausea and vomiting occur in almost all patients treated with Platinol, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within one to four hours after treatment and last up to 24 hours. Various degrees of nausea and anorexia may persist for up to one week after treatment.

Other Toxicities

Hyperuricemia

Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid

generally occur between 3 to 5 days after the initial dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity

Neurotoxicity, usually characterized by peripheral neuropathies, has occurred in some patients. Loss of taste and seizures have also been reported. Neuropathies resulting from Platinol and Platinol-AQ treatment may occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose.

Platinol and Platinol-AQ therapy should be discontinued when the symptoms are first observed. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients.

Various degrees of visual loss have been reported in the course of combination therapy including cisplatin as part of the combination. Visual function was regained in those cases in which cisplatin was immediately discontinued.

Anaphylactic-like Reactions

Anaphylactic-like reactions, possibly secondary to Platinol therapy, have been occasionally reported in patients previously exposed to Platinol. The reactions consist of facial edema, wheezing, tachycardia and hypotension within a few minutes of drug administration. All reactions may be controlled by intravenous epinephrine, corticosteroids or antihistamines. Patients receiving Platinol or Platinol-AQ should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Other toxicities reported to occur infrequently are cardiac abnormalities, anorexia and elevated SGOT.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No overdosage occurred during clinical trials. In the event of overdosage or toxic reactions, symptomatic supportive measures should be taken. The anticipated complications would be nephrotoxic, ototoxic, neurotoxic and hematotoxic. Patients should be monitored for 3-4 weeks in case of delayed toxicity.

DOSAGE AND ADMINISTRATION

The recommended dose of Platinol (cisplatin) or Platinol-AQ (cisplatin injection) in adults and children as single-agent therapy is 50 to 75 mg/m^2 as a single intravenous dose every 3 to 4 weeks, or 15 to 20 mg/m^2 intravenous daily for 5 days every 3 to 4 weeks. Pretreatment hydration with 1 to 2 litres of fluid infused for 8 to 12 hours prior to a Platinol or Platinol-AQ dose is recommended. The drug is then diluted in 2 litres of 5% Dextrose in 1/2 or 1/3N Saline containing 37.5 g of mannitol, and infused over a 6 to 8-hour period. Adequate hydration and urinary output must be maintained during the following 24 hours.

A repeat course of Platinol or Platinol-AQ should not be given until the serum creatinine is below 1.5 mg/100 mL and/or the BUN is below 25 mg/100 mL. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets 100,000/mm^3, WBC 4,000/mm^3). Subsequent dose of Platinol and Platinol-AQ should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

When employed in combination with other antitumour drugs, the dose of Platinol or Platinol-AQ should be adjusted appropriately.

PREPARATION OF INTRAVENOUS SOLUTIONS

Intravenous needles, syringes or sets having aluminum components should not be employed in preparation or administration of Platinol and Platinol-AQ solutions. An interaction will occur between aluminum and platinum from Cisplatin causing a black precipitate which is visible in the reconstituted solution.

Dry Powder:

Dissolve Platinol 10 mg with 10 mL Sterile Water for Injection U.S.P. For Platinol 50 mg, add 50 mL of Sterile Water for Injection U.S.P. Each mL of the resulting solution will contain 1 mg of cisplatin.

Reconstitution as recommended results in a clear, colorless injection.

The reconstituted solution should be used intravenously only and should be administered by intravenous infusion over a 6 to 8-hour period.

STABILITY

Platinol (Cisplatin) Powder

The reconstituted solution is stable for 20 hours at room temperature (27°C).

Important Note:

Once reconstituted, the injection should be kept at room temperature (27°C). If the reconstituted injection is refrigerated, a precipitate will form.

Platinol-AQ (Cisplatin Injection) (0.5mg/mL and 1.0mg/mL)

The diluted solution should not be refrigerated and should be used up within 20 hour period from the time of the dilution.

HANDLING AND DISPOSAL

1. Preparation of Platinol and Platinol-AQ should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2. Personnel preparing Platinol and Platinol-AQ should wear PVC gloves, safety glasses, disposable gowns and masks.

3. All needles, syringes, vials and other materials which have come in contact with Platinol and Platinol-AQ should be segregated and incinerated at 1000°C or more. Sealed containers may explode sealed. Intact vials should be returned to the Manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

4. Personnel regularly involved in the preparation and handling of Platinol and Platinol-AQ should have bi-annual blood examinations.

AVAILABILITY

Platinol is supplied in a 20 mL amber glass vial containing 10 mg of cisplatin or a 100 mL amber glass vial containing 50 mg of cisplatin.

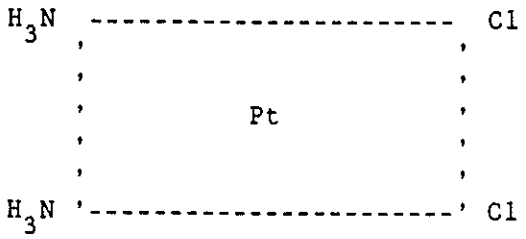
Platinol-AQ is supplied in 20, 50 and 100 mL amber glass vials. Each mL contains 0.5 mg of cisplatin and 9 mg of sodium chloride in water for injection. Hydrochloric acid added to adjust pH.

Platinol-AQ is supplied in 10, 50 and 100 mL amber glass vials. Each mL contains 1.0 mg of cisplatin and 9 mg of sodium chloride in water for injection. Hydrochloric acid and/or Sodium Hydroxide is added to adjust pH.

PHARMACOLOGY

CHEMISTRY

Common Name - Cisplatin



Empirical Formula: $Pt\ N_2H_6Cl_2$ Molecular Weight: 300.06

Chemical Name: Cis-diamminedichloroplatinum II

Description: Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chlorine atoms and two ammonia molecules in the cis position. It occurs as a fine yellow powder and is soluble in dimethylacetamide to an extent of 1% maximum.

Cisplatin causes immunosuppression, which is shortlived (18-72 hours) and followed by a rapid increase in host immune response. This increase in the host immune response has been postulated to cause tumour regression in animals.

Antitumour activity of cisplatin was first demonstrated against sarcoma 180 and L1210 leukemia. Subsequent investigations have shown significant activity of cisplatin i.p. as single agent in several experimental tumours.

1. Transplantable animal tumours, including Walker 256 carcinosarcoma, Dunning ascitic leukemia, Lewis lung carcinoma, Ehrlich ascites tumour, P-388 leukemia, B-16 melanoma, and the intracerebrally implanted ependymoblastoma tumour in mice.

2. Chemically-induced primary tumours, including the 7, 12-dimethylbenzanthracene (DMBA)-induced mammary tumours in rats, and the N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT)-induced murine bladder cancer.

3. The virally-induced Rous sarcoma.

Cisplatin has demonstrated synergism in activity against L1210 leukemia when combined with other chemotherapeutic agents including cyclophosphamide, ICRF-159, ifosfamide, cytosine arabinoside, hydroxyurea, phosphoramide mustard, azacytidine, 5-fluorouracil, emetine, adriamycin and methotrexate. No apparent synergism was noted with BCNU.

Cisplatin was distributed in highest concentrations in kidney, liver, gonads, spleen and adrenals at early times (1-2 hours) after i.v. injection into dogs, but remained significantly elevated only in kidney, liver, ovary and uterus for up to six days post treatment. The tissue: plasma ratio of platinum was 3:1 and 4:1 for liver and kidney, respectively, at 6 days post treatment (2).

After a single i.v. injection of cisplatin in dogs, the rapid-phase half-time was less than one hour and the slow-phase half-time was approximately 5 days. Approximately 60-70% of the dose was recovered in the urine in the first four hours after treatment (2).

TOXICOLOGY

TOXICOLOGICAL PARAMETERS OF CISPLATIN

	INTRAVENOUS ROUTE							
	MICE		DOGS				MONKEYS	
	SINGLE DOSE		SINGLE DOSE		QD X 5 DAYS		QD X 5 DAYS	
	mg/kg	mg/m	mg/kg	mg/m	mg/kg	mg/m	mg/kg	mg/m
Highest non toxic dose (HNTD)	-	-	0.625	13.2	0.187	3.75	0.156 (or less)	1.94
Toxic dose low (TDL)	-	-	1.25	22.5	0.375	7.75	0.313	8.0
Toxic dose high (TDH)	-	-	2.5	47.3	0.75	14.9	1.25	15.9
Lethal dose (LD)	-	-	5.0	105.7	1.5	31.1	2.5	33.6
LD_{50}	13.38	40.15	-	-	-	-	-	-

Acute Toxicity

At lethal dose or LD_{50} death occurred in mice, dogs, and monkeys within 2 to 8 days. Dogs showed severe, mostly hemorrhagic enterocolitis, severe or marked hypoplasia of the bone marrow, moderate or marked hypocellularity of the lymphoid tissues, marked or moderate renal tubular necrosis, together with azotemia, marked or moderate necrosis of the peripancreatic and omental fat tissue and pancreatitis. Monkeys exhibited severe enterocolitis or colitis, severe atrophy of the lymphoid tissues and moderate to severe hypoplasia of the bone marrow. One of the two monkeys furthermore exhibited severe nephrosis, marked focal myocardial necrosis, myocarditis, severe pancreas atrophy and marked atrophy of prostatic gland and testes.

Subacute Toxicity

Surviving dogs and monkeys showed reversible toxic signs including dose related emesis, anorexia, dehydration, weakness, leukocytosis, anemia, hypochloremia, proteinuria and appearance of leukocytes, erythrocytes and casts in the urine. Monkeys showed temporary azotemia and sporadic elevation of the transaminases.

Toxic signs disappeared within two weeks following treatment, and dogs and monkeys did not exhibit histopathology after an observation period of from 61 to 129 days, with the exception of one dog that showed marked atrophy of the prostatic gland and one monkey that exhibited possible drug related interstitial nephritis.

Mutagenicity

Cisplatin has been shown to be mutagenic in E. coli after prolonged cultivation of cells with sublethal levels of cisplatin (3).

Chromosome aberrations were observed in Chinese hamster bone marrow cells after an 8 mg/kg treatment of cisplatin (4).

In the Ames test, cisplatin was shown to be a mild to moderate mutagen (5).

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