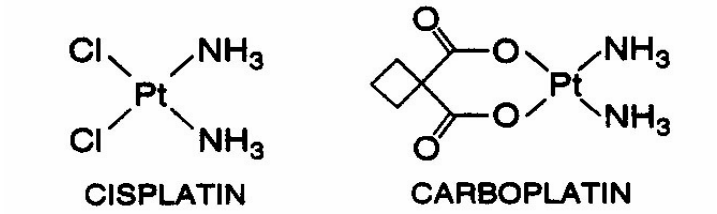
COVALENT DNA-BINDING DRUGS

PLATINUM DRUGS

CARBOPLATIN
(PARAPLATIN®)



Reference: The Pharmacologic Basis of Therapeutics 9th ed. Pg 1270.

I. MECHANISM OF ACTION
Similar to cisplatin. Aquation is slower and less efficient and necessitates a larger dose.

II. PHARMACOKINETICS
Similar to cisplatin. Better tissue concentrations especially to the brain. There is less protein binding than cisplatin. Renal elimination of unchanged drug is 32%. 65% of a dose is eliminated renally in 24 hr.

III. DOSAGE AND ADMINISTRATION
Given as an infusion in D_5W over 30 - 60 minutes. It is stable in NS but for a shorter time period

Dosage adjustment for renal impairment:

A) Renal Function

mL/minute (CrCL)	Dose
≥ 60 mL/min	360 mg/m^2
41 - 59 mL/min	250 mg/m^2
16 - 40 mL/min	200 mg/m^2

B) Calvert Equation

Dose (mg) = Target AUC (mg/mL/minute) X [GFR (mL/min) + 25]

AUC = 7 when patient is untreated

AUC = 5 when patient is previously treated

C) NOTE: typically no adjustments are made for most adult BMT preparative regimens that contain carboplatin. Doses are not made according to AUC in BMT. Examples of doses used in BMT include 600mg/m^2 in testicular BMT protocols, and 500mg/m^2 in STAMP-V for breast cancer. Dose modifications are made in pediatric BMT preparative regimens.

IV. TOXICITY

A) Myelosuppression – All cell lines can be affected but platelets have the deepest nadir. The platelet nadir occurs by day 20 with recovery by day 30. WBC nadir at day 21 – 28 and recover by day 35.
B) Nausea and vomiting – Severe vomiting in about 7% of patients. Under-appreciated. Although less dramatic than with cisplatin, it is severe enough to warrant similar antiemetic regimens.
C) Nephrotoxicity – Elevation of serum creatinine occurs in 7.4% of patients. Can also cause tubular injury and interstitial nephritis.
D) Neurotoxicity – Peripheral neuropathy in about 7% and hearing changes in 15%.
E) Alopecia.

V. CLINICAL MONITORING

A) Physical exam – neurologic status, skin and hair, urine output.
B) Labs – CBC with differential and platelets, electrolytes. Does not usually require intense monitoring of electrolytes as does CDDP.
C) No prior hydration needs be given with carboplatin.

CISPLATIN (CDDP)
(PLATINOL®, PLATINOL®-AQ)

I. MECHANISM OF ACTION

A) Cisplatin (CDDP) belongs to the alkylating agent class of antineoplastics. In its form containing two chloride atoms, it is relatively inactive, but when water molecules react with cisplatin it becomes a very reactive species, which can bind to any protein structure it can find. In simple terms, cisplatin forms permanent bonds with DNA, RNA and cell proteins such that these nucleic acids and proteins are permanently impaired. It is non cell-cycle specific.

B) Resistance is due to impaired membrane transport, increased cytosolic glutathione concentration (offers sulfhydryl group for binding), and augmented DNA repair.

II. PHARMACOKINETICS

A) Distribution- Rapidly distributes to skin, bone, skeletal muscle, liver, and kidney. Cisplatin binds extensively to serum proteins and RBC's.

B) Metabolism- Overall 75% of a dose is chemically deactivated.

C) Elimination- 25% is eliminated renally as unchanged drug and eventually most of the metabolites. Ninety percent of all renal elimination happens in the first 67 min after a dose. Cisplatin can be detected in urine for weeks after a dose.

III. DOSAGE AND ADMINISTRATION

A) Administer as a short or long infusion but not IV push.

B) Prehydration with 500 mL over 30 min - 2 hours, or 1000 mL NS over 2 - 4 hours. Compound the cisplatin in 500 mL NS and give over 1-2 hr. Post-hydration give 500-2000 mL NS over 1 - 4 hours. In general, give 1500-3500 mL total over a 6-hour period with and around the CDDP. These are only suggested orders and should be modified relative to the patient's ability to eliminate the fluid, cardiac status, and hydration status.

C) Do not administer through an aluminum needle.

D) Intraarterial and intraperitoneal administration has also been done. When giving intraperitoneal cisplatin, intravenous sodium thiosulfate is usually given to prevent systemic toxicity.

IV. TOXICITY

A) Nephrotoxicity- Cisplatin is toxic to the tubules, the Loop of Henle, and the collecting ducts of the kidneys. Nephrotoxicity usually presents with rising serum creatinine, rising BUN, falling serum magnesium, and decreased urine output. There is an initial injury but the clinical signs and symptoms may not appear for 7 days or more after a dose. Many patients show a rise in serum creatinine and BUN a week after therapy, but the labs usually correct themselves. There can be acute renal failure in the first hours or days after CDDP administration. Over time there is a cumulative decline in renal function and the damage is such that serum creatinine may not fairly represent the true renal function. Risk factors include inadequate hydration with a saline fluid, the dose each time (> 100 mg/m^2), cumulative dose, and recent or concurrent nephrotoxic drugs. Preventative measures include hydration with NS prior to cisplatin, administration of cisplatin in NS or 3% NS, and administration of furosemide and mannitol. Nephrotoxicity is worse with bolus administration.

B) Nausea and vomiting- Often a dose limiting adverse effect. Adequate control can be achieved with a serotonin antagonist and dexamethasone. Delayed emesis is seen in approximately 20-30% of patients at 3-5 days post treatment. Administration of oral dexamethasone for 5 days post-treatment significantly reduces the incidence of delayed emesis.

C) Neurotoxicity-
   1) Vision changes- cortical blindness, papilledema, retrobulbar neuritis, and color changes.
   2) Peripheral neuropathy- stocking and glove distribution with loss of propioception and vibratory sensation. Resembles B_{12} deficiency and may be the result of disturbed cobalt physiology.
   3) Auditory toxicity- Caused by loss of outer hair cells in the basal turns of the cochlea. Often affects higher frequency sounds outside normal hearing but can eventually become a clinical problem. More common in older patients and those receiving higher doses or a higher total dose. Some patients have ear pain or tinnitus without any toxicity and some have toxicity without any symptoms. 10-15% may have a clinically evident loss.

D) Electrolytes - Cisplatin has been known to cause frequent renal wasting of magnesium and potassium. Calcium is sometimes low secondary to hypomagnesemia.

E) Hypersensitivity - Observed in patients who worked in platinum-using industries. Can occur in 1 - 20% of patients due to either prior CDDP therapy or industrial exposure.

F) Anemia - after prolonged therapy. Responsive to erythropoietin.

G) Ischemic vasculature events

V. CLINICAL MONITORING

A) Labs- SCr, BUN, Mg, K, Ca, Na, CBC with differential and platelets

B) Creatinine clearance assessed by a 24-hour urine collection or from a serum creatinine is initially helpful but over time loses its utility.

C) Perform strict I/O's and daily weights. Be aware of fluid status since the patient is receiving hydration at up to 250 mL/hr. Since NS is used, CHF may be a risk in some patients.

D) Maintain a urine output of 200 mL/hour initially, then 100 mL/hour.

E) The orders should be clear about which antiemetics to give and when. The patient should be made aware of the potential for cisplatin to cause vomiting. Non-pharmacologic intervention like removing odors from the room should also be tried.

F) Physical exam- renal function, neurologic status, hydration status

G) Cisplatin is not generally myelosuppressive.

OXALIPLATIN
(ELOXATIN®)

I. MECHANISM OF ACTION

A) Similar to cisplatin and belong to the alkylating agent classes of antineoplastics. It is the third generation of platinum derivatives, the1,2-diaminocyclohexane (DACH) carrier ligand-based platinum compound.

B) The major cytotoxic lesions are intrastrand platinum-DNA adducts, formed by cross-linking between activated platinum species and specific base sequences, notably 2 adjacent guanine residues or 2 adjacent guanine-adenine bases.

C) A greater degree of inhibition of DNA synthesis and cytotoxicity has been associated with the DACH-platinum adducts of oxaliplatin compared with CDDP adducts formed by CDDP and carboplatin. The bulky DACH carrier ligand of oxaliplatin is thought to contribute to this enhanced activity as well as to the lack of cross-resistance between oxaliplatin and cisplatin. The DACH ligand may also hinder DNA repair by preventing or reducing the binding of specific damage repair proteins such as the mismatch repair enzyme complex, thereby decreasing the replicative bypass of platinum-DNA adducts.

D) Cytotoxicity is cell cycle nonspecific.

II. PHARMACOKINETICS

A) Distribution- At the end of a 2-hour infusion of oxaliplatin, approximately 15% of the administered drug is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. Highly protein bound (>90%) to albumin and gamma globulins, also binds irreversibly and accumulates (approximately 2-fold) in erythrocytes, where it appears to have no relevant activity.

B) Metabolism- Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism *in vitro*.

C) Excretion- primarily by renal route; at five days after a single 2-hour infusion of oxaliplatin, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%.

III. DOSAGE AND ADMINISTRATION

A) Usually administered as a 2- hour infusion. Prolongation of infusion time for oxaliplatin from 2 hours to 6 hours decreases the C_{max} by an estimated 32% and may mitigate acute toxicities.

B) No pre or post hydration is required routinely.

C) Only stable in D_5W, NOT normal saline solution.

D) Do not administer through an aluminum needle.

IV. TOXICITY

A) Neuropathy- dose limiting (incidence 74%); study-specific neurotoxicity scale (see table) instead of NCI Common Toxicity Criteria is used for grading. Oxaliplatin is associated with two types of neuropathy (acute and delayed):

1) Acute- reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing. An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% of patients is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia, and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed.
Preventative measures: (a) Ice (mucositis prophylaxis) should be avoided during the infusion of oxaliplatin because cold temperature can exacerbate acute neurological symptoms; (b) Administration of calcium gluconate 1g IV and magnesium infusion 1g IV given before and after oxaliplatin infusion has been shown to reduce the incidence and intensity of acute oxaliplatin-induced symptoms and might delay cumulative neuropathy [Reference: Gamelin L, et al. *Clin Cancer Res* 2004;10:4055 - 61].

2) Delayed (>14 days)- A persistent (>14 days), cumulative primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysethesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g. writing, buttoning, swallowing, and difficulty walking from impaired proprioception). These forms of neuropathy occurred in 48% of the study patients receiving oxaliplatin with infusional 5-FU/LV. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed Grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms improve in most patients upon discontinuation of oxaliplatin.

OXALIPLATIN-SPECIFIC NEUROTOXICITY GRADING SCALES

Grading scale	Grade 1	Grade 2	Grade 3	Grade 4
Oxaliplatin-specific neurotoxicity scale	Dysesthesias that completely regressed before the next cycle of therapy and did not interfere with functioning	Dysesthesias or paresthesias persisting between courses of therapy that interferes with function but not daily activities	Dysesthesias or paresthesias causing functional impairment that interferes with daily activities	Persistent impairment that is disabling or life-threatening.

B) Gastrointestinal-Nausea and vomiting -mild to moderate with oxaliplatin alone. Premedication with antiemetics, including 5-HT_3 blockers with or without dexamethasone, is recommended. Diarrhea- Grade 1 & 2 diarrhea has been reported in patients with advanced colorectal cancer treated with oxaliplatin monotherapy.
C) Hematologic- Anemia: most common (64%); Neutropenia: rare (7%) when used alone versus but frequently occurred when used with infusional 5-FU and leucovorin (73%); Thrombocytopenia: 30% when used alone versus 60% when used with infusional 5-FU and leucovorin (73%).
D) Pulmonary- Oxaliplatin has been associated with pulmonary fibrosis (0.7% of study patients), which may be fatal. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.
E) Renal Toxicity- About 10% of patients in all groups had some degree of elevation of serum creatinine. The incidence of Grade 3/4 elevations in serum creatinine in the oxaliplatin and infusional 5-FU/LV-combination arm was 1%.

V. CLINICAL MONITORING

A) Labs: Creatinine, BUN, Mg, K, Ca, Na, CBC with differential and platelets, LFT's.
B) Physical exam- neurologic status.