DRUG NAME: PLICAMYCIN

SYNONYM(S): Mithramycin

COMMON TRADE NAME(S): MITHRACIN®

CLASSIFICATION: Antitumour Antibiotic (emergency release)

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION: [1,2]

Plicamycin is an antibiotic isolated from Streptomyces plicatus. It binds to DNA and inhibits DNA, RNA, and protein synthesis in a manner similar to dactinomycin. Cell cycle phase-nonspecific. Plicamycin also lowers serum calcium levels by blocking parathyroid hormone action on osteoclasts, unrelated to cytotoxicity. Although plicamycin was originally studied as therapy for testicular cancer, its present role is confined almost exclusively to therapy of malignant hypercalcemia.

PHARMACOKINETICS: [3,4,5,6]

Oral Absorption	no	
Distribution	cleared from plasma in 2 hours	
	cross blood brain barrier?	yes, CSF = plasma levels
	Vd	no information found
	PPB	not protein bound
Metabolism	metabolic fate unknown	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	major route of elimination	
	urine	40% within 15 hours
	t½	2-24 hours
	Cl	no information found

USES: [1,2]

Hypercalcemia

Less frequent uses include:
Chronic myelogenous leukemia
Testicular cancer

SPECIAL PRECAUTIONS:

Plicamycin is potentially ***carcinogenic and mutagenic.*** Its safe use in ***pregnancy*** and its effects on ***fertility*** have not been established. ***Breast feeding*** is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS: [5,6,7,8]

ORGAN SITE	SIDE EFFECT	ONSET			
central nervous system	headache, irritability, lethargy		E		
dermatologic	facial flushing reaction, skin thickening, hyperpigmentation (33%)	I			
	toxic epidermal necrolysis (rare)		E		
extravasation hazard (refer to Appendix 2)	**VESICANT**	I			
gastrointestinal	nausea and vomiting (onset 1-2 hours, duration 12-24 hours)	I			
	metallic taste (rare)		E		
	diarrhea		E		
	mild stomatitis		E		
	anorexia		E		
hematologic	myelosuppression, mild leukopenia, significant thrombocytopenia, nadir 5-10 days, recovery 10-18 days		E		
hepatic	elevated liver function tests (16%, transient)		E		
	acute necrosis		E	D	
	depression of clotting factors, hemorrhage		E		
injection site	chemical phlebitis	I			
renal/metabolic	decreased serum Ca, K, Mg, PO_4	I			
	hypocalcemia	I			
	azotemia		E		
	tubular necrosis		E	D	
other	fever	I			

Dose-limiting side effects are underlined.
I = immediate (onset in hours to days); E = early (days to weeks);
D = delayed (weeks to months); L = late (months to years)

The ***tissue necrosis*** that happens with ***extravasation*** may happen days to weeks after the treatment.

Patients must be observed for delayed reactions and prior injection sites carefully inspected.

Plicamycin blocks the production of many intracellular enzyme systems necessary for normal ***hepatic function***. ***Coagulation factors*** II, V, VII and X which are synthesized by the liver are depressed. ***Hemorrhage*** may occur in 12% of patients receiving plicamycin on a daily basis. Rare with doses used to treat hypercalcemia and with alternate day dosing. Patients should be observed for nosebleeds, bruising, facial flushing and prolonged coagulation test times. The development of coagulopathy is heralded by the abrupt onset of nose bleeds, ecchymoses, facial flushing and prolonged coagulation times. Plicamycin must be discontinued immediately. A mortality of 1.6% is associated with 10 or fewer doses of <30 mcg/kg/day and 5.7% for larger doses.

Plicamycin ***lowers serum calcium*** at doses much lower than are needed to treat sensitive cancers. The fall in serum calcium begins within hours of injection with peak effectiveness reached within 72 hours. The duration of action of single doses is 7-10 days, therefore weekly doses have been successful in managing hypercalcemia resulting from widespread metastatic disease.

Nausea and vomiting persisting for several hours occurs in approximately 89% of patients receiving 25-50 mcg/kg infusion.

Azotemia occurs in 40% of patients at doses of 25-50 mcg/kg for five consecutive days. Declining renal function is related to cumulative doses. Alternate day therapy produces much lower incidence of nephrotoxicity.

INTERACTIONS:

No significant interactions reported to date.

SOLUTION PREPARATION AND COMPATIBILITY: [9,10,11,12]

Injection: 2.5 mg (2500 mcg) vial. Also contains mannitol and disodium phosphate to adjust pH. Store in refrigerator; reported to be stable at room temperature (25°C or less) for at least 5 days.

Reconstitute powder with 4.9 mL SWI to a final concentration of 0.5 mg/mL (500 mcg/mL).

Reconstituted solution for injection: Chemically stable for 48 hours refrigerated. However, the manufacturer recommends reconstitution immediately prior to use and that unused solutions be discarded.

Diluted solution for infusion: Stable for 24 hours in 1000 mL D5W in glass or PVC containers.

Filtration of a 2.5 mg/L D5W or NS solution through a cellulose ester membrane (IVEX-2) filter resulted in substantial (14% and 9.9%, respectively) loss of potency. Filtration through Abbott IVEX in-line filters, which are specially treated with a proprietary agent, resulted in losses of only 4% from D5W or NS.

It is recommended that plicamycin ***not be mixed with other drugs. Incompatible*** with di- and trivalent cations (eg, zinc, calcium, iron).

PARENTERAL ADMINISTRATION: [4,6]

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Direct intravenous	not recommended due to more frequent and severe GI side effects
Intermittent infusion	Preferred in 1000 mL appropriate solution over 4-6 hours. Has been given in 100-500 mL over 2-6 hours.
Continuous infusion	not used due to corrosive nature
Intraperitoneal	not used due to corrosive nature
Intrapleural	not used due to corrosive nature
Intrathecal	not used due to corrosive nature
Intra-arterial	not used due to corrosive nature
Intravesical	not used due to corrosive nature

DOSAGE GUIDELINES: [4,6,13,14,15,16,17,18]

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

***Adults*:**

Testicular cancer: 25-30 mcg/kg/day IV x 8-10 days

Chronic myelogenous leukemia: 25 mcg/kg/day IV q2d x 3 weeks, then 1-3x per week

For hypercalcemia: 25 mcg/kg/day, with repeat doses given no sooner than 48 hours
q2d: 1 mg/m^2 x 2-3 doses

Dosage in myelosuppression: decrease dose to 12.5 mcg/kg when thrombocytopenia potentially dangerous

Dose in renal failure:

GFR (mL/sec)	% usual dose
0.2-0.8	75%
<0.2	50%

Dose in hepatic failure: decrease dose to 12.5 mcg/kg

***Children*:**

Intravenous: q3-4d: 25 mcg/kg, repeat prn

PLICAMYCIN FACT SHEET
FOR THE HEALTH CARE PROFESSIONAL

OTHER NAMES	Mithramycin, MITHRACIN®
USES	hypercalcemia, chronic myelogenous leukemia, testicular cancer (emergency release)
DOSAGE FORMS	injection: 2.5 mg (2500 mcg) vial for reconstitution (refrigerate)

USUAL DOSE RANGE	Adults: 25 mcg/kg/day, with repeat doses given no sooner than 48 hours 1 mg/m^2 q2d x 2-3 doses Children: 25 mcg/kg IV q3-4d, repeat prn
DOSE REDUCTIONS	low WBC, RBC, platelets (myelosuppression) liver (hepatic) failure kidney (renal) failure

IV COMPATIBILITY	dextrose 5%
ROUTES	intermittent IV (in 100-1000 mL over 2-6 hours, more dilute preferred)
EXTRAVASATION HAZARD Management	**VESICANT** (tissue damage on extravasation) stop IV, aspirate, elevate limb, cold intermittent compresses

ONSET	**SIDE EFFECT** * may be life-threatening side effects in ***bold, italic*** type are common
IMMEDIATE (hours to days)	vein irritation (phlebitis) ***nausea and vomiting*** (90%, onset 1-2 hours, duration 12-24 hours) electrolyte problems (hypocalcemia) fever
EARLY (days to weeks)	* liver problems (elevated liver function tests, acute necrosis, depression of clotting factors leading to hemorrhage) * low WBC, RBC, ***platelets*** (usually mild, myelosuppression, nadir 5-10 days, recovery 10-18 days) ***skin problems*** (facial flushing reaction, skin thickening, hyperpigmentation, 33%; toxic epidermal necrolysis, rare) GI problems (diarrhea, stomatitis, anorexia, metallic taste) kidney problems (azotemia, tubular necrosis) central nervous system problems (headache, irritability, lethargy)
DELAYED/LATE (weeks to years)	* liver problems (acute necrosis) kidney problems (tubular necrosis)

CONTRAINDICATIONS	known hypersensitivity to mithramycin pregnancy and breast feeding

SIGNIFICANT INTERACTIONS	none reported to date
LABORATORY MONITORING	each treatment: CBC, electrolytes periodically: coagulation time, liver function, kidney function

TEACHING AIDS	· *For the Patient: Plicamycin* · *For the Patient: Nausea* · *Chemotherapy and You: a Guide to Self-help During Treatment*

NOTES:
- The incidence and severity of gastrointestinal side effects is increased with rapid administration.
- **Hemorrhage** secondary to thrombocytopenia and decreased clotting factors may occur in 12% of patients receiving plicamycin >30 mcg/kg/day and/or for more than 10 doses. It is rare with doses used to treat hypercalcemia and with alternate day dosing. Signs of impending hemorrhage include facial flushing, nosebleed (epistaxis), bruising, hemorrhagic spots on skin or mucosa (petechia, ecchymoses) and prolonged coagulation times. Facial flushing and nosebleed are indications to discontinue treatment, at least temporarily.
- Acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of hemorrhage.

FOR THE PATIENT: Plicamycin

Other names: Mithramycin, MITHRACIN®

- **Plicamycin** (pli-ka-MY-sin) is a drug that is used to lower calcium levels in your blood. It is a clear liquid that is injected into a vein.
- A **blood sample** will be taken before each treatment. The dose and timing of your chemotherapy may be changed based on your blood counts and/or other side effects.
- Other drugs may **interact** with plicamycin. Tell your doctor if you are taking any other drugs as your dose may need to be changed. Check with your doctor or pharmacist before you start taking any new drugs.
- The **drinking of alcohol** (in small amounts) will not affect the safety or usefulness of plicamycin.
- Plicamycin may damage sperm and may harm the baby if used during pregnancy. It is best to **use birth control** while being treated with plicamycin. Tell your doctor right away if you or your partner becomes pregnant. **Do not breast feed** during treatment.
- **Tell** doctors or dentists that you are being treated with plicamycin before you receive any treatment from them.

SIDE EFFECTS	MANAGEMENT
Plicamycin **burns** if it leaks under the skin.	Tell your nurse or doctor ***immediately*** if you feel burning, stinging or any other change while the drug is being given.
Pain or tenderness may occur where the needle was placed.	·Apply cool compresses or soak in cool water for 15-20 minutes several times a day.
Nausea and vomiting may occur 1-2 hours after your treatment and may last for 12-24 hours. Some people have little or no nausea.	You may be given an antinausea drug with your treatment and a prescription to take at home. It is easier to prevent nausea than treat it once it has occurred. ·Follow antinausea drug directions closely. ·Drink plenty of liquids. ·Eat often in small amounts. ·Try the ideas in the *For the Patient: Nausea*.
Your **white blood cells** may decrease 5-10 days after your treatment. They will return to normal 10-18 days after your last treatment. White blood cells protect your body by fighting bacteria (germs) that cause infection. When they are low, **you are at greater risk**	To help prevent infection: ·Wash your hands often and always after using the bathroom. ·Take care of your skin and mouth. ·Avoid crowds and people who are sick. ·Call your doctor ***immediately*** at the first sign of an infection such as fever (over 100°F

SIDE EFFECTS	MANAGEMENT
of having an infection.	or 38°C), chills, cough, sore throat or burning when you pass urine.
Your **platelets** may decrease 5-10 days after your treatment. They will return to normal 10-18 days after your last treatment. Platelets help to make your blood clot when you hurt yourself. **You may bruise or bleed more easily than usual**.	To help prevent bleeding problems: ·Try not to bruise, cut or burn yourself. ·Clean your nose by blowing gently, do not pick your nose. ·Avoid constipation. ·For minor pain, take acetaminophen (eg, TYLENOL®). Do not take ASA (eg, ASPIRIN®) or ibuprofen (eg, ADVIL®).
Sore mouth may occur a few days after treatment. Mouth sores can occur on the tongue, the sides of the mouth or in the throat. **Mouth sores or bleeding gums can lead to an infection.**	·Brush your teeth gently after eating and at bedtime with a very soft toothbrush. If your gums bleed, use gauze or your finger instead of a brush. ·Make a mouthwash with ½ teaspoon baking soda or salt in 1 cup warm water and rinse several times a day.
Hair loss is rare with plicamycin. Your hair will grow back once you stop treatment with plicamycin. Colour and texture may change.	·Use a gentle baby shampoo and soft brush. ·Avoid hair spray, bleaches, dyes and perms.
Your **skin may redden, thicken and darken** in some areas including your face.	This should slowly return to normal once you stop treatment with mithramycin.

SEE YOUR DOCTOR OR GET EMERGENCY HELP *IMMEDIATELY* IF YOU HAVE:

- Signs of an **infection** such as fever (over 100°F or 38°C); chills; cough; sore throat; pain or burning when you pass urine; redness, pain or swelling of any area of your body; sores forming anywhere on your body.
- Signs of **bleeding problems** such as nosebleed; black, tarry stools; blood in urine; small or pinpoint red spots on skin.

SEE YOUR DOCTOR AS SOON AS POSSIBLE (DURING OFFICE HOURS) IF YOU HAVE:

- Signs of **liver problems** such as yellow eyes or skin, white or clay-coloured stools.
- Signs of **low blood calcium** such as muscle or abdominal cramps.

CHECK WITH YOUR DOCTOR IF ANY OF THE FOLLOWING CONTINUE OR BOTHER YOU:

- Uncontrolled nausea, vomiting, loss of appetite or diarrhea.
- Easy bruising or bleeding.
- Redness, swelling, pain or sores where the needle was placed.
- Redness, swelling, pain or sores on your lips, tongue, mouth or throat.
- Headache, weakness, drowsiness.

REPORT ADDITIONAL PROBLEMS TO YOUR DOCTOR.

See ***Chemotherapy and You: a Guide to Self-help During Treatment*** available free from the Canadian Cancer Society for more information on managing side effects.

Notes:

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