PRODUCT MONOGRAPH

[Pr]BLEOMYCIN FOR INJECTION USP

(as bleomycin sulphate)

15 units of bleomycin/vial

Sterile Powder

THERAPEUTIC CLASSIFICATION

Antineoplastic agent

Pfizer Canada Inc.
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Kirkland, Québec
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ACTION AND CLINICAL PHARMACOLOGY

Experiments with isolated DNA have shown that bleomycin binds to the DNA molecule and cleaves it. This results in the inhibition of DNA synthesis. There is also evidence of lesser inhibition of RNA and protein synthesis.

Bleomycin exhibits a wide spectrum of *in vitro* and *in vivo* activity. It demonstrates inhibition of DNA synthesis in *E. coli, B. subtilis,* Ehrlich ascites cells, HeLa cells, PHA-stimulated lymphocytes, L-929 fibroblasts, L5178Y cells and Novikoff hepatoma ascites cells, at concentrations within a general range of 4-20 microgram/mL under typical incubation conditions.

The activity of bleomycin seems to be cell phase-specific. Cyclic and continuous administration of bleomycin has been shown to be more effective than bolus dosing in *in vivo* systems.

Bleomycin is well absorbed after parenteral (intravenous, subcutaneous, intramuscular, and intrapleural) but not after oral administration. Tissue distribution was evaluated in mice and was found to be high in skin, kidney, lung, peritoneum, lymphatics and solid tumour and tumour cells in ascites. Bleomycin does not cross the blood-brain barrier.

Several tissues have demonstrated a capacity to degrade bleomycin. The liver and GI tract show the highest rate of inactivation. The skin, lungs and kidney show a lower rate which may account for the site-specific toxicity of the drug.

Bleomycin half-life varies with creatinine clearance and is of 2 to 5 hours after intravenous administration to patients with normal kidney function.

Bleomycin is rapidly absorbed after intramuscular administration. Bleomycin peak concentration is obtained after approximately 45 minutes with a half-life clearance of about 2.5 hours.

In patients with creatinine clearances greater than 50 mL/min., the composite intraperitoneal plasma half-life, approximately 5.3 hours, is significantly longer than the intrapleural and intravenous half-lives, approximately 3.4 and 4.0 hours, respectively.

With continuous intravenous infusion, the terminal half-life of bleomycin is 9 hours for adults and about 2.3 hours for children. In children less than 3 years of age, the terminal half-life of bleomycin administered by rapid intravenous injection is 3 hours.

In patients with normal renal function, bleomycin excretion during the first 24 hours is lower in most cases following intracavitary administration than following intravenous administration.

Approximately 45% of bleomycin administered by the intracavitary route is absorbed into the systemic circulation.

Pharmacokinetics in patients with impaired renal functions: The serum half-life of bleomycin is markedly prolonged in patients with renal dysfunction. The bleomycin half-life increases as the creatinine clearance decreases.

INDICATIONS AND CLINICAL USES

Bleomycin for Injection USP should be used as first-line therapy and/or adjuvant to surgery and radiation therapy. It has been shown to be useful in the following neoplasms:

Squamous Cell Carcinoma: Skin, larynx and paralarynx, penis, cervix and vulva. Bleomycin in combination with radiotherapy shows improved results in lung cancer and cervical carcinoma.

Lymphomas: Hodgkin's lymphoma and non-Hodgkin's lymphoma including reticulum cell sarcoma and lymphosarcoma.

BACOP, M-BACOP, COP-BLAM and MACOP-B are used as first-line therapy in the treatment of diffuse large cell lymphoma.

MOPP/ABVD is used as first-line therapy for Hodgkin's lymphoma. Bleomycin is useful in Hodgkin's patients with disseminated disease (Stage IV) no longer treatable by bone marrow depressant agents. Bleomycin, added to the widely used MOPP regimen, increases the responses as well as survival rates of patients with advanced Hodgkin's disease; furthermore, bleomycin does not show cross-resistance to MOPP.

Testicular Carcinoma: Embryonal cell carcinoma, choriocarcinoma, and teratocarcinoma. PEB, PVB and VAB-6 are used as first-line therapy for testicular cancer.

Pleurodysis and pleural fluid accumulation: Bleomycin is effectively used in the prevention of pleurodysis and pleural fluid accumulation due to metastatic carcinoma, metastatic melanoma, oesophageal carcinoma and ovarian cancer.

Other: Bleomycin has been shown to produce responses in some renal carcinomas and soft tissue sarcomas.

CONTRAINDICATIONS

Bleomycin for Injection USP is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to the drug. When used as indicated, the physician must carefully weigh the therapeutic benefit versus risk of toxicity which may occur.

WARNINGS

Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of lymphoma patients treated with bleomycin. Since these usually occur after the first or second dose, careful monitoring is essential after these doses.

It is recommended that bleomycin be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Since facilities for necessary laboratory studies must be available, hospitalization of patients is recommended.

Patients receiving bleomycin must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function. Patients who are undergoing bleomycin treatment are predisposed to respiratory failure following exposure to high concentrations of O_2 (general anesthesia). Since this effect may be observed for up to one year after treatment with bleomycin, the oxygen administration to these patients should be kept at the lowest possible concentrations in order to minimize the risk of severe pneumonitis.

Pulmonary toxicities occur in approximately 10% of treated patients. In approximately 1%, the non-specific pneumonitis induced by bleomycin progresses to pulmonary fibrosis and death. Although this is age- and dose- related, the toxicity is unpredictable.

A method suggested to lower the incidence of pulmonary toxicity is the continuous intravenous administration of bleomycin.

Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported infrequently. However, these toxicities may occur at any time after initiation of therapy.

Usage in Pregnancy: Safe use of bleomycin in pregnant women has not been established.

PRECAUTIONS

General

Bleomycin for Injection USP should be administered preferably to patients who are hospitalized and who can be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function due to disease other than malignancy and in patients over 70 years of age because of the apparent increased danger of pulmonary toxicity.

Frequent roentgenograms are not a preferable method of follow-up or detection of pulmonary toxicity from bleomycin. Current practice consists of frequent physical examination (cough, basal rales and pleuritic chest pain are frequently first signs of toxicity) and baseline evaluation of carbon monoxide diffusion capacity which also allows for the exclusion of patients with low pulmonary reserve, as well as for follow-up of progression of the pneumonitis after cessation of bleomycin therapy.

If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug-related. Pneumonitis due to bleomycin should be treated with corticosteroids in an effort to prevent progression to pulmonary fibrosis. Infectious pneumonitis should receive appropriate antibiotic therapy.

ADVERSE REACTIONS

Skin

50% of the patients develop either hyperpigmentation of the skin, hyperkeratosis of hands and nails, and edema and erythema of the hands and feet. The skin toxicity occurred more frequently at higher doses: 200 to 300 unit range and can be dose-limiting. Rash forms on the pressure areas of the body and abdominal skin creases. It is a common side effect (due to accumulation of the bleomycin in the skin) and is reported to occur in 8% of treated patients within a few days to 2 to 3 weeks at doses of 1.25 to 35 mg/m^2.

Pulmonary

Pulmonary toxicity is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent manifestation is pneumonitis occasionally progressing to pulmonary fibrosis which may result in death.

Approximately 1% of patients treated succumb to pulmonary toxicity. Pulmonary toxicity is usually both dose- and age- related, being more common in patients over 70 years of age receiving over 400 units total dose. However, this toxicity is unpredictable and has been seen occasionally in young patients receiving low doses.

The identification of patients with pulmonary toxicity due to bleomycin has been extremely difficult due to the lack of specificity of the clinical syndrome, the X-ray changes and even the tissue changes seen on examination of biopsy and autopsy specimens.

Bleomycin-induced pneumonitis apparently produces dyspnea and fine rales that are in no way different from those produced by infectious pneumonias or the signs and symptoms produced by primary or metastatic lung disease in some patients.

The microscopic tissue changes due to bleomycin toxicity are frequently present as bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous edema

and interstitial fibrosis and are in line with interstitial pneumonitis. These microscopic findings are non-specific.

Serial pulmonary function tests in approximately 20% of patients receiving bleomycin therapy reveal some demonstrable alteration. The most common changes are decrease in total lung volume and decrease in vital capacity. However, there are no predictive correlations between these changes and the development of pulmonary fibrosis.

Frequent roentgenograms are not a preferable method of follow-up or detection of pulmonary toxicity from bleomycin. Current practice consists of frequent physical examination (cough, basal rales and pleuritic chest pain are frequently first signs of toxicity) and baseline evaluation of carbon monoxide diffusion capacity, which also allows for the exclusion of patients with low pulmonary reserve, as well as for follow-up of progression of the pneumonitis after cessation of bleomycin therapy.

If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug-related. Sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DL_{CO}) during treatment with bleomycin may be an indicator of subclinical pulmonary toxicity. It is recommended that the DL_{CO} be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus the drug should be discontinued when the DL_{CO} falls below 30 to 35% of the pretreatment value.

Concurrent or prior lung irradiation will also predispose patients to increased pulmonary toxicity.

The reaction, which may be immediate or after several hours delay, occurs only after the first or second dose. It consists of hypotension, fever, chills, mental confusion and wheezing.

In order to minimize the incidence of pneumonitis due to bleomycin therapy, it is recommended not to exceed total dose 200 units/m^2, not to exceed 100 units/m^2 if concurrent lung irradiation is also given, not to exceed 100 units/m^2 in patients over the age of 70, and to use continuous infusion to avoid peak serum levels.

Fever

Pretreatment with antipyretics or antihistamines is frequently given as fever occurs in 50% of patients with intravenous administration and 25% with intramuscular administration.

GI toxicity

Mucositis and stomatitis occur in 30% of patients.

Other

Fever, chills and vomiting are frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumor site, phlebitis and other local reactions are reported infrequently.

There are also isolated reports of Raynaud's phenomenon occurring in patients with testicular carcinomas treated with a combination of bleomycin and vinblastine. It is currently unknown if the cause for the Raynaud's phenomenon in these cases is the disease, either drug, or a combination of any or all of these.

Toxicity to the renal, hepatic and central nervous system is rare, but as with any potent drug, these symptoms should be monitored. It is noteworthy that there has been little evidence of bone marrow or immunological depression to date. This is contrary to the currently available antineoplastic drugs.

DOSAGE AND ADMINISTRATION

Each mg of Bleomycin contains 1.5 to 2.0 units of sterile Bleomycin Sulphate USP.

Because of the possibility of anaphylaxis, all lymphoma patients should be started with 2 units or less for the first 2 doses. If no acute reaction occurs, then the regular dose schedule may be followed.

Bleomycin may be given by the intramuscular, intravenous, intra-arterial, intracavitary or subcutaneous routes.

The following dose schedule is recommended:

Squamous cell carcinoma, lymphosarcoma, reticulum cell sarcoma, testicular carcinoma
0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously or intramuscularly, weekly or twice weekly.

Hodgkin's Disease:
0.25 to 0.50 units/kg (10 to 20 units/m^2) intravenously or intramuscularly, weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily subcutaneously or 5 units weekly intravenously or intramuscularly should be given.

Toxicity of bleomycin sulphate appears to be dose-related with a striking increase when the total dose is over 400 units. Total doses over 400 units should be given with great caution.

Hodgkin's and testicular improvement are prompt and noted within two weeks. If no improvement is seen by this time, chances of improvement are very low. Squamous cell cancers respond more slowly, sometimes requiring as long as three weeks before improvement is noted.

Note: When bleomycin is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses. In order to decrease pulmonary toxicities, administration by continuous infusion rather than intravenous bolus is recommended.

Intra-arterial
For intra-arterial infusion/perfusion where increased drug concentrations at the cancer site are desired, the suggested dosage schedule is 30 to 60 units once or twice a week, until a total recommended dosage of 300 units has been administered.

Intracavitary:

The following dosage schedule is recommended when used as a sclerosing agent to control pleural effusions due to metastatic tumours or to manage pneumothorax (associated with acquired immunodeficiency syndrome and pneumocytis pneumonia):

50 to 60 units of bleomycin diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection (not exceeding 1 unit/kg or 40 units/m^2 in the case of geriatric patients). The solution is instilled into the chest through a thoracostomy tube. The tube is then clamped, the patient is rotated periodically and the fluid subsequently removed after 24 hours.

Note: Prior to the above administration to patients with effusions, the pleural cavity is drained via the thoracostomy tube (by gravity or suction) since efficacy may be reduced if the bleomycin solution is instilled into the pleural cavity while fluid drainage exceeds 100 mL per 24 hours.

Impaired renal function:

For patients with impaired renal function, the following dosage schedule is recommended:

- Patients with moderate renal failure (GFR 10 to 50 mL/min) - reduce to 75% of normal dose at the normal dosage interval.
- Patients with severe renal failure (GFR <10 mL/min) - reduce to 50% of normal dose at the normal dosage interval.
- Patients with GFR greater than 50 mL/min - no dosage adjustment is required.

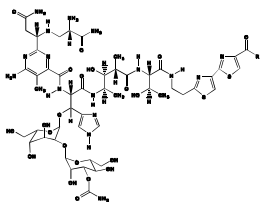
PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Bleomycin Sulphate

Molecular Formula: $C_{55}H_{84}N_{17}O_{21}S_3$

Chemical Structure:



Molecular weight: Approximately 1400

Description: Bleomycin Sulphate is a mixture of glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus* and converted into sulphates. It is supplied as a white lyophilized powder which is highly soluble in water. Approximately 60% of the bleomycin mixture is represented by bleomycin A_2, a complex glycopeptide.

Bleomycin Sulphate is readily soluble in water, partially soluble in methanol, and insoluble in acetone, chloroform, ether, ethanol and ethylacetate. It is soluble in aqueous solutions of pH 3.5 to 12. However, it is hydrolyzed in strong acids and bases.

Bleomycin Sulphate, 10 units/mL (aqueous solution), has a pH of 4.5 to 6.0.

Composition: Bleomycin for Injection USP is supplied in vials; each vial contains sterile lyophilized Bleomycin Sulphate equivalent to 15 units of Bleomycin. Sulfuric Acid or Sodium Hydroxide may be used as pH adjusters.

Stability and storage recommendations

Store vials of Bleomycin for Injection USP between 2 and 8°C, protected from light.

The product is available in 10 mL clear Type I glass vial with rubber stopper and aluminum seal. The product is packaged in an ONCO-TAIN® (clear plastic polyethylene terephthalate) sleeve to protect from breakage. It is recommended that the vial remains in the carton until time of use. The Bleomycin for Injection USP vial should be inspected for damage and visible signs of leaks before use. If there are signs of breakage or leakage from the vial, do not use. Incinerate the unopened package.

Preparation for Use and Reconstitution

Intramuscular or Subcutaneous: Dissolve the contents of the vial in 1 to 5 mL of either sterile water for Injection or 0.9% sodium chloride injection.

Intravenous or Intra-arterial: Dissolve the contents of the vial in 5 to 10 mL of either sterile water for injection or 0.9% sodium chloride injection.

Intracavitary

Intrapleural:	Dissolve the contents of 1 to 8 vials (15 to 120 units) in 100 mL of either 0.9% sodium chloride injection or 5% dextrose injection.
Intraperitoneal:	Dissolve the contents of 4 to 8 vials (60 to 120 units) in 100 mL of 0.9% sodium chloride injection.

Reconstituted solutions may be stored at room temperature for 24 hours or refrigerated between 2 to 8°C for up to 48 hours. Unused portions should be discarded after this time.

Warning: As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoluoration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

Handling and disposal:

1) Preparation of cytotoxic agents such as bleomycin sulphate should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2) Personnel preparing cytotoxic agents should wear PVC gloves, safety glasses, disposable gowns and masks.

3) All needles, syringes, vials and other materials which have come in contact with bleomycin should be segregated and incinerated at 1000°C or more. Sealed containers may explode.

4) Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.

AVAILABILITY OF DOSAGE FORMS

Bleomycin for Injection USP is supplied as single use ONCO-TAIN® vials containing 15 units of bleomycin activity (as sterile lyophilized bleomycin sulphate) for injection.

Bleomycin for Injection USP is available in a conventional glass vial.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:

  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001.

The leaflet was prepared by:

Pfizer Canada Inc., Kirkland, Québec H9J 2M5

CLINICAL PHARMACOKINETICS

Bleomycin is excreted primarily by renal mechanisms. In pharmacokinetic studies, bleomycin has been measured by both radio-immunoassay (RIA) and microbiologic assay. The methods correlate well, although the RIA techniques are reported to be more specific and sensitive, and less prone to interference by typical concurrent chemotherapeutic drugs.

Intravenous Administration

Bleomycin plasma decay kinetics and urinary excretion were studied in nine patients after IV bolus injections of 13.7 to 19.9 U/m2. RIA was used to measure bleomycin in plasma and urine samples. The resulting data obtained from all patients were fitted to a multiexponential equation using a nonlinear regression computer program.

Bleomycin initial and terminal plasma half-lives and volume of distribution for all plasma decay data from eight patients with normal serum creatinine were 24.4 $\pm$ 4.0 min, 237.5 $\pm$ 8.5 min, (approximately 4 hours), and 17.3 $\pm$ 1.5 L/m^2, respectively. Mean 24 hour urinary excretion accounted for 44.8 $\pm$ 12.6% of the dose in seven patients who had normal serum creatinine values and complete urine collections. The total body clearance and renal clearance in these seven patients averaged 50.5 $\pm$ 4.1 $mL/min/m^2$ and 23.0 $\pm$ 1.9 $mL/min/m^{2,}$ respectively. One patient with a serum creatinine of 1.5 mg% (normal 0.7 to 1.3 mg%) who was given 15.6 U/M^2 had a terminal plasma half-life of 624 min, a volume of distribution of 36.3 L/m^2, and 24 hour urinary excretion of 11.6% of the dose.

With continuous intravenous infusion, the terminal half-life was 9 hours for adults and about 2.3 hours for children.

In children less than 3 years of age, the terminal half-life of bleomycin administered by rapid intravenous injection was 3 hours.

Intramuscular Administration

After a single intramuscular dose of 15 mg (15 units), a mean ± S.D. of 318 ng/mL was obtained. Peak concentration was obtained approximately 45 minutes after the IM dose. The serum t 1/2ß was estimated to be about 2.5 hours, and most of the administered dose was excreted in the urine in 24 hours.

Intracavitary Administration

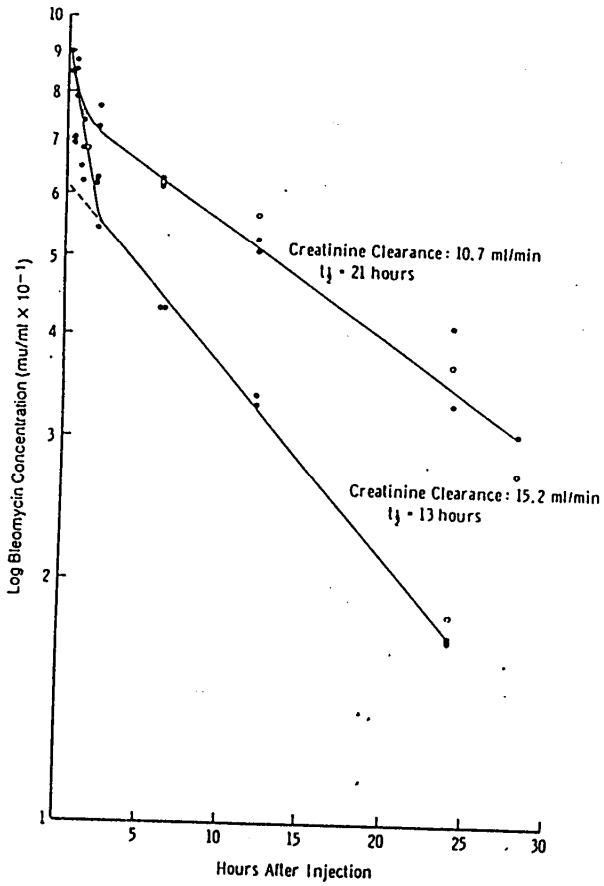
Alberts, *et al*, 1979, reported peak plasma concentrations of 0.4 to 5.0 mU/mL following an intraperitoneal or intrapleural bleomycin dose of 60 U/m^2 . The mean terminal phase plasma half life was 3.4 ± 0.3 hours after intrapleural administration and 5.3 ± 0.4 hours after intraperitoneal instillation.

Renally impaired patients

Figure 1 shows the serum bleomycin levels at two creatinine clearances, as determined by radioimmunoassay, after an IV dose of 15 units (7.5 U/m^2). The figure shows that the serum half-life of bleomycin was 21 hours when the creatinine clearance was 10.7 mL/min., and 13 hours when the creatinine was 15.2 mL/min., demonstrating that clearance of bleomycin was markedly prolonged in renal dysfunction, and that, in this individual patient, it varied as the creatinine clearance varied. Figure 1 also shows that equivalent results were obtained on serum and plasma.

FIGURE 1

Bleomycin concentrations in serum an plasma as determined by RIA.
The open circles indicate bleomycin concentrations in heparinized blood.
The closed circles represent bleomycin concentrations in serum.
(The open circle at 15 minutes corresponds to the curve for a creatinine clearance of 15.2 mL).
From Crooke, et al, 1977



Bleomycin concentrations in serum and plasma as determined by RIA.
The open circles indicate bleomycin concentrations in heparinized blood.
The closed circles represent bleomycin concentrations in serum.
(The open circle at 15 minutes corresponds to the curve for a creatinine clearance of 15.2 mL).
From Crooke, et al, 1977

Arterial and venous samples pre- and post- dialysis failed to demonstrate any reduction in the serum concentration of bleomycin, suggesting that bleomycin was not dialyzable.

TOXICOLOGY

Acute Toxicity

The acute toxicity of bleomycin is summarized in Table 1.

Table 1

Acute Toxicity of Bleomycin (units/kg)

	Sex	IV	IP	SC
Mice	M	210	312	200
Mice	F	187	190	188
Rats	M		168	168
Rats	F		143	226
Dog	M	>100		

In general death was delayed and preceded by weight loss, decreased appetite, leucocytosis, and hepatotoxicity. Renal toxicity and gastrointestinal toxicity were not observed.

Subacute and chronic toxicity

Repeated injections in mice and dogs at subacute doses showed that hepatotoxicity was reversible in surviving animals. Alopecia, inflammation of the skin and nail deformation became evident. Toxicity in mice may have been age and sex related, increasing in males and with age. Pulmonary damage was seen in mice administered 100 U/kg bleomycin IV as a single dose, although clinical toxicity symptoms were not evident.

In a chronic study, bleomycin was administered to 14 dogs at doses from 0.312 to 5.0 mg/kg I.V. every 4 days for 6 to 28 weeks. The resultant toxicity was atypical for most antitumor agents in that non-dose-related interstitial pneumonia and pulmonary fibrosis restricted to pleural and subpleural areas were the treatment limiting toxicity and occurred in 93% of the dogs.

Pulmonary changes did not occur as a simple dose-related phenomenon. The lesions required at least 38 days to become apparent and appeared to increase in severity with time. Even at the lowest dose used (0.625 mg/kg body weight), very severe changes were seen 128 days after cessation of therapy. Morphological features of interstitial pneumonia were subpleural localization, focal mesothelial hyperplasia, marked hyperplasia and metaplasia of type II pneumocytes, fetalization of alveoli, and a pleomorphic inflammatory infiltrate. In cross-sections of lung lobes selected for histology, approximately 1 to 22% of the parenchyma contained lesions. Involved areas showed marked elastosis, and increased acid mucopolysaccharides.

Bleomycin-induced lesions in dogs occurred in organs previously reported to contain the highest concentrations of the compound, i.e., lung, kidney, and skin.

The earliest pathological changes were local inflammation and exudation of alveolar phagocytes. In time, thickening of the pleura and hyperplasia and metaplasia of type II pneumocytes occurred. Eventually alveoli were replaced by a considerable increase in interstitial collagen, reticulin, elastin, and acid mucopolysaccharides.

The finding of interstitial pneumonia and pulmonary fibrosis in dogs treated with low doses over prolonged periods, predicts the need to monitor pulmonary function in humans treated with bleomycin.

Epithelial toxicity in the chronic toxicity study in dogs, was manifested as dermatitis, ulceration at friction sites, onychoptosis and alopecia, and occurred in 70% of the animals. Hematologic changes and hepatotoxicity were minor and reversible, while dose-related anorexia and up to a 60% weight loss were observed. Serum globulin changes in 2 dogs treated with 5.0 mg/kg included an increased alpha 2 level, a decreased alpha 1 level, and appearance of a second alpha 1 electrophoretic band. Severe nephrosis and/or nephritis also occurred in dogs treated with 2.5 or 5.0 mg/kg and contributed to the moribund condition of both dogs treated with the largest dose.

Mutagenicity

Most chemicals which inhibit DNA synthesis and cause DNA strand breakage, also exhibit their effect on chromosomes and are potentially mutagenic. Bleomycin has been shown to product genetic aberrations in yeast and in preparations of metaphase chromosomes from bone marrow cells of cancer patients treated with bleomycin but not in traditional test systems such as *Salmonella*.

Carcinogenicity

Repeated doses of bleomycin SC at 2-8 mg/kg every two weeks reduced body weight and life expectancy of rats in a dose-related pattern in a life time duration carcinogenicity study. Tubular cell damage and cell proliferations were seen as a symptom of major toxicity in the kidneys. Bleomycin was carcinogenic; treatments resulted in significant dose-related incidences of animals with tumors at the site of application (fibrosarcomas) and with renal tumors (adenomas, adenocarcinomas, sarcomas).

It should be noted that the number of animals per dosage group was quite small (30M, 30F). The subcutaneous route of administration is not the most commonly used route of administration of bleomycin clinically, and may stimulate formation of tumors at the site of application, to a greater extent than other parenteral routes.

Teratogenicity

Teratological studies in Sprague-Dawley rats and Dutch-belted rabbits were conducted. Bleomycin was administered throughout the period of organogenesis in both species as well as for continuous 4 day intervals during organogenesis in rats. Treatment intervals were segmented in rats to determine the period of teratogenic sensitivity. Maximum tolerated doses were predetermined in pregnant animals to aid in the selection of optimal dose levels for the teratology studies. Bleomycin was a comparatively weak teratogen resulting only in increased numbers of skeletal defects and a low incidence of soft tissue anomalies in rats. It did not appear to be teratogenic in the rabbit although there was some increase in abortion rate.

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