Bleomycin for Injection, USP

**INDICATIONS AND USAGE**

Bleomycin for Injection, USP is a mixture of cytotoxic glycopeptides antibiotics isolated from a strain of Streptomyces verticillus. It is freely soluble in water.

**DESCRIPTION**

Bleomycin for Injection, USP is a mixture of two closely related antibiotics. It is a protein complex. The most active component of bleomycin is known as bleomycin A2 and another protein is known as bleomycin B1. In humans, bleomycin A2 is biologically active and bleomycin B1 is biologically inactive. Protein binding of bleomycin has not been studied.

Bleomycin is widely distributed throughout the body with a mean volume of distribution of 14 L/kg (range 10-30 L/kg).

**CLINICAL PHARMACOLOGY**

**Mechanisms of Action**

Bleomycin has no primary effect on the immune system. It is inactivated by a cytosolic cysteine proteinase enzyme, bleomycin hydrolase. The enzyme is encoded by the bleomycin resistance (ble) gene which is present in tumor cells. Bleomycin is minimally plasma bound. Protein binding of bleomycin has not been studied.

**Absorption**

Absorption has not been studied following intramuscular, subcutaneous, intraperitoneal, or intravenous administration. Rates of absorption following intravenous bolus injection range from 30 to 60 minutes. Systemic bioavailability of bleomycin following intravenous bolus injection is 100% and 70% following intramuscular and subcutaneous administrations, respectively, and 45% following intramuscular and intravenous administrations, respectively, following intramuscular and subcutaneous administrations, respectively, and 45% following intramuscular and subcutaneous administrations, respectively, and 45% following intramuscular and subcutaneous administrations, respectively.

Following intramuscular and subcutaneous administrations, the peak plasma concentration occurs approximately 45 minutes after injection. Following intravenous bolus injection, the peak plasma concentration occurs within 2 minutes and the terminal half-life is approximately 3 hours. Following intravenous bolus injection, the peak plasma concentration occurs within 2 minutes and the terminal half-life is approximately 3 hours.

**Distribution**

Bleomycin is widely distributed throughout the body with a mean volume of distribution of 15 L/kg in patients following a 5 unit/kg intravenous bolus dose. Plasma clearance in patients with normal renal function is 180 mL/min.

**Metabolism**

Bleomycin is inactivated by a cytosolic cysteine protease enzyme, bleomycin hydrolase. The enzyme is encoded by the bleomycin resistance (ble) gene which is present in tumor cells. Bleomycin is minimally plasma bound.

**Excretion**

The primary route of excretion is the urine. About 65% of the administered dose is excreted in urine within 24 hours. In patients with normal renal function, plasma concentrations of bleomycin decrease biexponentially with a mean terminal half-life of 2 hours following intravenous bolus administration. Total body clearance and renal clearance averaged 112 mL/min and 23 mL/min, respectively.

Following intramuscular administration to patients with normal renal function, a lower percentage of the dose is excreted in urine than with intravenous administration.

**Special Populations**

**Age**

The effects of age, gender, and race on the pharmacokinetics of bleomycin have not been evaluated.

**Pediatric**

Children of 3 years of age have higher total body clearance than adults, 71 mL/min versus 51 mL/min, respectively, following intravenous bolus administration. Children of more than 8 years of age have comparable clearance as in adults.

In children with normal renal function, plasma concentrations of bleomycin decline biexponentially with a mean volume of distribution and terminal half-life of bleomycin in children appears comparable to that in adults.

**Aged**

Renal insufficiency markedly alters bleomycin elimination. The terminal half-life of bleomycin in patients with normal renal function decreases. Dose reductions were proposed for patients with creatinine clearance values <60 mL/min (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

**Hepatic Insufficiency**

The effect of hepatic insufficiency on the pharmacokinetics of bleomycin has not been evaluated.

**Drug Interactions**

**WARNINGS**

It is recommended that for Bleomycin for Injection, USP be administered under the supervision of a qualified physician experienced in the use of cytotoxic chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

**Pulmonary Fibrosis**

The most serious toxic effect associated with bleomycin is pulmonary fibrosis. The most frequent presentation in patients uncomorbid for pre-existing pulmonary disease is eosinophilic pneumonitis. The incidence of pulmonary fibrosis in patients receiving bleomycin has been observed in young patients and those treated with low doses.

A severe idiopathic reaction consisting of hypogammaglobulinemia, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of patients treated with bleomycin.

**ADVERSE REACTIONS**

**Idiosyncratic Reactions**

**Pulmonary**

Because bleomycin is eliminated predominantly through renal excretion, the incidence of pulmonary fibrosis is greater in patients with impaired renal function. In studies of bleomycin, total body clearance of bleomycin decreased from 130 to 10 mL/min as the cumulative dose of bleomycin increased from 300 mg. Terminal half-lives of bleomycin also increased from 4 to 8 hours. Fatal pulmonary toxicity has been reported in a patient with unreported concomitant-induced renal oliguria.

**Clinical Studies**

**Malignant Pleural Effusion**

The activity and efficacy of bleomycin 60 units and tetracycline (1 g) is a treatment for malignant pleural effusion. Patients were randomized to placebo or bleomycin plus tetracycline. The patients were followed for 35% survival. Bleomycin has been shown to be effective in patients with malignant pleural effusion. Specifically, in one report of 12 children receiving concomitant captopril with bleomycin, total body clearance of bleomycin decreased by 10% to 18 mL/min as the cumulative dose of captopril increased to 300 mg. Terminal half-lives of bleomycin also increased from 4 to 8 hours. Fatal pulmonary toxicity has been observed in a patient with unreported concomitant-induced renal oliguria.

**INDICATIONS AND USAGE**

Bleomycin for Injection, USP should be considered a palliative treatment. It has been shown to be useful in the management of the following malignancies either as a single agent or in proven combinations with other approved chemotherapeutic agents:

**Squamous Cell Carcinoma**

Head and neck (including mouth, tongue, larynx, esophagus, skin, sebaceous, and sweat glands, parotid, submandibular salivary, exocrine pancreas, skin, breast, larynx, anus, cervix, and vulva.

**Malignant Pleural Effusion**

Bleomycin for Injection, USP should be considered the mainstay of management of malignant pleural effusion and prevention of recurrent pleural effusions.

**CONTRAINDICATIONS**

Administration of bleomycin is contraindicated in patients who have demonstrated a hypersensitivity or an idiosyncratic reaction to it.

**WARNINGS**

Pulmonary toxicity following 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.

Pulmonary fibrosis is a dose-related effect that appears to be reversible. It is dose related in nature and 100 units/kg of bleomycin every other day is not associated with pulmonary fibrosis. The frequency of pulmonary fibrosis increases with dose administration. Frequent chest X-ray examinations are recommended (see ADVERSE REACTIONS).

A severe idiopathic reaction consisting of hypogammaglobulinemia, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of patients treated with bleomycin. These reactions may occur at any time after initiation of therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function.

**Usual daily dose**

A single daily dose of bleomycin can be given intravenously, intramuscularly, subcutaneously, intrapleurally, or intraperitoneally. The usual daily dose is 60 units/kg/day. This dose should not be exceeded. A single intravenous bolus injection of 30 units/kg is recommended.

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cell cancers respond more slowly, sometimes requiring as long as 3 weeks before a partial response (PR) occurs. However, these changes are not predictive of the development of pulmonary fibrosis.

The microscopic tissue changes due to bleomycin treatment include bronchial squamous metaplasia, reactive microabscesses, alveolar epithelial cell fibrosis, fibrosis of the alveolar duct, and alveolar wall thickening. These changes may cause capillary changes and subsequent fibrosing exudation into alveoli producing a change similar to those found in fibrosing alveolitis. Therefore, histologic changes are seen in patients who have been treated with bleomycin and in those with idiopathic pulmonary fibrosis resembling the Hamman-Rich syndrome. These microscopic findings are nonspecific; similar changes are seen in radiation pneumonitis and pneumotoxic pneumonitis.

To monitor the extent of pulmonary toxicity, roentgenograms of the chest should be performed before, during, and 6 to 8 weeks after therapy. If primary changes are seen in the chest x-ray, treatment should be discontinued until it can be determined if they are drug related. Pulmonary fibrosis, or fibrosing alveolitis, may be a complication of treatment of bleomycin. There is a lack of correlation between the diffusion capacity for carbon monoxide (DLco), treatment with bleomycin may be an indicator of subclinical pulmonary toxicity. It is recommended that the DLco be monitored monthly if it is to be employed to detect pulmonary toxicity, and that it be increased in the presence of bleomycin treatment. In the presence of bleomycin treatment. In the presence of bleomycin treatment.

Because of bleomycin's sensitization of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when surgery is administered in surgery. While long exposure to very high oxygen concentrations is a known cause of lung damage, after bleomycin administration, lung damage can occur at lower concentrations that are usually considered safe. Supported recommendations suggest the use of oxygen concentrations of approximately that of room air (21%) during surgery and the postoperative period.

2. Monitor carefully fluid replacement, focusing more on colloid administration than on crystalloid replacement.

Sudden onset of an acute chest pain syndrome suggestive of pulmonary embolism has been reported during bleomycin infusions. Although each patient must individually evaluated, further courses of bleomycin should not be continued.

Pulmonary fibrosis does not appear to be related to the intrathoracic administration of bleomycin has been reported.

Idiopathic Reactions

In addition to the fibrotic changes in the lung tissue, patients treated with bleomycin, an idiopathic, non-cancer chemotherapy, has been noted frequently. This reaction may be delayed up to several hours, and usually occurs after the first or second dose of bleomycin. It consists of hypotension, mental confusion, fever, chills, and widening. Treatment is symptomatic including voluntary evacuation of the bowel and rectum, and corticosteroids.

Integument and Mucous Membranes

These adverse reactions have been reported in approximately 30% of patients treated with bleomycin. The most common skin reactions are erythema, rash, pruritus, and tenderness of the skin. Hyperpigmentation, netrtraception, pruritus, and pruritus have also been reported. It was necessary to discontinue bleomycin for Injection in 2% of treated patients because of these toxicities.

Scleroderma-like skin changes have been reported.

Skin toxicity is a relatively late manifestation usually developing in the second and third weeks of therapy. Erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperpigmentation, netrtraception, pruritus, and pruritus have also been reported. It was necessary to discontinue bleomycin for Injection in 2% of treated patients because of these toxicities.

Other

Vascular toxicities coincident with the use of bleomycin in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous and include pulmonary embolism, myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications but also are reported. The occurrence of pulmonary embolism in patients treated with bleomycin in combination with vincristine, without prophylaxis or in patients with bleomycin as a single agent. It is currently unknown if the cause of Raynaud's phenomenon in these patients is similar to hyaline membrane formation and progressing to a diffuse interstitial pulmonary fibrosis resembling the Hamman-Rich syndrome. These microscopic findings are nonspecific; similar changes are seen in radiation pneumonitis and pneumotoxic pneumonitis.

Fever, chills, and vomiting have been reported. Anorexia and weight loss have been reported in approximately 50% of treated patients. They consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperpigmentation, netrtraception, pruritus, and pruritus have also been reported. It was necessary to discontinue bleomycin for Injection in 2% of treated patients because of these toxicities.

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In approximately 1% of the lymphoma patients treated with bleomycin, an idiosyncratic reaction has been noted. The reaction may be delayed up to several hours, and usually occurs after the first or second dose of bleomycin. It consists of hypotension, mental confusion, fever, chills, and widening. Treatment is symptomatic including voluntary evacuation of the bowel and rectum, and corticosteroids.

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