PRODUCT MONOGRAPH

PrBiCNU*

carmustine for injection U.S.P

Lyophilized Powder, 100 mg/vial

Antineoplastic Agent

Marcan Pharmaceuticals Inc.
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THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION: BiCNU (CARMUSTINE) IS A POTENT DRUG 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.

ACTIONS AND CLINICAL PHARMACOLOGY

BiCNU alkylates DNA and RNA and has been shown to inhibit several enzymes by carbamoylation of amino acids in proteins. Carmustine is not cross resistant with other alkylating agents.

It is thought that the antineoplastic and toxic activities of BiCNU may be due to metabolites. In a series of in vivo and in vitro experiments with formate ^{14}C, adenine-8-^{14}C and DL-leucine-4,5-^{3}H, Wheeler and Bowdon obtained results indicating that carmustine interferes with the de novo synthesis of purine nucleotides and with the conversion of purine nucleotides to components of DNA but to a much lesser extent of RNA. Inhibition of DNA synthesis occurred in the absence of inhibition of the synthesis of protein. In a more recent study, D.P. Groth et al confirmed that carmustine altered de novo purine biosynthesis. It is suggested that carmustine inhibits a reaction(s) involved with the insertion of the C-8 position of the purine ring. These biochemical effects are quite similar to those described by Wheeler and Alexander for the accepted biological alkylating agents like nitrogen mustards, and suggest the inclusion of carmustine in this class of agents.

On the other hand, by chemical evaluation the alkylating properties of carmustine have been shown to be quite weak compared to the above mentioned alkylating agents and it is still an open question whether this activity is sufficient to account for the observed biological effects of carmustine.

Because of the high lipid solubility and the relative lack of ionization at a physiological pH, BiCNU readily crosses the blood brain barrier. Intravenously administered BiCNU is rapidly degraded, with no intact drug detectable after 15 minutes. Approximately 60 to 70 percent of a total dose is excreted in the urine in 96 hours and about 10 percent as respiratory CO_2. The fate of the remainder is undetermined.

INDICATIONS AND CLINICAL USES

BiCNU (carmustine) is indicated as palliative therapy to surgery and radiotherapy or in combination therapy with other chemotherapeutic agents in the following:

1. Primary brain tumors

   An overall 47% response rate with BiCNU compares favorably with any other method of treating brain tumors, such as glioblastoma, brainstemglioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors.

2. Malignant lymphomas

   Hodgkin's disease, non-Hodgkin's lymphomas either alone or in combination with other chemotherapeutic agents, in patients who became resistant or did not respond to standard chemotherapeutic agents including radiotherapy.

   In studies in which BiCNU was used to treat patients with Hodgkin's disease resulted in a 40-50% response rate.

3. Multiple myeloma

   BiCNU is effective in the treatment of myeloma producing improvement in 30% of the patients. In combination with prednisone, it is particularly active in that it shows 70% response. BiCNU has been used as part of a five-drug regimen (melphalan, cyclophosphamide, prednisone and vincristine) in 29 patients with a 90% response rate.

4. Malignant melanoma (disseminated)

   In combination with vincristine sulfate, BiCNU has been shown to give response rates up to 45% in malignant melanoma.

5. Gastrointestinal carcinoma

   A 12.5% response rate was obtained with BiCNU in the therapy of gastrointestinal cancer. Such a result suggests the use of BiCNU only after other more appropriate agents have failed in advanced disease.

CONTRAINDICATIONS

BiCNU (carmustine) is contraindicated in individuals who have demonstrated a previous hypersensitivity to it or any component of its formulation.

WARNINGS

Pulmonary Toxicity: Early onset pulmonary toxicity usually occurs within 3 years of therapy and is characterized by pulmonary infiltrates and/or fibrosis, and cases of fatal pulmonary toxicity have occurred. Age of onset has been reported from 1 year and 10 months to 72 years of age. Risk factors include smoking, the presence of a respiratory condition, pre-existing radiographic abnormalities, sequential or concomitant thoracic irradiation, and association with other agents that cause lung damage. The incidence appears to be dose related with total cumulative doses of 1200-1500 mg/m^2 being associated with increased likelihood of lung fibrosis.

Cases of late pulmonary fibrosis, occurring up to 17 years after treatment, have also been reported. In a recent long-term follow-up of 17 patients who survived childhood brain tumors,

eight (47%) died of lung fibrosis. Of these eight deaths, two occurred within 3 years of treatment, and six occurred 8-13 years after treatment. Of the patients who died, the median age at treatment was 2.5 years (ranging from 1-12); the median age of the long term survivors was 10 years (5-16 years at treatment). All five patients treated below the age of 5 years have died of pulmonary fibrosis. In this series, dose of BiCNU did not influence fatal outcome nor did co-administration of vincristine or spinal irradiation. Of the remaining survivors available for follow-up, evidence of lung fibrosis was detected in all patients. The risks and benefits of BiCNU therapy must be carefully considered, especially in young patients, due to the extremely high risk of pulmonary toxicity.

Bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, is a common and severe toxic effect of BiCNU (carmustine).

The occurrence of acute leukemia and bone marrow dysplasias have been reported in patients following nitrosourea therapy.

BiCNU has been administered directly into the carotid artery; this procedure is investigational and has been associated with ocular toxicity.

PRECAUTIONS

BiCNU (carmustine) should be administered by individuals experienced with antineoplastic therapy. Since delayed bone marrow toxicity is the major toxicity, complete blood counts should be monitored frequently for at least 6 weeks after a dose. Repeat doses of BiCNU should not be given more frequently than every 6 weeks. The bone marrow toxicity of BiCNU is cumulative, and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see Dosage Adjustment Table under DOSAGE AND ADMINISTRATION).

Liver and renal function should also be monitored.

Baseline pulmonary function studies should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70 percent of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DL_{co}) are particularly at risk.

Since pulmonary toxicity has been reported to occur with a frequency ranging up to 30%, patients on BiCNU therapy should be instructed to report immediately any signs of respiratory complications. In such cases, therapy should be discontinued and evaluation of respiratory gas exchange and spirometry should be performed. If necessary, patients should then be treated with corticosteroids.

Injection site reactions may occur during the administration of BiCNU (see ADVERSE REACTIONS). Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

Pregnancy

Safe use in pregnancy has not been established. BiCNU is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. BiCNU also affects fertility in male rats at doses somewhat higher than the human dose. BiCNU is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. The benefit to the mother versus the risk of toxicity to the mother and fetus must be carefully weighed.

Nursing Mothers: It is not known whether BiCNU is excreted in human milk. Because of the potential for serious adverse events in nursing infants, nursing should be discontinued while taking BiCNU.

Pediatric Use: BiCNU should be used with extreme caution in children due to the high risk of pulmonary toxicity (see ADVERSE REACTIONS).

Geriatric Use: No data from clinical studies of BiCNU are available for patients 65 years of age and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dose range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

BiCNU and its metabolites are substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and renal function should be monitored.

Drug Drug Interaction

Greater myelotoxicity (e.g. leukopenia and neutropenia) has been reported when carmustine was combined with cimetidine.

ADVERSE REACTIONS

Hematopoietic

Thrombocytopenia (platelets below 100,000 cells/mm^3) and leukopenia (leukocytes below 4,000 cells/mm^3).

Delayed myelosuppression is a frequent and serious adverse event associated with BiCNU administration. It usually occurs 4 to 6 weeks after drug administration and is dose-related. Platelet nadirs occur at 4 to 5 weeks; leukocyte nadirs occur at 5 to 6 weeks post therapy. Myelosuppression is the major dose limiting factor with BiCNU as is with so many drugs of this type. Thrombocytopenia is generally more severe than leukopenia; however, both may be dose limiting toxicities. Anemia also occurs but it is generally less severe.

BiCNU may produce cumulative myelosuppression (see WARNINGS).

The occurrence of acute leukemia and bone marrow dysplasias have been reported in patients following long term nitrosourea therapy.

Greater myelotixicity (e.g. leukopenia and neutropenia) has been reported when carmustine was combined with cimetidine (see PRECAUTIONS, Drug Drug Interaction).

Pulmonary Toxicity: BiCNU-induced pulmonary toxicity has been reported to occur with a frequency ranging up to 30% (see WARNINGS).

Hepatic: BiCNU produces reversible hepatic toxicity which is manifested by increased transaminase, alkaline phosphatase and bilirubin levels when high doses are employed. It has been rarely noted at therapeutic doses. Hepatotoxicity is delayed up to 60 days after dosing.

Skin: Burning and hyperemia at the site of injection are common, but true thrombosis is rare. Accidental contact of reconstituted BiCNU with the skin has caused hyperpigmentation of the affected areas. Within 2 hours after rapid IV administration of BiCNU intense flushing of the skin and suffusion of the conjunctiva could last for about 4 hours. Skin rash has also been reported.

Local soft tissue toxicity has been reported following extravasation of BiCNU. Infiltration of BiCNU may result in swelling, pain, erythema, burning sensation and skin necrosis.

Renal: Renal abnormalities consisting of decreases in kidney size, progressive azotemia and renal failure have been reported in patients who receive large cumulative doses after prolonged therapy with BiCNU and related nitrosoureas. Kidney damage has also been reported occasionally in patients receiving lower total doses.

Neurological: There have been rare instances of encephalopathy reported.

Gastrointestinal: Nausea and vomiting frequently appear within 2 hours and usually last 4-6 hours and are dose-related. Prior administration of antiemetic and sedatives is effective in diminishing and sometimes preventing this adverse event.

Endocrine: Gynecomastia has been observed in a few rare cases.

Cardiovascular: Hypotension, tachycardia.

Other: Muscular pain has been infrequently reported. Neuroretinitis, chest pain, headache, allergic reactions.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the case of overdosage, the patient should be treated symptomatically.

DOSAGE AND ADMINISTRATION

BiCNU (carmustine) is administered by slow intravenous infusion over a 1- to 2-hour period. BiCNU SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION. (See ADVERSE REACTIONS and PHARMACEUTICAL INFORMATION - Preparation of Intravenous Solutions)

The recommended dose of BiCNU as a single agent in previously untreated patients is 200 mg/m² intravenously every 6 weeks. This may be given as a single dose or divided into daily injections such as 100 mg/m² on 2 successive days. When BiCNU is used in combination with

other myelosuppressive drugs or in patients in whom bone marrow reserve is depleted, the doses should be adjusted accordingly.

A repeat course of BiCNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000cells/mm^3, leukocytes above 4,000cells/mm^3) this usually occurs within six weeks. Blood counts should be monitored frequently and repeat courses should not be given before six weeks because of delayed toxicity.

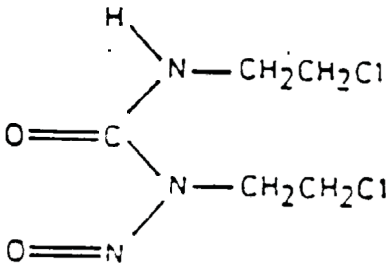
Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:

Nadir After Prior Dose		Percent of Prior Dose to be Given
Leukocytes	Platelets	
> 4000	> 100,000	100%
3000 - 3999	75,000 - 99,999	100%
2000 - 2999	25,000 - 74,999	70%
< 2000	< 25,000	50%

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Trade Name: BiCNU
Proper Name: Carmustine
Chemical Name: 1,3 Bis (2-chloroethyl)-1-nitrosourea



Molecular Formula: $C_5H_9N_3O_2Cl_2$
Structural Formula:

Molecular Weight: 214.06

Description: BiCNU, (carmustine) is a nitrosourea which comes in the form of thin, lacy, brittle, pale yellow flakes having a melting point of 30.5 - 32.0°C. It is light sensitive and vesicant and decomposes readily at room temperature. It is poorly soluble in water and in saline; quite soluble in propylene glycol; soluble in 50% alcohol and highly soluble in lipids.

It is most stable at pH 4, but in more acidic as well as in aqueous solutions of pH greater than 7, it is short lived.

The mode of decomposition of carmustine has been shown by Montgomery et al to vary considerably with the experimental conditions. The following decomposition products were identified, 2-chloroethanol, 1-3-bis (2-chloroethyl) urea, acetaldehyde, HCl, N_2 and derivatives of 2-chloroethyl isocyanate.

STABILITY AND STORAGE RECOMMENDATIONS

The unopened vial may have a physical appearance ranging from lacy flakes to a congealed mass, with no evident degradation of the active ingredient, carmustine. Do not use if product has liquified.

Unopened vials of the dry powder should be shipped and stored under refrigeration (2°C to 8°C). Alternatively, BiCNU may be shipped on dry ice and subsequently stored under refrigeration (2°C-8°C). The recommended storage of unopened vials prevents significant decomposition until expiration date indicated on package. Normal room temperature storage (22°C) of the unopened vials will result in a slow decomposition of the drug (approximately 3%) in 36 days.

IMPORTANT NOTE

BiCNU (carmustine) has a low melting point (approximately 30.5-32.0°C). Vials of the drug exposed to this temperature or above will cause the drug to liquify and appear as an oil film in the bottom of the vials. This is a sign of decomposition and vials should be discarded. If there is a question of adequate refrigeration upon receipt of this product, immediately inspect the larger vial in each individual carton. For inspection, hold the vial to a bright light. The carmustine will appear as a very small amount of dry flakes or dry congealed mass. If this is evident, BiCNU is suitable for use and should be refrigerated immediately.

Glass containers were used for the stability data provided in this section. Only use glass containers for BiCNU administration.

RECONSTITUTION

Preparation of Intravenous Solutions

To facilitate reconstitution, allow the supplied sterile diluent (absolute ethanol) to come to controlled room temperature (15° to 30°C) before mixing.

Dissolve BiCNU completely with 3 mL of the supplied sterile diluent and then aseptically add 27 mL of Sterile Water for Injection, U.S.P. to the alcohol solution. Each mL of the resulting solution will contain 3.3 mg of BiCNU in 10% ethanol. (Solution in the ethanol must be complete before sterile water for injection is added). Accidental contact of reconstituted BiCNU with the skin has caused transient hyperpigmentation of the affected areas. If BiCNU lyophilized material or solution contacts the skin, immediately wash thoroughly with soap and water. If BiCNU lyophilized material or solution contacts mucosa, flush thoroughly with water.

Reconstitution as recommended results in a clear, colorless to light yellow solution which may be further diluted with Sodium Chloride for Injection, U.S.P. or 5% Dextrose for Injection, U.S.P. The reconstituted solution should be used intravenously only and should be administered by IV infusion over a 1- to 2-hour period. Injection of BiCNU over shorter periods of time may produce intense pain and burning at the site of injection. (See ADVERSE REACTIONS)

Stability of Reconstituted Solutions

The lyophilized dosage formulation contains no preservatives and is not intended as a multiple dose vial.

After reconstitution as recommended, BiCNU is stable for 24 hours under refrigeration (2°C - 8°C).

The reconstituted solution further diluted with 500 mL of Sodium Chloride Injection, U.S.P. or 5% Dextrose Injection, U.S.P., in glass containers, results in a solution which should be utilized within 8 hours and be protected from light. These solutions are also stable for 24 hours under refrigeration (2-8°C) and an additional 6 hours at room temperature (25°C) protected from light. Further diluted BiCNU should be used immediately if not refrigerated.

NOTE: Reconstituted vials stored under refrigeration should be examined for crystal formation prior to use. If crystals are observed, they may be redissolved by warming the vial to room

temperature with agitation.

SPECIAL INSTRUCTIONS

Handling and Disposal

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Accidental contact of reconstituted BiCNU with the skin has caused burning and hyperpigmentation of the affected area.

Personnel preparing BiCNU should wear safety glasses and disposable gowns and masks. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing BiCNU lyophilized powder for injection. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

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

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

3. Personnel regularly involved in the preparation and handling of BiCNU should have bi-annual blood examinations.

AVAILABILITY

BiCNU (carmustine) is available in a package that includes a 30 mL amber glass vial containing 100 mg of carmustine and a glass vial containing 3 mL of sterile diluent.

PHARMACOLOGY

ANIMAL

Plasma Level

After a single IV injection of 10 mg/kg in the dog, the plasma level of intact carmustine reaches a peak level of 30 mcg/mL with a half-life of less than 15 minutes. The same half-life has also been found in the mouse. It is interesting to note that plasma samples taken as early as 5 minutes after oral or parenteral administration in the monkey did not contain intact carmustine.

In the monkey, the half-life of ^{14}C labeled carmustine and its degradation products as determined by ^{14}C counts is prolonged up to 22 hours after a single IV injection of 10 mg/kg.

One minute after IV infusion, intact carmustine could be detected in the CSF of the dog and it reaches 48% of the plasma concentration after equilibration.

Following IV injection, intact carmustine was not characterized in the CSF of the monkey.

Studies with ^{14}C labeled carmustine showed that in the dog, after a 10 mg/kg IV injection, radioactivity enters the CSF rapidly and reaches 18% of the plasma level one minute following drug administration. Equilibration occurs by 15 minutes and the concentration of carmustine reaches about 60% that of plasma.

In the monkey, 15 minutes after IV injection, the level of carmustine in the CSF was 73% that of plasma and after 90 minutes as high as 90%.

Urinary Excretion

Ten minutes after a single intravenous injection in the dog, intact carmustine begins to appear in the urine. The excretion reaches a peak at about 2 hours and then gradually tapers off until 3 hours later. Nevertheless, in no case is the total amount of unchanged carmustine excreted in 4 hours in excess of 0.1% of the dose.

In mice, the urinary excretion of ^{14}C carmustine is fast. For instance, 4 hours after a 10 mg/kg IV injection it reached 62% of the administered dose. This excretion is initially faster after intraperitoneal administration than subcutaneous or oral, but after 24 hours no significant differences are noted between the different dose routes: the excretion level being close to 80%.

In the monkey, 48 hours after a 10 mg/kg IV injection of ^{14}C carmustine, an average of 68% of ^{14}C radioactivity is recovered in the urine. Further urinary excretion is minimal after 48 hours.

In the dog, the urinary excretion is rather slow with 16% in 2 hours and 30% in 6 hours after a 10 mg/kg IV dose of ^{14}C carmustine.

Pulmonary Excretion

Expired CO_2 was collected from mice given an intraperitoneal dose of ^{14}C labeled carmustine. The 24 hours recovery of $^{14}CO_2$ accounted for an average of 8.5% of the radioactive dose. After IV administration into monkeys no more than 2% of the dose was collected as $^{14}CO_2$.

HUMAN

Protein Binding

The average extent of binding of carmustine with human plasma proteins is about 80% at 0°C. (The experiments were carried out at 0°C because of the extreme instability of carmustine in plasma).

Plasma Level

Plasma samples taken as early as 5 minutes after oral or parenteral drug administration did not contain intact carmustine. Plasma levels of the radioactivity were prolonged with a half-life of about 34 hours for the orally and 67 hours for the intravenously administered ^{14}C carmustine.

C.S.F.

After IV administration of ^{14}C carmustine, radioactive ^{14}C was found in the CSF of man equilibrating with plasma radioactivity in about 1 hour showing 97 and 30% of plasma level in 2 men, respectively.

Urinary Excretion

Extremely small amounts of intact carmustine were detected in urine samples collected at one-half hour following drug administration (IV or oral). After the second half hour urine samples did not contain unaltered carmustine.

Urinary excretion of the radioactivity was strikingly similar in all patients regardless of the route of administration (IV or oral) and quite comparable to monkeys. By 96 hours, an average of 65% of the isotope had been recovered in the urine.

Pulmonary Excretion

Over 24 hours, the radioactivity excretion of ^{14}C carmustine as $^{14}CO_2$ was approximately 10% of the dose after oral administration and 6% when given IV. Although carmustine is well absorbed after oral, intraperitoneal and subcutaneous administration, it is mainly used by the intravenous route. The active moiety of carmustine is still unknown but the high degradation rate of carmustine in plasma suggests that the biological activity as well as the delayed toxicity of carmustine are related at least partly to its degradation products. The in vitro decomposition of carmustine has been studied quite extensively. However, to date, nothing is known on its biodegradation except for the fact that part of it is excreted as CO_2 as determined with ^{14}C labeled carmustine.

TOXICOLOGY

Acute Toxicity

LD_{50} of carmustine was established in the rat and the mouse after different administration routes.

Species	Dose Range (mg/kg)	Route	Calculation of LD_{50} Based on Observations period of	LD50
Mouse	25.1 - 79.4	IV	21 days	45
Mouse	50.0 - 60.0	IM	48 days	23
Mouse	15.9 - 100.0	Oral (methyl-cellulose)	21 days	42
Mouse	20.0 - 112.0	IP	25 days	45
Rat	14.0 - 50.0	IV	23 days	20
Rat	10.0 - 39.8	Oral	23 days	20
Rat	10.0 - 39.8	Oral in saline	23 days	20

It is interesting to note the similarities between the IV and oral route toxicity both in the mouse and the rat.

Delayed toxic manifestations of carmustine have been shown in various animals including the mouse, rat, dog and monkey. They involve chronologically the following systems:

Hematopoietic System

Initially carmustine deletes the several hematopoietic elements of the marrow and lymphoidal components of the spleen and nodes resulting in marked and prolonged (2-3 weeks) leukopenia and thrombocytopenia. Marrow depression was reversible if the animal survived.

Liver

Although delayed toxicities are commonly seen after exposure of experimental animals to alkylating agents, carmustine has shown striking delayed hepatic toxic manifestations ranging from 14 to 119 days.

After a single oral dose of carmustine in rats, the hepatic function was assessed by a series of standard techniques. By 1 week, all doses of carmustine prolonged pentobarbital hypnosis and BSP retention, later, elevations of serum bilirubin appeared, but these were delayed by as long as 63 days at the lowest dose. Serum bilirubin was direct-reacting at early stages but later shifted to indirect-reacting coincidental with a reduction of BSP retention.

Histopathologic study revealed early pericholangitis and necrosis of bile ductules. Later biliary hyperplasia and cirrhosis developed. These findings disclose a unique ability of carmustine to produce a prolonged and progressive bimodal toxicity resulting in hyperbilirubinemia. These toxic manifestations were also coupled with an increase in ALT and AST as well as alkaline

phosphatase.

Renal

Renal damage without distinctive kidney pathology was reflected by elevated BUN in the monkey and the dog following oral or IV dosage of carmustine.

Others

It may be noted that weight loss during treatment with carmustine was often seen and it appears that this is a manifestation of distinct toxic effects of carmustine. Pertinent to that observation is the finding that carmustine causes a significant reduction in glucose (54.4%) and water (50.0%) absorption from the gut.

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