Administration of BCNU into the carotid artery as treatment for malignant astrocytomas has produced retinal and brain toxicity. It is unclear whether the BCNU diluent, ethanol, is the cause of the toxicity, but the elimination of the ethanol is an attractive possibility. Clinically, decreasing the ethanol from 2.0 ml/100 mg BCNU to 0.75 ml/100 mg BCNU resulted in a marked decrease in eye toxicity. To simulate this clinical situation, three 500-mg solutions of BCNU, ethanol, and saline were prepared, decreasing the ethanol concentration from 3.0 ml to 2.0 ml to 0.75 ml/100 mg BCNU. The amount of BCNU recovered in vitro after simulated clinical administration of the three solutions decreased from 84.9% to 38.3% as the diluent decreased. Therefore, drug delivery at a fixed BCNU dose will decrease with the amount of ethanol diluent used. The clinical decrease in eye toxicity must be partly attributed to a decrease in the amount of BCNU delivered to the retina. Simulated administration of a solution of 500 mg BCNU/150 ml of 5% dextrose in water (D\textsubscript{5}W) gave 83.7% BCNU recovery. The D\textsubscript{5}W gives solubility comparable to that provided by 3.0 ml ethanol to each 100 mg BCNU, and its use eliminates ethanol as a potential retinal and brain toxin.

**KEY WORDS**  
malignant astrocytoma • intra-arterial chemotherapy • BCNU solubility • glioma • ethyl alcohol

*I* intra-arterial BCNU (1,3-bis-(2-chloroethyl)-1-nitrosourea) has been increasingly used in the regional treatment of malignant supratentorial gliomas.\textsuperscript{1,5,7} Although this treatment modality is becoming more common, it is not without risk of serious complications. Delayed ipsilateral ocular toxicity, with retinal hemorrhages and nerve fiber-layer infarcts producing visual loss have been reported in animal and human studies with intracarotid BCNU infusions.\textsuperscript{4,6,8,11} The susceptibility of human brain tissue to damage by intra-arterial BCNU is also suggested by several reports.\textsuperscript{2,8,9}

The manufacturer of BCNU\textsuperscript{*} recommends that each 100 mg of drug be reconstituted with 3.0 ml absolute ethyl alcohol (ETOH) before adding a suitable volume of normal saline or water for administration. Early clinical trials with BCNU reported solubility of up to 150 mg BCNU/ml absolute ETOH, and also described drug solubility in water of up to 4 mg BCNU/ml water.\textsuperscript{3} Initial clinical trials at the University of Michigan used 2 cc ETOH/100 mg BCNU but this was decreased to 0.75 cc ETOH/100 mg BCNU with a concomitant decrease in the incidence of eye toxicity. We did not know whether the decrease in alcohol diluent reduced drug solubility and delivery, or if a relationship existed between the amount of alcohol used in intra-arterial BCNU chemotherapy and the treatment complications.

This study was undertaken to compare in vitro recovery of 500 mg BCNU using three different alcohol mixing systems, simulating our clinical administration techniques. Since alcohol elimination is attractive, we also measured drug recovery from a BCNU and water solution.

**Materials and Methods**

The BCNU is supplied in light-resistant vials containing 100 mg of lyophilized powder, accompanied by 3.0-ml vials of absolute ETOH diluent. Since 500 mg BCNU is not an uncommon dose, at 200 to 300 mg/
BCNU solubility in ethanol or dextrose and water

sq m, four different 500-mg BCNU solutions were prepared for study.

Solution 1 was prepared according to the manufacturer's recommendations by adding 3.0 ml ETOH to each of five vials of 100 mg BCNU. The vials were agitated by hand before adding 7.0 ml normal saline to each. After further mixing, the ETOH was withdrawn by needle from consecutive vials into a single 50-ml plastic syringe and the total volume was corrected to 50 ml with normal saline. The syringe was gently agitated to further mix the solution.

Solution 2 was prepared by adding 2.0 ml ETOH to each of five vials of 100 mg BCNU. The vials were agitated, as in Solution 1, before and after the addition of 8.0 ml normal saline to each. The remainder of the procedure described for Solution 1 was completed, resulting in a 50-ml solution in one syringe.

Solution 3 was prepared by adding 0.75 ml ETOH to each of five vials of 100 mg BCNU. The vials were agitated, as in Solution 1, before and after the addition of 9.25 ml normal saline to each vial. The reconstituted BCNU solution was further prepared as described for Solution 1.

Solution 4 was prepared by adding 30 ml 5% dextrose and water (D_2W) to each of five vials of 100 mg BCNU. Hand agitation for approximately 30 minutes was required to dissolve the BCNU. Agitation stopped when no residue or particulate matter could be seen in the vials. Once dissolved, each vial of ETOH was transferred by needle to one of three 50-ml plastic syringes. The syringes were then gently agitated.

Immediately after reconstitution and withdrawal to syringes, five 0.1-ml samples were taken from each solution. In a darkened room, each solution was then "hand administered" through plastic intravenous extension tubing in line with a 0.22-μ hyperalimentation filter into a graduated cylinder. The system was then flushed with 50 ml normal saline resulting in a total volume of 100 ml for each of Solutions 1, 2, and 3, and 200 ml for Solution 4. The above procedure simulated the clinical situation. Immediately after infusion, the solutions in the graduated cylinders were mixed, followed by withdrawal of five 0.1-ml samples from each.

The BCNU content of the drug solution samples was assayed by high performance liquid chromatography. No sample preparation was necessary. Triplicate 5-μl injections of the drug solutions were accurately and reproducibly injected using the Wisp autosampler.† Intact BCNU was quantitated using a reverse-phase micron Bondapak C18 chromatography column‡ and ultraviolet detection at 254 nm. The mobile phase was a 50% methanol/water solution and the flow rate was 2.0 ml/min.

The drug peak heights were recorded and BCNU concentration determined from a calibration curve constructed from triplicate 5-μl injections of standard BCNU solutions. The variability of the triplicate injections was routinely less than 3%.

**Results**

The mean percentage of BCNU recovered varied markedly between solutions, and for Solutions 1, 2, and 3, declined significantly in relation to the amount of ETOH diluent (Table 1). Prior to administration, a mean percentage recovery of 88.8% was obtained from Solution 1 (3.0 ml ETOH/100 mg BCNU). The per-

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† Wisp autosampler manufactured by Waters Associates, Millipore Corp., 34 Maple Street, Milford, Massachusetts.
‡ Reverse-phase micron Bondapak C18 chromatography column manufactured by Waters Associates, Millipore Corp., 34 Maple Street, Milford, Massachusetts.
centage recovery of BCNU from Solution 2 (2.0 mg ETOH/100 mg BCNU) and Solution 3 (0.75 ml ETOH/100 mg BCNU) was 57.3% and 42.9%, respectively. The mean percent of BCNU recovered from Solution 4 (30 ml DsW/100 mg BCNU) was 98.3%.

Infusion of the solutions through tubing and a 0.22-μ hyperalimentation filter decreased the percent of BCNU recovered in all solutions. For the ETOH-diluted solutions, the mean percentage lost through infusion and filtering was 3.3%. The percentage lost from Solution 4 was 14.6%. After "infusion" and filtering, the greatest percentage recovery of BCNU was obtained from Solution 1 (84.9%) and Solution 4 (83.7%).

Discussion

Our results demonstrate a dramatic decrease in BCNU recovered in vitro as the alcohol diluent per 100 mg BCNU was decreased from 3.0 ml to 0.75 ml. Filtering the drug mixture with a 0.22-μ hyperalimentation filter, which is essential for safe drug administration, would further reduce the drug delivered to the patient. This study suggests that an anticipated drug dose of 250 mg/sq m would actually be 221 mg/sq m, 140 mg/sq m, and 95 mg/sq m, respectively, as the alcohol diluent is decreased from 3.0 ml to 2.0 ml to 0.75 ml/100 mg BCNU. When mixing these three study solutions, clarity and homogeneity visibly decreased as the alcohol decreased. A yellow oily residue adhered to the inside of the syringe after administration of Solutions 2 and 3, suggesting that less of the drug was in solution.

The alcohol and saline solvent system represents common clinical practice and, until recently, it was our practice to dilute 100 mg BCNU with 2.0 ml ETOH. We decreased the diluent to 0.75/100 mg BCNU, hoping to decrease ocular complications. Since decreasing the alcohol diluent, we have decreased the incidence of eye toxicity from approximately 60% to 15% (HS Greenberg, unpublished data). However, our recovery results indicate that we may also have decreased the amount of drug delivered by over 17% (comparing Solution 2 to Solution 3).

Recovery of BCNU after administration of the BCNU/DsW solution was excellent: the 83.7% recovered after filtering Solution 4 was comparable to the 84.9% recovered from Solution 1. The 14.6% BCNU lost after filtering the clear BCNU/DsW solution suggests that the drug was not completely dissolved. Preparation of a BCNU/DsW solution is time-consuming, requiring 30 minutes of vigorous shaking before there is no visible white powder. Subjectively, the BCNU/DsW solution was clearer than the BCNU/alcohol solutions. We suspect that few, if any, clinicians dissolve BCNU in water, perhaps due in part to lack of solubility information or to the inconvenient length of time required to dissolve the drug in water.

Ross, et al., recently described an in vitro BCNU solubility study comparing three different 100-mg BCNU mixtures: 2.0 ml ETOH/100 mg BCNU/25 ml normal saline, 30 ml 2% dimethyl sulfoxide (DMSO) and water/100 mg BCNU, and 30 ml DsW/100 mg BCNU. Percentages of drug recovered were, respectively: 102.2%, 97.9%, and 87.4% of predicted concentrations. Osmolarity of the alcohol/saline preparation was reported as far above the physiological range (1663 mOsm/liter). The clinical significance of this is unknown.

Our BCNU recovery results have prompted us to begin a trial of BCNU/DsW intra-arterial infusions. To prevent toxicity, the BCNU dose has been decreased from 250 to 150 mg/sq m, since drug solubility will double (comparing Solution 4 to Solution 3). Six patients have been treated with BCNU/DsW and the incidence of eye pain has remained unchanged. We have observed no other complications; however, no patient has received more than two treatments.

In summary, it is unclear whether ethyl alcohol used as a diluent for BCNU is toxic to human retinal and brain tissue. Studies suggest that BCNU with its solvent ethyl alcohol produces morbidity and mortality when given via the intra-arterial route for the treatment of malignant gliomas. Intra-arterial BCNU, in varying doses diluted with varying amounts of alcohol, is being administered. This study suggests that widely varying amounts of drug may be delivered to the patients, depending on the amount of alcohol diluent, further compromising comparison between protocols. Several factors combine to support the elimination of alcohol from BCNU solutions for intra-arterial use. Alcohol may contribute to retinal and brain toxicity, the osmolarity is far above the physiological range, and a comparable amount of drug can easily be delivered to the patient in a solution with dextrose and water.

References


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Address reprint requests to: Harry S. Greenberg, M.D., Department of Neurology, B4913 CFOB, Box M056, University of Michigan Hospitals, Ann Arbor, Michigan 48109.