Treatment of Human Glioma and Medulloblastoma Tumor Lines in Athymic Mice with Diaziquone and Diaziquone-based Drug Combinations

S. Clifford Schold, Jr., 1 Henry S. Friedman, 2 Thorir D. Bjornsson, 3 and Darell B. Bigner 4

Departments of Medicine (Neurology) [S. C. S.], Pediatrics [H. S. F.], Pharmacology (Clinical Pharmacology) [T. D. B.], and Pathology (Neuropathology) [D. D. B.], Duke University Medical Center, Durham, North Carolina 27710

ABSTRACT

We used diaziquone (NSC 182986) alone and in combination with other antineoplastic drugs to treat six human glioma and one human medulloblastoma tumor lines growing s.c. in athymic mice. Pharmacokinetic studies of diaziquone in the plasma of athymic mice indicated rapid clearance with a half-life of approximately 11.5 min. Diaziquone produced significant growth delays in at least one experiment using each of seven different tumor lines, and it produced consistent and significant delays in five of the seven. There was no obvious difference between a single dose and a dose administered once daily for 5 days, and tumor regressions to a volume smaller than that at treatment were uncommon in any of the single-drug experiments. Using our most extensively characterized human glioma line, D-54 MG, we found striking enhancement of the therapeutic effect by using nontoxic combinations of either diaziquone and carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea, NSC 409962) or diaziquone and procarbazine (NSC 77213). These combinations produced significant increases in the median growth delay, significant increases in the number of tumor regressions, and some instances in which no palpable tumors were present 100 days after treatment. In contrast, in experiments using diaziquone-based chemotherapy combinations with either cyclophosphamide, cis-platinum, or vincristine, there was only slight enhancement of the therapeutic effect. These results, using human glioma and medulloblastoma tumor lines in athymic mice, suggest a broad range of activity of diaziquone against primary nervous system tumors and enhancement of its therapeutic effect with either 1,3-bis(2-chloroethyl)-1-nitrosourea or procarbazine. If Phase II and Phase III clinical trials corroborate these findings, the value of the nude mouse system for the evaluation of new therapeutic approaches to brain neoplasms would be further confirmed.

INTRODUCTION

Diaziquone is a lipid-soluble synthetic benzoquinone that has been introduced recently into clinical trials for the treatment of patients with primary anaplastic tumors of the nervous system. Its potential importance lies in its impressive efficacy against standard animal brain tumor models (12), its activity against human brain tumors in early clinical trials (1, 5, 6, 19), and its modest toxicity in humans (14). Little is known yet about its spectrum of efficacy, mechanisms of sensitivity and resistance, optimal doses, mode of administration, or schedules, and its use in combination with other agents active against human brain tumors. In this paper, we are reporting pharmacokinetic data of diaziquone in athymic mice, its activity against a series of human brain tumor lines growing in these animals, and the activity of diaziquone-based chemotherapy combinations against D-54 MG, the most extensively characterized glioma line available in this laboratory. Results indicate rapid plasma clearance in mice, variable sensitivity of the tumor lines to the drug, and enhancement of the therapeutic effect of diaziquone by combination with other agents, notably BCNU 6 and procarbazine.

MATERIALS AND METHODS

Animals. Homozygous nu/nu BALB/c athymic mice at least 6 weeks old were used for these experiments. Animals were derived from an independent breeding colony at Duke University and maintained as described previously (4, 18).

Drug Administration and Toxicity. Diaziquone was supplied by the Division of Cancer Treatment of the National Cancer Institute. The parent compound was dissolved in dimethyl acetamide and diluted in phosphate buffer (0.01 M, pH 6.5). The lethal toxicity of diaziquone in our animal colony was determined by probit analysis using 3 doses between an LD 10 and an LD 90 (21). An LD 10 dose was calculated for both a once daily for 5 days schedule and a single dose. The drug was administered i.p. in a volume of 30 ml/sq m. Procarbazine HCl was supplied by Hoffmann-La Roche Inc., Nutley, NJ. The other drugs were purchased commercially. All animals were weighed twice weekly after drug administration.

Analysis of Plasma Diaziquone. Concentrations of diaziquone were determined in plasma samples pooled from 3 non-tumor-bearing animals at each time point after a single i.p. injection of the drug. Samples were obtained at 5, 15, 30, and 60 min after a single injection of 28 mg/sq m and at 10, 30, 60, and 120 min after a single injection of 6.75 mg/sq m. The blood was collected after decapitation and anticoagulated with heparin. The plasma volumes obtained from each animal at each time point were similar. Plasma diaziquone was analyzed by a high-pressure liquid chromatographic assay (11). The lower limit of sensitivity of this method is approximately 20 ng/ml. The coefficient of variation of the assay is 3.0%. The elimination half-life, t 1/2, of diaziquone was determined by linear regression analysis after transformation of diaziquone concentrations to natural logarithmic values; the slope of the regression line is −β, and the half-life is 0.693/β. Total clearance was determined from the total area under the plasma diaziquone concentration versus time curve, which was measured by the trapezoidal method, with the area after the last data point being determined by dividing plasma diaziquone at that time by β; total clearance is dose divided by area under curve. The

1 Recipient of support from NIH Grant RO1-NS-20581. To whom requests for reprints should be addressed, at Box 2905, Duke University Medical Center, Durham, NC 27710.
2 Recipient of a Brain Tumor Research Association fellowship, in memory of Bryce Davis, and of American Cancer Society Junior Faculty Clinical Fellowship 707.
3 Nanaline H. Duke Scholar.
4 Recipient of support from NIH Grants PO1-NS 20223, RO1-CA 11988, and PO1-CA 32672.
5 The abbreviations used are: BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; LD 10, 10% lethal dose; LD 90, 90% lethal dose; PCB, procarbazine; CPA, cyclophosphamide; CDP, cis-platinum; VCR, vincristine; i.e., intracerebrally.

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apparent volume of distribution was determined by dividing total clearance by $\beta$.

**Tumor Transplantation.** Experimental animals received tumor that had been removed from the s.c. space of donor animals and processed as described previously (18). Each animal received 30 $\mu$L of the tumor suspension into the s.c. space of the right flank.

**Tumor Lines.** Seven different human brain tumor lines were used: D-54 MG; U-118 MG; U-251 MG; TE-671; N-456; N-519; and N-735. D-54 MG is the Duke University subline of the human glioma line A-172 initiated by G. Todaro (9). Its morphology, biochemistry, antigenicity, and karyotype have been extensively investigated (3, 22), and its sensitivity in athymic mice to a variety of antineoplastic agents has been determined (16). It grows in mice with an average volume doubling time of between 1.5 and 2.5 days. U-118 MG and U-251 MG are human glioma lines initiated in Uppsala, Sweden, by Professor B. Westermark and Professor J. Ponten. Their *in vitro* characteristics, as well as their sensitivities in athymic mice to BCNU, PCB, and mithramycin, have been reported (3, 16). TE-671 is a human medulloblastoma line initiated by J. McAlister (13). Its *in vitro* characteristics, karyotype, and *in vivo* sensitivity to a series of antineoplastic compounds and radiation have been reported (7, 8). N-456, N-519, and N-735 are human glioblastoma xenograft lines initiated in athymic mice at Duke University. The morphology and growth characteristics of N-456 and N-519 have been reported, as have their sensitivities to BCNU, PCB, and mithramycin (16). N-735 had not been treated previously in mice with chemotherapy. It grows s.c. with an average volume doubling time of 4.8 days in the seventh animal passage.

**Drug Treatment.** All lines were treated between a fifth and 30th animal passage level. Tumors were measured serially until the median tumor volume exceeded 200 cu mm. Animals were then divided into groups of 10, so that there were no significant differences in mean tumor volume among the groups, and treatment was administered. Tumors were then measured 2 to 3 times weekly until their volume exceeded 2 ml.

In the single-drug experiments, treatment animals received either 6.75 mg of diaziquone/sq m daily for 5 consecutive days or, in single-dose experiments, 26 mg/sq m. In the combination chemotherapy experiments, diaziquone was administered first, and there was a 30-min interval before the second drug was given. Drugs used in combination were those that had shown some activity as single agents against D-54 MG and included BCNU, PCB, CPA, CDP, and VCR. BCNU was administered in a 12% ethanol solution; PCB, CPA, and VCR were diluted and administered in normal 0.9% NaCl solution (saline); and CDP was dissolved in sterile water and diluted in saline. Diaziquone was given at either 75% or 67.5% of the calculated LD$_{50}$ in our colony of animals, whereas the second agent was given at variable percentages of the standard dose as noted (Table 2). Animals in the control groups received equal volumes of drug vehicle.

**Evaluation of Response.** Determination of therapeutic response was based on growth delay in days until a tumor volume of 5 times the tumor volume at treatment was reached, as reported previously (16). Median growth delay, treated minus control, was the median difference in days between the time from treatment to 5 times the treatment volume in the treated animals and the median time from treatment to 5 times the treatment volume in the control animals. Values in treated and control animals were compared by the Wilcoxon rank-sum test. Additionally, tumors regressing to a volume less than the volume at the beginning of treatment were recorded, and a comparison between control and treated animals was made by the Fisher exact test.

**RESULTS**

**Diaziquone Toxicity.** We have treated 131 tumor-bearing animals with diaziquone (6.75 mg/sq m daily for 5 days, 75% of the calculated LD$_{50}$) in these experiments. Three animals (2.3%) died of drug toxicity, and the average weight loss in the surviving animals was 5.2% of their body weight on the first day of treatment. Two of 60 animals (3.3%) receiving a single dose of 26 mg/sq m (75% of the calculated LD$_{50}$) died, and the average maximum weight loss for the survivors was 13.8%. There were no obvious signs of toxicity other than weight loss and reduced activity.

**Plasma Diaziquone Levels.** Concentrations of diaziquone in the pooled plasma samples were 5.52, 3.96, 1.10, and 0.22 $\mu$g/ml at 5, 15, 30, and 60 min, respectively, after 26 mg/sq m i.p. (Chart 1). The apparent half-life was 11.5 min, the total clearance was 81 ml/min/kg, and the apparent volume of distribution was 1.33 liter/kg. The plasma diaziquone concentration was 0.35 $\mu$g/ml at 10 min after 6.75 mg/sq m i.p. and below detectable limits at 30, 60, and 120 min.

**Single-Agent Therapeutic Effect.** Median growth delays in experiments using diaziquone alone daily for 5 days were: D-54 MG: 12.0, 15.6, and 12.8 days; U-118 MG: 3.0 and 2.0 days; U-251 MG: 1.9 and 8.3 days; TE-671: 2.9 and 3.8 days; N-456: 2.3 days; N-519: 16.4 days; and N-735: 11.3 and 6.4 days (Table 1). All values for D-54 MG, N-519, and N-735 were statistically significant ($p < 0.01$). One each of the values for U-118 MG, U-251 MG, and TE-671 was significant at $p < 0.01$, whereas in the other experiment with these 3 lines, the significance was less ($p = 0.016$, $p = 0.067$, and $p = 0.022$, respectively). The growth delay for N-456 using diaziquone once daily for 5 days was not significant.

Successive growth delays in D-54 MG using the single-dose schedule of diaziquone were 12.7 and 13.0 days. Both values differed significantly from controls ($p < 0.01$), but they were not significantly different from results obtained with administration once daily for 5 days. Growth delays were 6.2 days in TE-671 ($p = 0.031$), 6.3 and 10.8 days in N-456 ($p < 0.01$), and 10.6 days in N-519 ($p < 0.01$) on the single-dose schedule.

There were few significant tumor regressions in any of the single-drug experiments. There were exceptions in one experiment with N-456, in which there were 5 regressions among 10 treated animals, and in one experiment with N-519, in which there were 3 of 8 tumor regressions. Generally, tumor volumes in the responding lines plateaued for varying periods beginning approximately 5 days after treatment before resuming growth.

**Combination Therapeutic Effect.** Diaziquone was used in combination with BCNU, PCB, CPA, CDP, and VCR in separate experiments (Table 2). Growth delays produced by each of these combinations were statistically significant ($p < 0.01$). The diazi...
DISCUSSION

Diaziquone is a lipid-soluble quinone that has shown activity against a variety of experimental i.e. tumors (12). It increased the median life span of mice bearing i.e. L1210 leukemia by 79 and 84% in successive experiments at optimal doses. Sixteen of 20 animals with the murine i.e. ependymoblastoma were apparently "cured" (no evidence of tumor at 60 days) by the drug, and the median increased life span exceeded 300%. These 2 experimental i.e. tumor models have been the most widely used animal systems for choosing agents to be tested against human gliomas (17).

The drug has now shown promising activity in preliminary studies in patients afflicted with primary brain tumors. In independent series, diaziquone as a single agent has produced unequivocal response of progressive disease, and in another 4, there was either clinical or radiographic improvement without evidence of disease progression (19). These results compare favorably with those reported with other single agents in the treatment of these diseases (15). However, responses have often been brief, and the ultimate role of this drug in the treatment of patients with primary nervous system tumors has not yet been established.

The pharmacokinetic parameters of diaziquone observed in athymic mice were comparable to those observed in humans (2, 14, 19). Studies in patients receiving doses ranging from 8 to 24 mg/sq m/day have revealed an average elimination half-life of approximately 0.5 hr, a total clearance of approximately 10 ml/min/kg, and an apparent volume of distribution of approximately 0.7 liter/kg. The major difference in the disposition of diaziquone in athymic mice is more rapid total clearance, resulting in a shorter half-life. Peak plasma concentration in the mice was 5.52...
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µg/ml, which is comparable to peak concentrations between 0.57 and 1.25 µg/ml observed in patients after a dose of 8 mg/sq m administered by rapid i.v. infusion over 20 min (19). The drug is apparently rapidly metabolized in both species, supporting the use of athymic mice as an experimental model to test the antitumor effects of diaziquone. However, it is not known whether the parent compound or a metabolite is the active form. The relative importance to therapeutic efficacy of peak drug concentrations and total area under the concentration curve is also not yet known.

We have developed an interest in the use of the athymic mouse for the investigation of a number of biological aspects of human glioma and medulloblastoma tumor lines, including their therapeutic sensitivities. Human anaplastic gliomas grow reliably after transplantation into athymic mice and continue after serial transplantation to resemble the tumors from which they were derived (10, 18). We have shown that drugs considered to be active clinically against human glial tumors, such as BCNU and PCB, are also active against the human glioma xenografts in athymic mice, whereas clinically inactive drugs, such as mithramycin, are ineffective in the mouse system (16). In this study, we have shown definite but variable activity of diaziquone when it was used as a single agent against a series of human gliomas growing s.c. in athymic mice. Significant growth delays were produced against each line in at least one experiment, and consistent growth delays were found in 5 of the 7 lines. However, the growth delays among the lines were highly variable, and significant growth delays were produced against each line in at least one experiment, and consistent growth delays were found in 5 of the 7 lines. However, the growth delays among the lines were highly variable, and consistent growth delays were found in 5 of the 7 lines. However, the growth delays among the lines were highly variable, and consistent growth delays were found in 5 of the 7 lines. However, the growth delays among the lines were highly variable, and consistent growth delays were found in 5 of the 7 lines. However, the growth delays among the lines were highly variable, and consistent growth delays were found in 5 of the 7 lines.

There was no a priori reason to anticipate therapeutic synergy in any of the diaziquone-based combinations, and results from combination chemotherapy experiments were of considerable interest, since synergism is often observed empirically. We found striking enhancement of the therapeutic effect using both the diaziquone-BCNU and diaziquone-PCB combinations. The combination of doses of 67.5% of the LD_{10} of diaziquone and 37.5% of the LD_{10} of BCNU produced growth delays that significantly exceeded those produced by either drug alone. Similarly, median growth delays produced by the diaziquone-PCB combination far exceeded those produced by either drug alone.

<table>
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<th>Diaziquone dose</th>
<th>2nd drug dose</th>
<th>Treatment day</th>
<th>Tumor volume doubling time in control animals (days)</th>
<th>Tumor volume at treatment (cm³)</th>
<th>Days from treatment to 5 times control treatment vol</th>
<th>Treated control animals</th>
<th>Treated animals</th>
<th>No. of tumor regressions/no. treated</th>
<th>No. of toxicity deaths/no. treated</th>
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<td>75.0</td>
<td>BCNU, 75.0</td>
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<td>2.2 ± 0.3</td>
<td>206.4 ± 59.1</td>
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<td>247.2 ± 68.7</td>
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<td>307.8 ± 73.0</td>
<td>4.4 ± 1.1</td>
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<td>244.5 ± 95.2</td>
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<td>186.7 ± 49.8</td>
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<td>4.7 ± 0.6</td>
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Chart 2. Diaziquone (dZQ) and BCNU treatment in athymic mice of s.c. tumors derived from the human glioma line D-54 MG. There were 10 treated and 10 control animals in each experiment. In the single-drug experiments, 75% of the calculated LDₕ₀ was used. In the combination experiment, diaziquone was used at 67.5% of its LDₕ₀, and BCNU was used at 37.5% of its LDₕ₀. Control animals were treated with drug vehicle. , median control tumor volumes; , individual treated tumor volumes. Median growth delay to 5 times the tumor volume at treatment was 13.0 days with diaziquone alone, 16.7 days with BCNU alone, and 29.8 days in the combination experiment, indicating enhancement of the therapeutic effect using the combination.}

Chart 3. Diaziquone (dZQ) and PCB treatment in athymic mice of s.c. tumors derived from the human glioma line D-54 MG. There were 10 treated and 10 control animals in each experiment. In the single-drug experiments, 75% of the calculated LDₕ₀ was used. In the combination experiment, diaziquone was used at 75% of its LDₕ₀, and PCB was used at 18.8% of its LDₕ₀. Control animals were treated with drug vehicle. , median control tumor volumes; , individual treated tumor volumes. Median growth delay to 5 times the tumor volume at treatment was 13.0 days with diaziquone alone, 26.2 days with PCB alone, and > 100 days using the combination.

did more than 50% of the tumors regress to a volume less than the treatment volume, even at toxic combination doses, and the combinations did not increase the number of tumor regressions in comparison to single-drug experiments. These regression statistics are in marked contrast to the consistent and uniform regressions seen in the BCNU- and PCB-diaziquone-based combinations. Since little information is available using diaziquone-based chemotherapy combinations in experimental tumor systems, these results have potential clinical relevance as well as possible implications for the mechanism of action of the drug.

These data suggest, but do not address directly, a number of other questions that are important for an understanding of both diaziquone-based combinations and single-drug treatments.
mechanisms of diaziquone activity and its proper clinical use. (a) The availability in mice and in culture of glioma lines with varying sensitivity to the drug will allow the investigations of mechanisms of sensitivity and resistance to it. (b) Although we found no definite schedule dependency, we did not look at this issue in detail. Since the optimal schedule for use in humans is not known, further studies are warranted. (c) Further studies of optimal diaziquone-based drug combinations will have implications for both an understanding of the mechanisms of drug action and its clinical use.

REFERENCES


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