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A Phase 1 Trial of Intravenous Boronophenylalanine-fructose Complex in Patients with Glioblastoma Multiforme

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1. INTRODUCTION

Boron neutron capture therapy (BNCT) of glioblastoma multiforme was initially performed at the Brookhaven National Laboratory in the early 1950's[1]. While this treatment for malignant brain tumors has continued in Japan[2], new worldwide interest has been stimulated by the development of new and more selective boron compounds. Boronophenylalanine (BPA) is a blood-brain barrier penetrating compound that has been used in BNCT of malignant melanomas[3]. BPA has been employed experimentally in BNCT of rat gliosarcoma[4] and has potential use in the treatment of human glioblastoma. As a preface to clinical BNCT trials, we studied the biodistribution of BPA in patients with glioblastoma.

2. METHODS

Patients were selected for the study if they were undergoing craniotomy for resection of suspected glioblastoma based on MRI scan. Blood chemistries, including renal and liver profiles, were required to be in the normal range. Appropriate informed consent was obtained. Two to three hours prior to the start of surgery an intravenous infusion of BPA-fructose complex (100-170 mg/kg) was administered. Vital signs, including arterial blood pressure and cardiac monitoring, were followed during and after the infusion. Frequent blood samples were drawn to monitor blood boron levels for 48 hours after the start of the infusion. Urine was also collected over this same time period.

At surgery, multiple samples of tumor were obtained. An effort was made to sample various areas of the glioblastomas. Specimens of surrounding normal brain, scalp, muscle and dura were also sent for boron analysis. Separate

histopathologic examination was determined on all tumor samples obtained. Post-operatively, liver, renal and hematologic blood analyses were performed.

3. RESULTS

Seven patients were studied, all with histologically confirmed glioblastomas. Five patients were administered BPA-fructose at 130 mg/kg infusion and one patient each at 100 mg/kg and 170 mg/kg. No adverse effects on vital signs or blood chemistries were seen.

The blood values (Fig 1) demonstrate a peaking of blood boron concentration at the end of the two hour infusion (the patient given 100mg/kg was infused for only 1.5 hours) with a biphasic clearance of BPA. The blood curves appear to scale linearly with the different infusion doses of BPA.

Figure 1.

Figure 1. Boron concentrations following a 2 hour intravenous infusion of BPA-fructose complex. Five patients were administered BPA-fructose at 130 mg/kg and one patient each at 100 mg/kg and 170 mg/kg.

Multiple samples of scalp were obtained from the patients over the course of the surgery. Scalp boron concentrations were approximately 1.2-1.4 times those in blood (Fig 2). These scalp to blood ratios are similar to those described in skin.[5]

Figure 2.

Figure 2. Scalp biopsy boron concentrations following BPA-fructose infusion (100-130 mg/kg dose). The blood curve for the patients administered 130 mg/kg is shown for comparison. Multiple scalp samples were obtained from each patient.

Variability in boron concentrations both between tumor samples and between patients was observed (Fig 3). In most patients, tumor boron concentrations were higher than concentrations in adjacent brain samples. Peak tumor boron concentrations were 11-26 μg/gm while brain boron concentrations ranged from 3-10 μg/gm.

Figure 3.

Figure 3. Boron concentrations in tumor and brain samples following BPA-fructose infusion (100-130 mg/kg dose). for each of the seven patients.

Histologic examination of glioblastomas revealed regional variable degrees of cellularity and necrosis. Tumor samples from the more cellular areas had higher boron uptake than necrotic regions (Fig 4).

Figure 4.

Figure 4. Gadolinium-enhanced T1-weighted MRI image of Patient 6 (administered BPA-fructose 100mg/kg) with corresponding boron concentrations in cellular and necrotic regions of glioblastoma. The boron concentrations for scalp, muscle and adjacent brain are included.

4. CONCLUSIONS

1) BPA-fructose infusions (100-170 mg/kg) were well tolerated.
2) Peak boron concentrations in tumor ranged between 11-26μg.gm.
3) Variability in BPA uptake from tumor to tumor and within the same tumor can be explained, in part, by the degree of regional cellularity and necrosis.

5. REFERENCES

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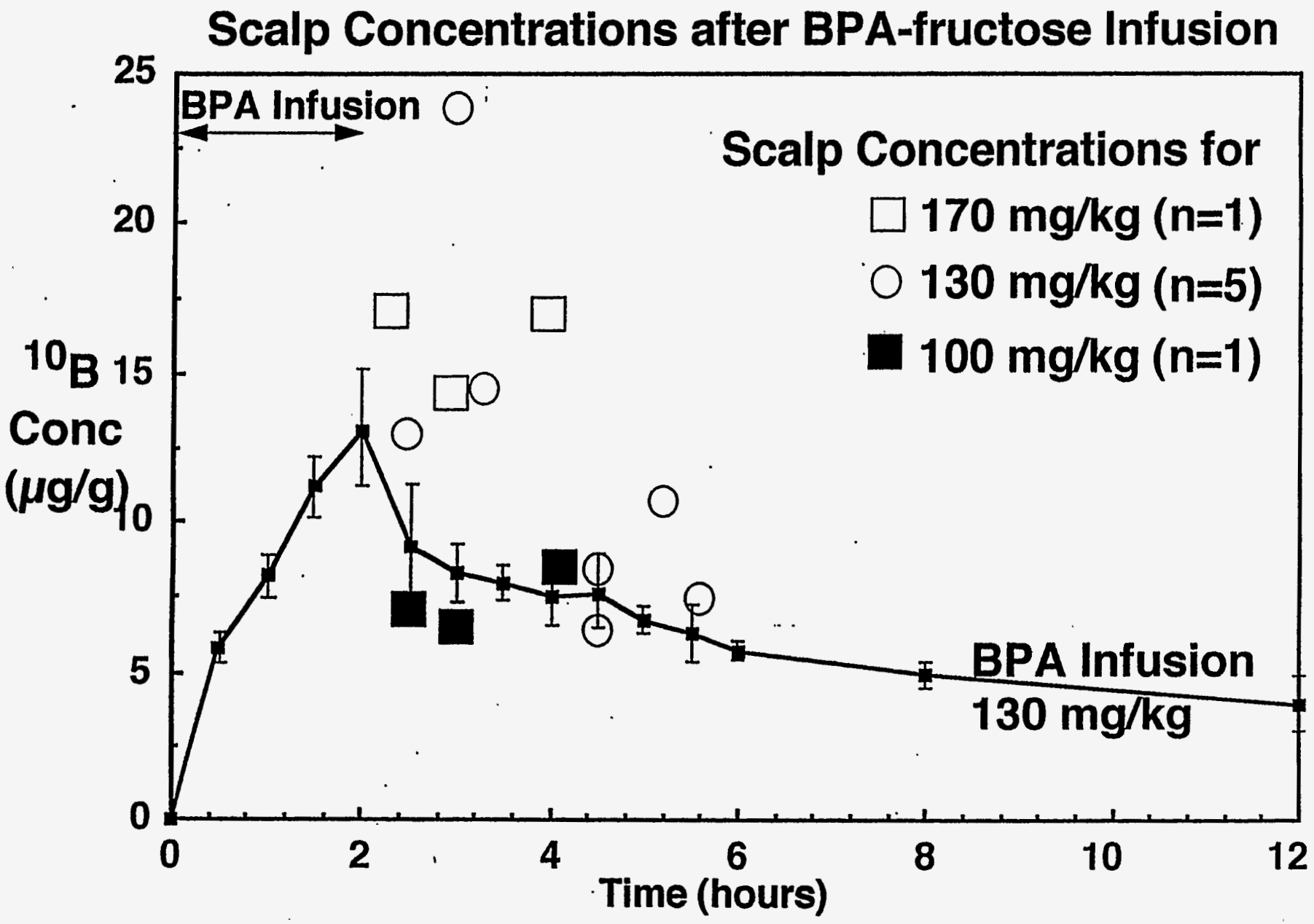
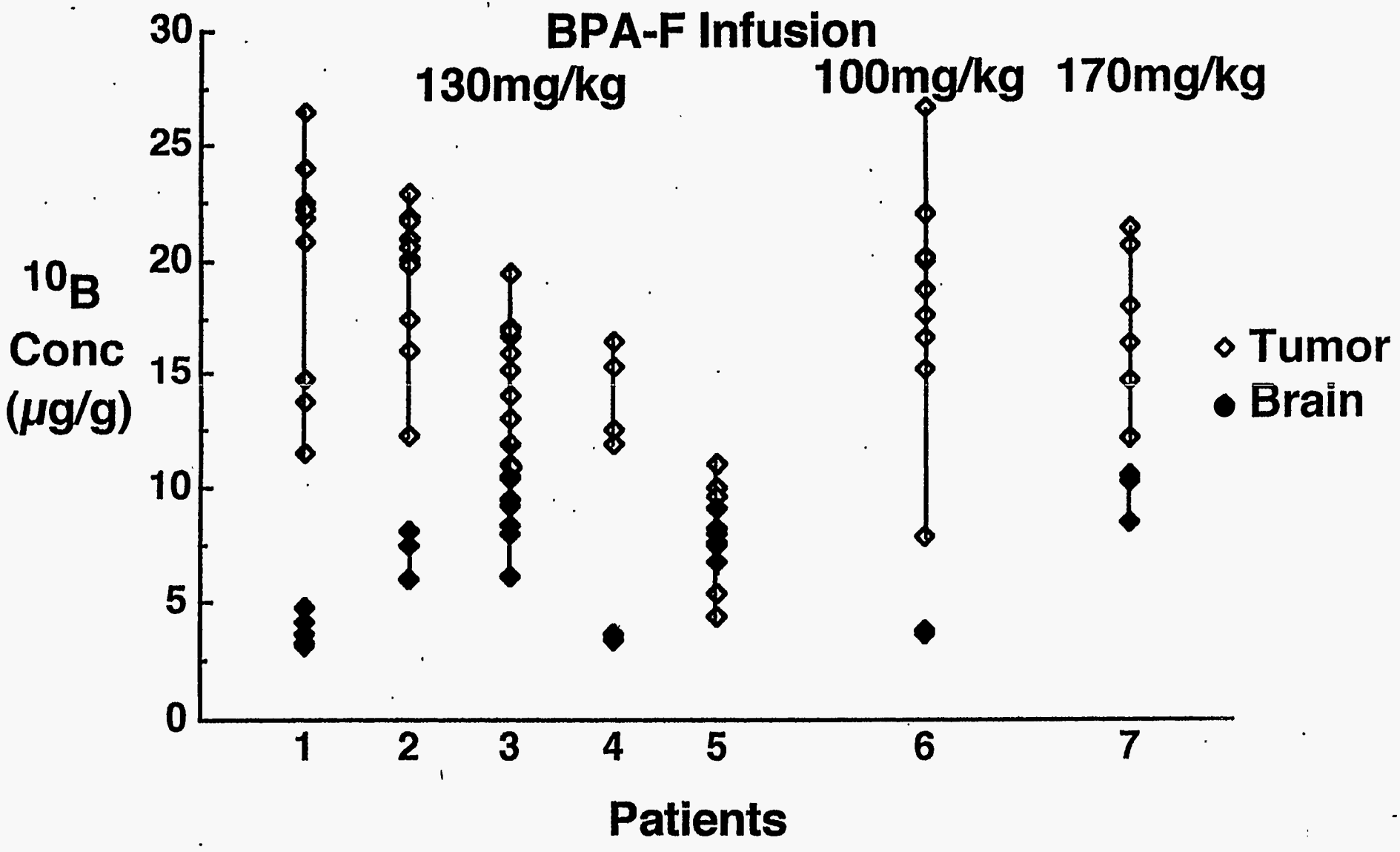
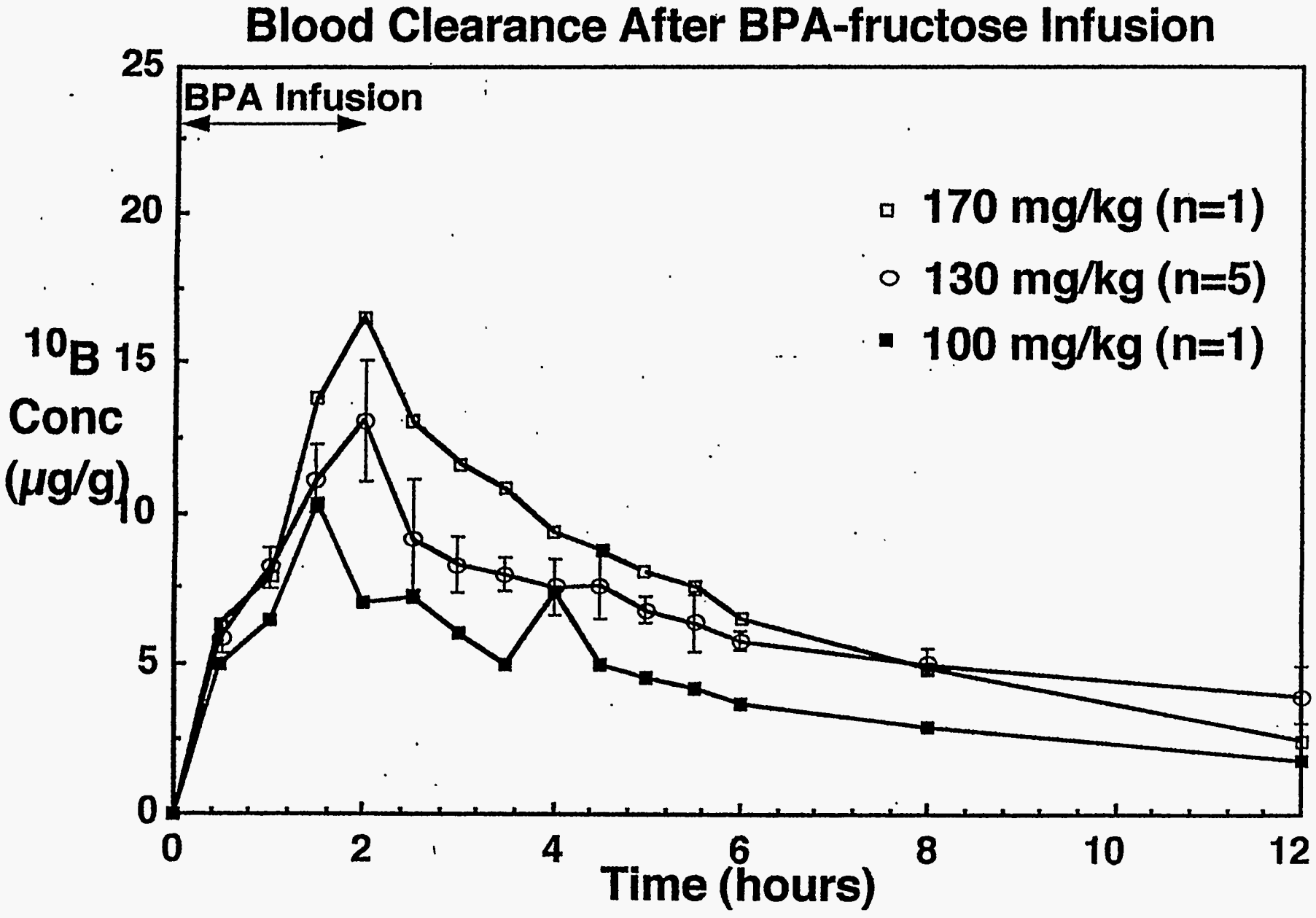

Scalp Concentrations after BPA-fructose Infusion
BPA Infusion
Scalp Concentrations for
170 mg/kg (n=1)
130 mg/kg (n=5)
100 mg/kg (n=1)
BPA Infusion
130 mg/kg
10B Conc (μg/g)
Time (hours)
0
5
10
15
20
25
0
2
4
6
8
10
12

Tumor and Brain Concentrations after BPA-fructose Infusion




Blood Clearance After BPA-fructose Infusion
BPA Infusion
170 mg/kg (n=1)
130 mg/kg (n=5)
100 mg/kg (n=1)
10B Conc (μg/g)
25
20
15
10
5
0
0
2
4
6
8
10
12
Time (hours)

Tumor and Brain Concentrations after BPA-fructose Infusion