PHARMACOKINETICS OF BORON SULFHYDRYL (BSH) IN PATIENTS WITH INTRACRANIAL TUMOURS.*

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INTRODUCTION

One prerequisite for successful BNCT is the determination of B-10 blood levels at the time of neutron irradiation, since the pharmacokinetics of BSH influences the optimal timing between injection of the boron compound and radiation. We collected extensive pharmacokinetic data from patients undergoing operation for intracranial tumours. This investigation is the corollary of the boron distribution study in tissues. We will also discuss these findings in perspective of comparable published studies.

METHODS

Four patients underwent a pharmacokinetic study over 7 days, consisting of repeated blood sampling and urine collection. BSH (95% B-10 enriched $Na_2B_{12}H_{10}SH$, Callery Chemicals, Pittsburg) at the dose of 10 mg/kg wt (=5 mg B/kg) was given as a constant rate 1 hour i.v. infusion. In a 5th patient, the dose was 10 mg B/kg. Blood was centrifuged, and plasma samples were kept frozen until analysis. Total urine collection (without catheter) was started simultaneously, divided into periods of 12 hours for the first day, and 24 hour thereafter. Laboratory values for haematology, electrolytes, creatinine and liver enzymes were obtained daily. Aliquots (0.5 g), diluted 10 times in de-ionised water, were analyzed in triplicates by Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES). Half-lives and V_z were calculated by fitting a 3 exponential after zero-order input model to the data, by non-linear extended least square regression (Siphar). Clearance , V_{ss} and MRT were calculated by the classic model-independent method (trapezoidal rule for AUC).

RESULTS

Peak plasma values ranged from 30 to 50 μg/g (ppm) for the 5 mg/kg dose, and 250 ppm for the higher dose patient, which correlates with the administered amount of 216-441 mg B. The data were best described (Akaike information criterion) by a 3 exponential-model, with $T_{1/2}$ alpha of 1.3 (± 1.0), beta of 8.0 (± 3.7) and gamma of 55.3 (± 26.6) hours. V_z and Vss averaged 0.91 (± 0.48) L/kg and 0.32 (± 0.18) L/kg, respectively, and CL was 0.21 (± 0.08) ml/min/kg. MRT averaged 29.9 (± 18.6) hours. The detailed values are reported in table 1.

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In urine, B excretion could be measured at least up to the 4th day after infusion. The total eliminated B during this period reached 50% of the injected dose in 2 patients, and 80 % of injected dose in 2 other.

Table 1:

dose (mg B)	T1/2 (h)	MRT (h)	V_z (L/kg)	V_{ss} (L/kg)	CL (g/min/kg)
243	2.6 14.1 82.4	54.5	0.76	0.40	0.107
216	1.8 7.4 78.2	40	1.72	0.61	0.255
389	0.5 6.6 32.3	14.2	0.823	0.251	0.294
318	1.2 7.8 60.3	31.6	0.78	0.28	0.149
441	0.3 4.0 23.5	9.2	0.465	0.127	0.229

DISCUSSION

Despite variable peak values in plasma at the end of BSH infusion, which did not correlate to tumour type, age, sex or weight, the decay of B-10 in all 5 patients appeared relatively similar. The second and third half-lives observed in our study are very close to those reported in the largest available pharmacokinetic study to date (ref. 1) in 12 patients receiving 1-34 mg B /kg intracarotid. However, the authors did not observe the very rapid distribution phase reported here, possibly because of the small number of samples in the early decay (about six points in the first 10 hours). In most patients, B was detected up to 8 days after the end of the infusion, even with our relatively low doses (detection limit : 0.1 ppm). Only in one patient with extensive intraoperative bleeding, could B no longer be detectable after 72 hours. In this latter patient, the fit to a 3 exponential-model was not as obvious as for the remaining four. Systemic clearance was low (13.1±7 g/min) and highly variable among the patients.

Despite a very high plasma protein binding - described by Sweet - the volume of distribution of B is relatively important. Together with the difference between the volume in the terminal phase V_z and V_{ss}, this could indicate a high affinity, slow releasing deep compartment. However, it should be emphasized that the reliability of V_z is highly dependent on the accuracy and precision of the later levels, and so upon the detection level and the length of sampling.

In 40 patients undergoing a biodistribution study (data not shown), B levels observed at discrete sampling times seem coherent with the pharmacokinetics in the five patients described here. We intend to pursue these studies at higher doses and repeated administration.

REFERENCE

1. Sweet WH, Messer JR, Hatanaka H: Supplementary pharmacological study between 1972 and 1977 on purified mercaptoundecahydrododecaborate, in Hatanaka H (ed): Boron Neutron Capture Therapy for Tumours. Niigata, Japan, Nishimura, 1986, pp 59-76