

THE TOLERANCE OF LARGE DOSES OF SODIUM BORATE INTRA-  
VENOUSLY BY PATIENTS RECEIVING NEUTRON  
CAPTURE THERAPY<sup>1</sup>

HERBERT B. LOCKSLEY AND LEE E. FARR

Medical Department, Brookhaven National Laboratory, Upton, New York

Received for publication April 30, 1955

The exploration of neutron capture therapy (Farr *et al.*, 1954; Godwin *et al.*, 1955; Farr *et al.*, 1954) for treatment of glioblastoma multiforme using B<sup>10</sup> as the capture element has developed a need for more information regarding the toxicology and pharmacology of boron compounds. It has become of immediate importance to establish the safe maximal intravenous dose of inorganic boron and whether or not repeated intravenous administration of inorganic boron compounds results in cumulative toxic effects. While the final solution to these questions remains in the future, experience with one group of patients has provided opportunities to observe some of the clinical effects of intravenous administration of large doses of boron. The present report is concerned with clinical manifestations, attributable to boron, shown by the first ten patients to receive neutron capture therapy. The clinical results of this exploratory treatment series has been published elsewhere (Farr *et al.*, 1954).

Clinical reports in the literature on the pharmacology of boron have been largely concerned with accidental ingestion of borax or boric acid or unexpected systemic absorption of boron-containing powders applied to abraded skin surfaces. Only a few reports in the American literature deal with intravenous administration of boron as boric acid or borax. It is in the latter that the present interest largely lies. Pfeiffer and Jenney (1950) have summarized the literature. The number of patients who have received large doses of boron intravenously or subcutaneously is small and is summarized herewith. After seven days death occurred in a 70 year old man who received 40 grams of boric acid (6.5 gm. boron) subcutaneously in a 4 per cent solution. A male who was given 28 grams of boric acid (4.5 gm. boron) in a similar fashion survived (Brooke and Boggs, 1951) as did a 45 year old female who received 20 grams of boric acid (3.3 gm. boron) as a 2 per cent solution (Sweet and Javid, 1952). Another female, age 42, recovered after receiving 15 grams of boric acid (2.4 gm. boron) intravenously (Brooke and Boggs, 1951). These data suggest that doses of boric acid ranging from 15 to 28 grams need not be lethal for an adult. Sweet and Javid (1952), during their studies on the concentration of boron in brain and tumor, gave two patients a dose of 15 grams of borax (1.5 gm. boron) intravenously with no untoward effects.

*Preparation and administration of borax.* On the basis of this evidence, together with the relatively numerous data on animal toxicity, it was decided that for our purposes an intravenous dose of 20 grams of borax (2.12 gm. boron) would pre-

<sup>1</sup> Research supported by the U. S. Atomic Energy Commission.

sumably be safe for an adult and this dose was given to the patients herein reported. No account was taken of variation in body weight.

For use in neutron capture therapy only boron of atomic weight 10 reacts with a thermal neutron to produce an alpha particle. Natural boron comprises a mixture of 81 per cent  $B^{11}$  and 19 per cent  $B^{10}$ . For studies on neutron capture an enriched boron containing approximately 96 per cent of  $B^{10}$  was used. This purified isotope was then synthesized into sodium borate ( $Na_2B_4O_7 \cdot 10H_2O$ ) and the solutions administered were in each instance analysed for boron content to determine the exact dosage given. Since a considerable fraction of natural boron is the isotope of weight 10, and since under the conditions of use the boron was a part of a borate ion, there are no grounds for expecting that a boron mixture in which the lighter isotope predominates will behave physiologically in a manner any different from the natural mixture.

These observations were made on ten patients. Five of the ten received a single neutron exposure and borax injection. One patient received two thermal neutron exposures and two boron injections; two patients each received three and two patients each received four. The intervals between neutron exposures and injections of borax varied from two weeks to three months but the more usual interval was four to six weeks. Fourteen of the 21 borax doses were 20 grams (2.12 gm. boron); two were 19 grams (2.01 gm. boron); three were 16 grams (1.70 gm. boron) and one each was 15 (1.59 gm. boron) and 14 grams (1.48 gm. boron). Each patient had previously been operated upon for glioblastoma multiforme. For each neutron capture treatment the patient was given, ten minutes before starting neutron exposure in the Brookhaven reactor, a dose of borax intravenously in a volume of 100 ml. of saline containing 20 per cent glycerine.

Prior to injection of the borax each patient was sedated and had received Dramamine in varying dosages. The borax dose was injected rapidly into a convenient vein, the average injection taking only 75 seconds.

*Clinical observations.* Within the first two minutes after injection nausea was experienced by the patients. Vomiting and retching was observed in all but two instances. Dramamine did not control this manifestation. Urgent defecation and micturition with incontinence were frequent. The face was usually noted to be flushed with a grey cast. In some patients this was followed by pallor.

The vigorous stimulation of the vomiting centers appeared to be accompanied during the first few minutes with an excitation. This in several occasions was great enough to produce grand mal seizures. Most of the patients were subject to such seizures by their disease but their grand mal attacks had been previously brought under adequate control with diphenylhydantoin. This somewhat excited phase disappeared within ten minutes and was followed by a mildly depressed, somnolent state which generally continued during the 45 minutes of neutron exposure. However on two occasions a significant respiratory depression occurred. Caffeine sodium benzoate appeared effective in combatting this, although in one instance it was accompanied with artificial respiration manually applied for about 5 minutes. Immediately following the capture therapy the patients generally were more alert than before treatment. This usually lasted for about one

to three hours and appeared to be related, although not necessarily causally, to the radiation experience. Following this a lethargic semi-somnolent phase began which was frequently accompanied by an exaggeration of previously existing abnormal neurological signs. Nausea and retching sometimes continued intermittently for a day or two although appetite was not necessarily affected. Diarrhea developed about half the time but was not severe.

The observations made during the days and weeks after treatment reflected the effects of both boron administration and radiation. After treatment some elevation of temperature from 100 to 103 degrees was frequently noted for several days. Since the fever incidence and severity correlated in no way with the radiation exposure this was believed largely to be a manifestation of boron toxicity. Until the fourth or fifth post-treatment day the patients generally remained rather lethargic and drowsy. After this time they became decidedly brighter and in many instances appeared to be more alert and vigorous than prior to treatment.

We know that the gastro-intestinal signs and symptoms of radiation illness can be described in part in the same manner as those of boron intoxication but the onset of nausea, vomiting and urgent defecation immediately after boron injection clearly pointed to the boron as the etiological agent. Furthermore, the gastro-intestinal signs and symptoms subsided or were subsiding at the time when one might most logically expect radiation illness to begin. Subsequent observations on additional patients have clearly shown that radiation illness is not induced in these patients by the radiation resulting from the capture reaction.

Further, in no instance did any hematological change occur which could be attributed to either radiation or to boron toxicity and no untoward renal effects were noted as measured by the urea clearance and routine urinalysis. Several mild dermatologic responses were observed which, on the basis of reports in the literature, we attributed to boron. The one patient, P.P. No. 4709, who received successive treatments at a two week interval showed a transient generalized petechial rash on the second day following the second treatment. Two other patients, A.B. No. 4653 and A.H. No. 5144, developed a generalized diffuse scarlatinaform rash with pruritus during the first week after injection: This led to a dry, scaly exfoliation which cleared in a few days.

We were both surprised and pleased at the paucity of severe toxic effects produced in this group of seriously ill patients. One patient, P.P. No. 4709, had a high intracranial pressure (600 mm.), fever, depressed respiratory rate and an unstable blood pressure, and had been in coma for several months. On the day of treatment he required respiratory stimulation with caffeine and an oxygen tent, yet tolerated the borax as well as other patients in much better condition. Another patient, J.H. No. 5227, had a moderately severe diabetes but showed no unusual sensitivity to borate. Some failure of smooth control of her diabetes during the ten days post-treatment could be adequately accounted for by the enforced dietary irregularity during that period.

Because of the reports in the literature suggesting an accumulation of boron in the tissues of the central nervous system, we endeavored to ascertain if cumula-

4001427

tive effects developed. There was in one patient, A. H. No. 5144, no evidence of lessened tolerance with successive doses up to a total of four with a total administration of 80 grams of borax given over a six month period. Likewise in J. H. No. 4709, a 54 year old female, a total dose of 60 grams given within a 10 week period caused no symptomatology suggestive of cumulative effects. The other patient, A. B. No. 4653, who received a total of 80 grams of borax in four doses developed an obscure disorder following his last treatment. This patient after receiving his fourth treatment was within the next few hours weak, "sick all over" and unequal to his usual post-treatment conviviality on which he was customarily most insistent. The following day he was somnolent, confused, weak and incontinent. Beginning about the third post-radiation day, he began to show a slow rise in temperature which over a six day interval gradually attained a peak of 102°F. and as gradually returned to normal. In addition, he continued to be depressed mentally, had hypotension of 90/60 with persistent nausea and occasional vomiting. A dusky violaceous color to lips and nails was persistent despite a good respiratory exchange. After two weeks he had gradually improved to a condition permitting him to fly home. His course was progressively downhill and death occurred 3½ weeks after return home. Whether or not this patient's interim systemic illness represented cumulative boron poisoning it is impossible to say with certainty. Circumstantially and symptomatically it was most suggestive. While the boron cannot be certainly excluded as the primary cause, the marked invasion of his tumor into the thalamus and corpus callosum together with post-radiation effects seem a more likely explanation although the boron administration promptly made manifest a possible latent symptomatology. With this might also be cited boron analyses of tissues from this patient obtained at autopsy which showed barely detectable concentrations. The maximum was 3 to 7 microgm. per gram in the area of tumor invasion of the cerebral white matter. Autopsy boron analysis of the tissues of another patient eight weeks after his last treatment gave values below the sensitivity of the method used.

*Discussion.* The tolerance of adult man to borax would appear to be greater than one might anticipate from reports in the literature. One great difficulty in evaluation of these reports is the absence in most of them of data concerning the patient's weight or precise information regarding the boron dose. It may be presumed that for such a compound as borax a reasonable uniformity in effects on a per kilogram basis might be expected. Certainly in the data here reported, the dose, while constant in total amount, varied widely on a milligram per kilogram basis. The patient whose protocol was reported in some detail received only 19 milligrams of boron per kilogram observed body weight. The median dose given was 25 milligrams of boron per kilogram and the maximum dose was 46 milligrams of boron per kilogram. Within this wide range of dosage, response was strikingly uniform both in intensity and duration. From this one might surmise that single doses well above 46 milligrams of boron per kilogram may be tolerated in adults. From data obtained in studies in mice in this laboratory as well as that reported by others for mice and other animals, one might predict that doses

of perhaps twice the amount given to these patients may not cause fatal reactions in humans whose kidney function is normal. In each instance, prior to administration renal clearance and concentration tests were done on our patients to be certain these lay within the normal range. Whether or not renal disability enhances the toxic effects of borate we cannot say, but subsequent, as yet unpublished, observations made on additional patients suggest this may be the case. The apparent greater lethality in infants of both enteral and parenteral borate poisoning may be in part related to renal disability since a sick infant frequently is dehydrated and in acidosis. Both of these factors reduce the level of renal function. The importance of a normally functioning kidney would seem to be paramount since the principal pathway of excretion is in the urine. In each of our patients close attention was paid to maintenance of fluid balance and prevention of electrolyte deficiencies caused by gastro-intestinal disturbances. These factors may have played a role in the ability of otherwise seriously ill patients to tolerate borate doses given.

It appeared to us that the great majority of the acute manifestations observed after borax administration in these patients represents in all probability the toxicological picture of boron. Normality of the values obtained by blood analysis and the maintenance of good renal function supports this belief. The one sign provoked by their primary illness was grand mal to which all patients were subject although as previously noted convulsions also have been reported as a sequelae to serious boron intoxication. These observations clearly demonstrate the necessity for extensive additional studies of the pharmacology and toxicology of boron compounds which are or may be used in this new therapeutic approach. Many of these are now under way in this laboratory and will be reported in the future.

#### SUMMARY

Clinical observations of the effects of intravenously administered borax in doses up to 20 grams (2.12 gm. boron) are reported. Immediate symptoms observed were intense gastro-intestinal stimulation leading to nausea, vomiting, retching, urgent defecation and diarrhea; mild peripheral vascular collapse; mild mental confusion; and a flushed violaceous discoloration of the skin of the face not attributable to respiratory embarrassment. Later symptoms were drowsiness, lethargy, variable degrees of continued gastro-irritability and in a few instances a scarlatinaform rash. These effects usually terminated by the third to fifth day.

No deaths occurred in these patients as a result of this borax administration and a poor general condition of the patient was not found to be an absolute contraindication to boron administration.

Dramamine exerted no significant effect on the early symptoms of nausea and vomiting.

Two successive administrations of 20 grams of borax (2.12 gm. boron) at an interval of two weeks and four successive administrations of the same dose to four patients at an interval of four weeks did not lead to enhanced toxic effects.

## REFERENCES

- BROOKE, C., AND BOGGS, T.: *Am. J. Dis. Child.*, **82**: 465, 1951.  
FARR, L. E., SWEET, W. H., ROBERTSON, J. S., FOSTER, C. G., LOCKSLEY, H. B., SUTHERLAND, D. L., MENDELSON, M. L., AND STICKLEY, E. E.: *Am. J. Roent. Rad. Therap. & Nucl. Med.*, **71**: 279, 1954.  
FARR, L. E., ROBERTSON, J. S., AND STICKLEY, E. E.: *Proc. Nat. Acad. Sci.*, **40**: 1087, 1954.  
GODWIN, J. T., FARR, L. E., SWEET, W. H., AND ROBERTSON, J. S.: *Cancer*, **8**: 601, 1955.  
PFEIFFER, C. C., AND JENNEY, E. H.: *Bull. of the Nat. Form. Comm.*, **18**: 57, 1950.  
SWEET, W. H., AND JAVID, M.: *J. Neurosurg.*, **9**: 200, 1952.