The Effect of Large Intravenous Doses of Sodium Borate on the Human Myocardium as Reflected in the Electrocardiogram

By Hadley L. Conn, Jr., M.D., Berniece B. Antal, M.S. and Lee E. Farr, M.D.

Large intravenous doses of sodium borate, given to seven patients with brain tumors, caused development of temporary but consistent hypoxic-type abnormalities in the S-T segments and the T waves of the electrocardiogram. Correlation of these electrocardiographic changes with blood boron concentrations, determined up to 48 hours after boron injection, indicated that the changes were probably the result of damage by boron, present intracellularly in the myocardium. The intracellular concentrations which cause electrocardiographic abnormalities are considered to be of the order of 100 µg per milliliter, similar to concentrations which have been shown to inhibit respiration in vitro myocardial preparations.

THE use of boron in neutron capture therapy for glioblastoma multiforme has stimulated renewed interest in the acute toxic effects of this element. The boron dosage employed, 2 to 3 Gm. given intravenously as borate, has been reported to cause toxic reactions. Observations, from this department, of the clinical effects of rapid intravenous borate administration have been published elsewhere. Circulatory depression and collapse are among the undesirable manifestations which we have seen and which have also been reported by others. We are not aware of published studies on the pathogenesis of this circulatory derangement or the direct in vivo cardiac effects of boron. The present report deals with electrocardiographic changes noted in patients, during and after neutron capture therapy, and relates these changes to effects on the myocardium of administered boron. While it has been our practice to endeavor to obtain electrocardiographic tracings on patients undergoing this procedure, it was not until this time that the procedure itself could be carried out in such a manner that satisfactory tracings could be obtained in the majority of instances.

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PROCEDURES

These observations were carried out on seven patients, during and after neutron irradiations. In each instance, immediately before thermal neutron exposure, the patients received a rapid intravenous injection of borax taking only 55 to 120 seconds for administration. The total dose of borax ranged from 18.6 to 27.3 Gm. (1.96 to 2.88 Gm. boron) which was equivalent to a range of 32 to 50 mg. of boron per kilogram of body weight.

Serial electrocardiograms were recorded on the Sunborn direct writing electrocardiographic recorder. Intermittent recordings, from the time of injection during the neutron capture therapy and up to about one hour afterwards, were made in all patients. In 6 of the 7 patients, additional records were obtained 24 to 48 hours after treatment. Standard limb leads were used in all recordings and the post-therapy tracings additionally included V leads.

Boron blood levels were determined on all seven patients after boron administration, at varying intervals from one minute to 48 hours. Estimation of boron concentration in whole blood was made by a modified quinalizarin method.

RESULTS

In all seven patients the electrocardiographic pattern was essentially the same during the first hour after the boron injection. For approximately five minutes after injection, no electrocardiographic abnormalities other than a modest increase in heart rate were observed. After the first 5 to 10 minutes, a frank sinus tachycardia always developed and cardiac rates of 100 to 160 per minute were usually present for several hours thereafter. More or
less coincident with the onset of tachycardia, the previously isoelectric S-T segments began to show a slight negative depression and the T waves began to decline in amplitude. After 10 to 20 minutes a maximal S-T depression, varying from 1 to 3 mm., was observed along with T waves which were of minimal positive amplitude, isoelectric, or, more commonly, diphasic. These abnormalities persisted without appreciable change during the ensuing 30 minutes over which initial recordings were made. On the day following treatment the electrocardiogram was normal in three patients, G. T. 6351, R. T. 5984, and E. D. 5972. In three patients, M. F. 6024, M. H. 6012, and S. M. 6480, the abnormal electrocardiographic pattern was only slightly improved after 24 hours. At this time, the tracing was approaching normal in a fourth patient, D. R. 6408. After 48 hours, the electrocardiogram was normal in all but two patients, M. F. 6024, and S. M. 6480. The tracings on these two patients later returned to normal, but the date of return was not established. No appreciable hypotension was observed in any patient during the period of the electrocardiographic studies.

Figure 1, showing serial recordings of the limb leads, demonstrates in moderate degree the abnormalities uniformly observed and also the typical time sequence of development and regression of these abnormalities.

Blood boron estimations, carried out on these patients, permit certain correlations and diversities to be pointed out. One patient, R. T. 5984, who received two irradiations six weeks apart, and the lowest boron dose, 32 mg. per Kg., showed a return to a normal tracing within 24 hours. The other two patients whose tracing returned to normal in 24 hours, G. T. 6351 and E. D. 5972, had each received a boron dose of approximately 42 mg. per Kg. On the other hand, M. G. 6012, who received the same dose but who clinically was much more toxic (presumably as a result of boron administration),

<table>
<thead>
<tr>
<th>TIME AFTER INJECTION</th>
<th>BLOOD BORON CONCENTRATION</th>
<th>STANDARD LEADS</th>
<th>LIMB LEADS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 MINUTES</td>
<td>189 μg/ml.</td>
<td></td>
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</tr>
<tr>
<td>25 MINUTES</td>
<td>78 μg/ml.</td>
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<tr>
<td>24 HOURS</td>
<td>12 μg/ml.</td>
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<tr>
<td>48 HOURS</td>
<td>2 μg/ml.</td>
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had not regressed to a normal tracing within this 24-hour period, following either of the two treatments given six months apart. Patient D. R. 6408, whose tracing was approaching normal after 24 hours, had received a dose of boron of 46.5 mg. per Kg. Patients M. F. 6029 and J. M. 6480, whose electrocardiogram remained abnormal after 48 hours, had received boron doses of 34 mg. and 50 mg. per Kg., respectively. That the electrocardiographic abnormalities are not caused specifically by high blood boron concentrations is shown by the fact that the deviations did not occur during the first five minutes after injection, when the concentration ranged as high as 249 μg. per ml. in J. M. 6480, and was from 170 to 180 μg. per ml. in most of the other patients. Delayed excretion of boron was marked in patients M. F. 6029 and M. H. 6012, and as evidenced by blood concentrations of <40 μg. per ml. and 12 μg. per ml., respectively, 24 hours post injection. The other patients, including J. M. 6480, showed blood concentrations at this time of 4 to 6 μg. per ml.

The onset of electrocardiographic changes was unrelated to the initiation of neutron bombardment of the tumor area and no characteristic changes were noted during the neutron radiation. In this study, the exposure area was 10 by 10 cm. and the thermal neutron flux was \(3 \times 10^9\) neutrons per square centimeter per second. In the group of 10 patients treated earlier, the exposure area was 5 by 10 cm. and the thermal neutron flux was \(2 \times 10^9\) neutrons per square centimeter per second. The total neutron dose was much larger in the present group of patients but the type of electrocardiographic changes was identical in both groups.

**Discussion**

These data indicated that blood boron concentration, per se, was not the critical factor in initiating electrocardiographic changes, for the electrocardiograms showed a normal pattern during the first five minutes, following boron injection, when blood levels ranged up to 249 μg. per ml., with a median concentration of 185 μg. per ml. The onset of cardiac disturbances, reflected by the electrocardiograph, was at 10 to 20 minutes after injection, at a time when significant amounts of boron have presumably entered the cell water. Approximate calculations, from blood boron disappearance curves and volume distribution data in these patients, suggests that a large fraction of the boron is within the cells. Agreement is found from similar calculations on blood boron disappearance curves and volume distribution data in dogs and mice, subjected to a rapid intravenous injection of boron. The present data also suggest that the period required for regression to a normal electrocardiogram is not dependent solely on blood boron concentration, *vide* J. M. 6480. However, in all the other patients, regression of electrocardiograms to normal had occurred, when the blood boron concentration was below 12 μg. per milliliter. One other patient, M. F. 6029, showed a blood boron concentration of 40 μg. per ml. after 48 hours because of severe oliguria and he continued to exhibit electrocardiographic changes. Prolongation of electrocardiographic changes would thus appear to be the result of cellular damage, resulting from a significant concentration of boron acting over some period of time.

The nature and general extent of the electrocardiographic changes were consistent and characteristic, although they were nonspecific abnormalities of the ST-T segments. This type of change is similar to that found with hypoxia of the myocardium and has often been referred to as the hypoxic or ischemic type of pattern. However, there is doubt whether this pattern specifically connotes hypoxia, because it occurs under other circumstances in which no cellular hypoxia has been demonstrated, such as alterations in electrolyte concentrations and distribution, particularly of sodium and potassium, and following digitalis administration. While we cannot exclude an intracellular electrolyte derangement as a consequence of flooding of the myocardial cell with boron, other experimental work, done in vitro on slices of mammalian myocardium, showed that concentrations of the order of 100 μg. per ml. of boron in the medium produced inhibition of respiration. This is in the range of the concentrations present in the in vivo perfusion medium of the patients, i.e. the blood.
A consideration of all the data we have presently at hand suggests this as a working hypothesis: the entrance of boron into the myocardial cell in appreciable concentrations produces an injury resulting in cell hypoxia which is reflected by a characteristic abnormal ST-T pattern in the electrocardiogram. Additional data are obviously required to validate this concept.

**Summary**

Serial electrocardiograms were recorded in seven patients receiving boron intravenously as a part of the neutron-capture therapy of glioblastoma multiforme. A consistent hypoxic type of electrocardiographic abnormality, involving decrease in amplitude or actual negativity of the ST-T segments, was observed acutely. When the boron was rapidly excreted or the total dose was less than 50 mg, per kilogram body weight the electrocardiogram returned to normal within 24 to 48 hours. A tentative hypothesis is advanced regarding the mechanism of action of boron in the myocardium.

**Summario in Interlingua**

Le administration intravenose de large doses de borato de natrium a 7 patientes con tumores cerebral causava le disveloppamento temporari sed infallibile de anormalitates hypoxicoidae in le segmento S-T e in le unda T del electrocardiogramma. Le investigation del correlation de iste alterationes electrocardiographic con le concentration de boro in le sanguine a periodos usque a 48 horas post le injection resultava in constatationes que indica que le alterationes mentionate es probabilmente le consequentia de damnos cause per le boro que es intracellularmente present in le myocardio. Le concentrationes intracellular de boro capac a evocar anormalitates electrocardiographic es probabilmente presso a 100 µg pro millilitro. Assi il se tracta de un concentration del grado general que es demonstratement capac a inhibir le respiration de preparatos in vitro de teixo myocardial.

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