Serum Cholinesterase Activity and Arterial Blood Pressure

By Louis J. Vorhaus, II, M.D.

Conflicting data have appeared in the literature regarding serum cholinesterase and blood pressure. The studies reported here were undertaken to establish or refute the existence of a direct relationship between these two factors. Two types of studies were performed. First, serum cholinesterase activity was measured in 63 unselected hypertensive patients. Second, a selected group of seven hypertensive patients and three healthy subjects was studied with a variety of drugs known to influence either blood pressure or serum cholinesterase. Results indicate that no direct relationship exists between blood pressure and serum cholinesterase and that fluctuations in these two factors occur independently of each other.

Many investigators have speculated whether a direct relationship exists between the cholinesterase activity of the serum and the arterial blood pressure. Antipol, Tuchman, and Schifrin,1 in 1937, first noted a tendency for patients with hypertension to have increased levels of serum cholinesterase activity. More recently, Farber8 and Morelli10 made similar observations in a small number of patients. The latter author suggested that essential hypertension might be due to an imbalance of the autonomic nervous system with sympathetic predominance, postulating that with increased circulating cholinesterase there would be abnormally great destruction of acetylcholine. On the other hand, Hall and Lucas6 found no correlation between blood pressure level's and serum cholinesterase activity in 162 general hospital patients. Reichert and Frisch12 made similar observations. Clinical and pharmacologic studies on the relationship of serum cholinesterase activity to various drugs have further confused the issue. Roepke5 demonstrated that tetramethylammonium chloride, a drug closely related to tetraethylammonium chloride, inhibits serum cholinesterase activity in vitro. Schürtz41 reported that prolonged barbiturate therapy caused a fall in serum cholinesterase activity both in guinea pigs and in man. Both of these drugs, when administered to hypertensive patients, generally mediate a fall in blood pressure. Torda and Wolff15 observed in vitro that vitamin K (menadione) in concentration of 2 x 10⁻⁶ mols caused a 70 per cent decrease in serum cholinesterase activity, and Morelli and Salvi11 observed that when vitamin K was given intravenously to hypertensive subjects it produced a drop both in serum cholinesterase activity and in blood pressure. On the other hand, Grob and co-workers4 noted that diisopropyl fluorophosphate (DFP), a drug which irreversibly inhibits serum cholinesterase activity, when given to normotensive subjects, was without effect on the blood pressure, even when cholinesterase activity reached very low levels. It has also been observed that very high levels of serum cholinesterase activity occur in patients ill with the nephrotic syndrome,4 6 17 and no hypertension is generally present in this condition. Davis and Hamilton5 reported that folic acid, when given orally, increases the serum cholinesterase activity, and it is known that this drug does not mediate a rise in blood pressure.

The discrepancies in previous observations suggested the need for further investigation into the possible relationship between hypertension and serum cholinesterase activity. The studies reported here were undertaken in an attempt to establish or disprove the existence of such a relationship, to learn

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whether drugs known to influence serum cholinesterase activity have any effect on blood pressure, and to determine if any of a variety of drugs used in treatment of hypertension mediate their effects through inhibition of the enzyme.

METHODS

Two types of observations were made. First, serum cholinesterase determinations were performed on 63 patients with essential hypertension, picked at random from the medical outpatient clinic of the Research and Educational Hospitals of the University of Illinois. Second, seven patients with essential hypertension were studied intensively on the research ward of the Research and Educational Hospitals. These were carefully chosen to include different types and grades of severity of hypertension. Data and four hypertensive patients were given sterile saline intravenously. During all of these studies frequent measurements of blood pressure and serum cholinesterase activity were performed. Results of the studies are tabulated in table 2.

RESULTS

I. Serum Cholinesterase Activity in Hypertensive Subjects

The range of serum cholinesterase activity in 63 hypertensive patients was 0.61 Δ pH per hour to 1.42 Δ pH per hour, with a mean value of 0.90 Δ pH per hour and a standard deviation of 0.19 Δ pH per hour. These data compare favorably with those reported by Vorhaus and associates16 for 68 healthy subjects, where the range was 0.68 Δ pH per hour

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Type of Hypertension</th>
<th>Average Morning Blood Pressure</th>
<th>Known Duration of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. K.</td>
<td>36</td>
<td>Male</td>
<td>White</td>
<td>Malignant, advanced</td>
<td>230/130</td>
<td>3 years</td>
</tr>
<tr>
<td>M. C.</td>
<td>16</td>
<td>Female</td>
<td>White</td>
<td>Malignant, moderately advanced</td>
<td>200/120</td>
<td>6 months</td>
</tr>
<tr>
<td>J. C.</td>
<td>59</td>
<td>Female</td>
<td>White</td>
<td>Benign, severe</td>
<td>220/120</td>
<td>15 years</td>
</tr>
<tr>
<td>M. Q.</td>
<td>52</td>
<td>Female</td>
<td>White</td>
<td>Benign, mild</td>
<td>190/100</td>
<td>1½ years</td>
</tr>
<tr>
<td>J. H.</td>
<td>40</td>
<td>Female</td>
<td>Negro</td>
<td>Benign, early</td>
<td>150/90</td>
<td>8 years</td>
</tr>
<tr>
<td>F. S.</td>
<td>67</td>
<td>Male</td>
<td>Japanese</td>
<td>Benign, moderately severe</td>
<td>185/95</td>
<td>2 years</td>
</tr>
<tr>
<td>R. C.</td>
<td>43</td>
<td>Female</td>
<td>White</td>
<td></td>
<td>200/110</td>
<td></td>
</tr>
</tbody>
</table>

on the seven patients are summarized in table 1. Normotensive subjects studied as controls were all healthy adult male volunteers.

Thorough clinical examination was made on each patient and complete blood count, urinalysis, routine blood chemistry studies (including serology, fasting blood sugar, nonprotein nitrogen, and serum albumin and globulin), electrocardiograms, urea clearances, chest fluoroscopies and intravenous pyelograms were performed. Cholinesterase activity of the serum was determined by the electrometric method of Michel.5,9

After a suitable control period, the following drugs were administered in sequence: vitamin K (as Hykinone), 20 to 72 mg. intravenously; folic acid, 15 to 90 mg. intravenously; sodium amytal, 180 mg. orally in three doses at hourly intervals; tetraethyl ammonium chloride, 3 cc. (300 mg.) intravenously; and diisopropyl fluorophosphate (DFP), 0.02 mg. per Kg. intramuscularly. Three patients were given cold pressor tests, two were treated with veratrum viride (Vertavis), one was given benzodioxane, 0.5 mg. intravenously, one was put on a rice diet for 17 days. As a control study, three normotensive subjects to 1.37 Δ pH per hour, with a mean of 0.94 Δ pH per hour and a standard deviation of 0.16 Δ pH per hour. In the hypertensive patients there was no correlation between the level of blood pressure and the serum cholinesterase activity. Patients with malignant hypertension showed no higher levels of serum cholinesterase activity than those with benign hypertension.

II. Studies on Changes in Blood Pressure and Serum Cholinesterase Activity following Administration of Various Drugs

A. Sterile Saline. As a control study, sterile saline was injected intravenously into three normotensive subjects and four hypertensive patients. In two cases (F. S. and W. T.) blood pressure recordings and serum cholinesterase determinations were performed in the manner described below with tetraethylammonium chloride. In the other five instances
the blood pressure recordings and serum cholinesterase determinations were performed in the manner described below with vitamin K. Insignificant changes in blood pressure and serum cholinesterase activity were noted following the administration of the saline and no correlation was observed between fluctuations in these two factors.

B. Vitamin K. The vitamin was administered to three normotensive subjects and seven hypertensive patients. Blood pressure and serum cholinesterase activity were recorded every 15 minutes for the first hour and activity were recorded as with vitamin K. While mild drops in blood pressure were noted in all the hypertensive patients, mainly within the first two hours after administration of folic acid, the changes were not consistent and were not considered significant. Moderate but significant drops in serum cholinesterase activity occurred. However, no correlation was observed between the fluctuations of blood pressure and cholinesterase nor was there any observable correlation between the magnitude of these fluctuations and the size of the dose of folic acid administered.

<table>
<thead>
<tr>
<th>Drug Administered</th>
<th>Number of Subjects Studied</th>
<th>Range of Maximal Blood Pressure Changes</th>
<th>Range of Maximal Changes in Serum Cholinesterase Activity</th>
<th>Mean Change in Serum Cholinesterase Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>%</td>
</tr>
<tr>
<td>Sterile Saline</td>
<td>7</td>
<td>Decrease 2 to 14</td>
<td>Decrease 2 to 10</td>
<td>+3 to -4</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>10</td>
<td>Decrease 10 to 32</td>
<td>Decrease 10 to 22</td>
<td>-3 to -17</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>12</td>
<td>Decrease 4 to 30</td>
<td>Decrease 0 to 12</td>
<td>0 to -20</td>
</tr>
<tr>
<td>Sodium Amytal</td>
<td>5</td>
<td>Decrease 18 to 62</td>
<td>Decrease 6 to 26</td>
<td>-2 to -5</td>
</tr>
<tr>
<td>Tetraethylammo-</td>
<td>7</td>
<td>Decrease 28 to 100</td>
<td>Decrease 10 to 48</td>
<td>-15 to -25</td>
</tr>
<tr>
<td>nium Chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diisopropyl Fluoro-</td>
<td>11</td>
<td>Decrease 0 to 38</td>
<td>Decrease 0 to 18</td>
<td>-37 to -94</td>
</tr>
<tr>
<td>phosphate</td>
<td></td>
<td>Increase 22 to 50</td>
<td>Increase 12 to 36</td>
<td>+3 to -4</td>
</tr>
<tr>
<td>Cold Pressor Test</td>
<td>3</td>
<td>Increase 30 to 150</td>
<td>Increase 12 to 80</td>
<td>+3 to -2</td>
</tr>
<tr>
<td>Viratrum Viride</td>
<td>2</td>
<td>Increase 40</td>
<td>Increase 18</td>
<td>-4</td>
</tr>
<tr>
<td>Diazodiocaine</td>
<td>1</td>
<td>Decrease 90</td>
<td>Decrease 30</td>
<td>+2</td>
</tr>
<tr>
<td>Rice Diet</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Change of statistical significance.

subsequently at half hour intervals up to four hours. In the hypertensive patients, mild drops in blood pressure were noted but there was no consistent period of time following administration of vitamin K when maximal effects occurred. No changes were noted in the normotensive subjects. All cases showed a significant drop in serum cholinesterase activity. No consistent correlation was observed in the fluctuations of blood pressure and serum cholinesterase activity, nor was any correlation observed between the magnitude of the fluctuations of either and the size of the dose of vitamin K administered.

C. Folic Acid. Folic acid was administered intravenously to five normotensive subjects and seven hypertensive subjects. For the most part, blood pressure and serum cholinesterase activity were recorded as with vitamin K. While mild drops in blood pressure were noted in all the hypertensive patients, mainly within the first two hours after administration of folic acid, the changes were not consistent and were not considered significant. Moderate but significant drops in serum cholinesterase activity occurred. However, no correlation was observed between the fluctuations of blood pressure and cholinesterase nor was there any observable correlation between the magnitude of these fluctuations and the size of the dose of folic acid administered.

D. Sodium Amytal. Sodium amytal was administered to five hypertensive patients. Blood pressure recordings were made every half hour, and serum cholinesterase activity was determined every hour for six hours. In all cases mild to moderate drops in blood pressure occurred. Slight but statistically significant drops in serum cholinesterase activity were noted in each case. No correlation was observed between fluctuations in blood pressure and in serum cholinesterase activity.

E. Tetraethylammonium Chloride. Tetraethylammonium chloride was administered to seven hypertensive patients. Blood pressure recordings were made every half minute for the first 10 minutes, every minute for the next 10 minutes, every 5 minutes for the next 10 minutes, and then every 10 minutes for 30
minutes. Serum cholinesterase activity was estimated every minute for 10 minutes and subsequently with each blood pressure recording. All patients had moderate to profound fall in blood pressure which occurred during the first three minutes following administration of the drug. In every case the serum cholinesterase activity was observed to decrease significantly. In most cases the fall in blood pressure preceded the fall in serum cholinesterase activity, and the changes in these factors did not produce curves which were parallel or similar in shape. No correlation was noted between the magnitude of the fall in the blood pressure and in the serum cholinesterase activity; in fact the patient who had the greatest drop in blood pressure exhibited the smallest drop in cholinesterase.

F. Diisopropyl Fluorophosphate (DFP). This substance, in oil, was administered intramuscularly to four normotensive individuals and seven hypertensive patients. Two of the hypertensive patients (E. K. and J. H.) were subsequently given repeated injections every other day for six days, and one (E.K.) was subsequently given weekly injections for three weeks. Blood pressure recordings were made at thirty minute intervals for three hours, then hourly up to eight hours, then daily thereafter. Serum cholinesterase determinations were made at intervals of one, three, and six hours after injection of diisopropyl fluorophosphate and then daily for six days. Diisopropyl fluorophosphate, a drug which irreversibly inhibits cholinesterase, produced the expected marked drop in serum cholinesterase activity in three to six hours, with a subsequent slow rise during the ensuing days as new serum cholinesterase protein was synthesized, in the manner already described by several investigators. In one case (F.S.) the drug administered came from an impotent lot, and only a small drop in serum cholinesterase activity occurred. In most cases, variable and insignificant drops in blood pressure occurred one to one and one-half hours after the injection, and in most cases the blood pressure returned to pre-injection levels while the serum cholinesterase depression remained marked. Multiple injections of diisopropyl fluorophosphate were without effect on blood pressure. In the patient who received an injection of impotent diisopropyl fluorophosphate the drop in blood pressure one and three-quarter hours later was as great as any in the group who had received the potent preparation.

G. Cold Pressor Tests. Three hypertensive patients were subjected to cold pressor tests, the right hand being immersed in ice water for one minute. Blood pressure was recorded every one-half minute for five minutes, and every minute thereafter for another five minutes. The serum cholinesterase activity was measured every minute for 10 minutes. In each case there was an abrupt rise in blood pressure during the first minute, with subsequent rapid fall to pre-test levels. Changes in serum cholinesterase activity were minimal and insignificant.

H. Veratrum Viride. Veratrum viride was administered to two patients. Patient M.C. received the drug for four days in amounts of 40 Craw units daily. This produced a mild drop in her blood pressure. No significant changes were noted in her serum cholinesterase activity. The second patient, E.K., received 40 to 100 Craw units daily for five days. No significant effect was observed in the blood pressure until early in the morning of the sixth day, when it suddenly dropped to 80/50, and remained at about this level for several hours, following which, over the next 12 hours, it rose to pretreatment levels. No significant alterations occurred in the serum cholinesterase activity at any time before, during, or after the abrupt drop in blood pressure.

I. Benzodioxane. One patient (M.C.) was given benzodioxane intravenously. During this procedure, her blood pressure rose slightly in the first one and one-half minutes, then gradually returned to the preinjection level. No significant alteration occurred in her serum cholinesterase activity.

J. Rice Diet. One patient (E.K.) was put on a strict rice diet for 17 days, which caused a moderate drop in blood pressure. No significant changes of serum cholinesterase were observed.
DISCUSSION

The present studies indicate that no direct relationship exists between the cholinesterase activity of the serum and the arterial blood pressure. When the values for serum cholinesterase activity in 63 hypertensive patients were compared with those obtained from healthy subjects, no significant differences were noted. Furthermore, there was no correlation between the levels of serum cholinesterase activity and the levels of blood pressure of the hypertensive patients. In other experiments reported here changes in serum cholinesterase activity and in blood pressure were compared after administration of a variety of substances which are known or reported to affect serum cholinesterase activity or blood pressure. In most instances, significant drops in blood pressure were noted following injection of sodium amytal, and tetraethylammonium chloride. In one case a severe drop in blood pressure followed administration of veratrum viride. The rice diet produced a moderate fall in blood pressure. Cold pressor tests caused significant rises in blood pressure. With the other test substances (sterile saline, vitamin K, folic acid, and diisopropyl fluorophosphate) slight, but statistically insignificant, drops in blood pressure were noted. Benzodioxane produced a slight and statistically insignificant rise in blood pressure in the one subject on which it was tried.

The serum cholinesterase activity, on the other hand, was noted to drop significantly after administration of vitamin K, folic acid, tetraethylammonium chloride, sodium amytal, and diisopropyl fluorophosphate.

When changes in blood pressure were compared with changes in serum cholinesterase activity, no correlation could be noted between the fluctuations of these two factors in any of the experiments, and it was concluded that the fluctuations were independent of each other.

SUMMARY

Normal levels of serum cholinesterase activity were found in a group of 63 unselected hypertensive patients. Seven patients were studied with a variety of drugs known to influence either blood pressure or serum cholinesterase activity, and the fluctuations in both factors were observed.

No correlation was noted between levels of serum cholinesterase activity and levels of blood pressure, nor could any correlation be established between the fluctuations of these two factors.

Significant drops in serum cholinesterase activity were noted following administration of vitamin K, folic acid, tetraethylammonium chloride and sodium amytal, and diisopropyl fluorophosphate.

It is concluded that no direct relationship exists between the blood pressure and the cholinesterase activity of the serum.

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REFERENCES


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