AN EFFECT OF PYRIDOXINE ON BLOOD UREA IN HUMAN SUBJECTS

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In 1942 pyridoxine was related to protein metabolism (1). Since that time this vitamin or a derivative thereof has been described as a component of transaminase (2) and of decarboxylase (3). Pyridoxine has been claimed to be beneficial in the treatment of a variety of diseases. An attempt to produce a deficiency of this vitamin in a human subject failed to give evidence of any significant change (4). Pyridoxine has been used with apparent success in the alleviation of nausea and vomiting in pregnancy and also of the same condition consequent to irradiation (5, 6). Hesseltine (7) described a controlled investigation in which pyridoxine therapy was compared with placebo administration, but the comparison was based only on subjective evaluation of the condition of the subjects. To date there has been no objective evidence of an effect of pyridoxine in humans. This report deals with a significant response obtained in blood urea levels before and after administration of pyridoxine in cases of nausea and vomiting in pregnancy.

Methods

Three groups of human subjects were used: (1) non-pregnant females in apparent health who were regularly engaged in laboratory work or as hospital dietitians; the latter were on a constant protein intake for 5 days before blood samples were taken and throughout the period of study; (2) pregnant females with no apparent abnormality in the prenatal clinic of the Toronto General Hospital; (3) pregnant females exhibiting definite nausea and vomiting during the first trimester of pregnancy and who were classified clinically as showing hyperemesis gravidarum. All cases in this third group were hospitalized, and following admission they received supportive therapy consisting of intravenous administration of 5 per cent glucose solution until urinary ketosis ceased. Subsequently, these patients were given a balanced adequate diet supplying 60 gm. of protein each day. Evening sedation to insure sleep was furnished if required.

Urea estimations on samples of venous blood taken after a 12 hour fast (except as noted below) and of urine were made in duplicate by the procedure of Archibald (8); the required color estimations were carried out in
a model No. 11 Coleman spectrophotometer. Urea clearances were expressed as percentages of standard clearance, by the method of Møller, McIntosh, and Van Slyke (9).

In all cases identical dosage of pyridoxine was employed, consisting of the oral administration of 40 mg. of pyridoxine hydrochloride in each of 3 successive days.

In accordance with the recommendation of Hawkins, MacFarland, and McHenry (10), a study was made of the effect of a test load of an amino acid. This was done by measurement of changes in blood urea subsequent to the oral administration of 30 gm. of DL-alanine dissolved in 300 cc. of unsweetened canned grapefruit juice. This solvent had been shown to cause no detectable change in blood urea in a group of control subjects. For convenience, alanine was given at about 7.30 p.m., following a light evening meal containing not more than 6 gm. of protein at about 5 p.m. Blood samples were taken prior to the administration of alanine and every 2 hours during the ensuing 12 hours; this regimen provided essentially a period of 12 hours without food and without disturbing the customary meal pattern of the subjects.

Table I contains the mean blood urea values for the three types of subjects before and after administration of pyridoxine. The data show that fasting blood urea was less in normal pregnant than in non-pregnant women, an observation which has been made frequently by others, and

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of subjects</th>
<th>Average blood urea with standard deviation</th>
<th>Significance of difference due to pyridoxine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg. per cent</td>
<td>mg. per cent</td>
<td></td>
</tr>
<tr>
<td>Normal non-pregnant females</td>
<td>28</td>
<td>21.3 ± 5.4</td>
<td>21.1 ± 6.0</td>
</tr>
<tr>
<td>Pregnant primiparae, all trimesters</td>
<td>40</td>
<td>12.4 ± 3.4</td>
<td>12.9 ± 3.6</td>
</tr>
<tr>
<td>Hyperemesis gravidarum</td>
<td>17</td>
<td>10.3 ± 3.1</td>
<td>15.5 ± 2.7</td>
</tr>
</tbody>
</table>

* Calculated by

$$t = \frac{d}{s_d \sqrt{n}}$$

where $d$ = the average of individual differences in blood urea for $n$ subjects, and $s_d$ = the standard deviation of the differences.
that in cases of hyperemesis gravidarum the blood urea was decreased below the value normally characteristic of pregnancy. Blood urea was increased after the administration of pyridoxine only in subjects suffering from nausea and vomiting, and the increase changed the previously low level to one typical of normal pregnancy. It should be noted that all subjects with nausea and vomiting showed urinary ketosis throughout the test period.

**Table II**

*Observations on Fasting Blood Urea*

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of subjects</th>
<th>Average blood urea with standard deviation</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mg. per cent</td>
<td><strong>t</strong></td>
</tr>
<tr>
<td>1. Normal non-pregnant females</td>
<td>50</td>
<td>22.1 ± 4.9</td>
<td>(1) vs. (2)</td>
</tr>
<tr>
<td>2. &quot; pregnant, 1st trimester</td>
<td>50</td>
<td>14.7 ± 1.8</td>
<td>(2) &quot; (3)</td>
</tr>
<tr>
<td>3. Normal pregnant, 2nd trimester</td>
<td>59</td>
<td>13.4 ± 3.5</td>
<td>(3) &quot; (4)</td>
</tr>
<tr>
<td>4. Normal pregnant, 3rd trimester</td>
<td>47</td>
<td>14.0 ± 4.7</td>
<td>(4) &quot; (5)</td>
</tr>
<tr>
<td>5. Normal pregnant, 5 days post partum</td>
<td>53</td>
<td>22.3 ± 5.3</td>
<td>(2) &quot; (6)</td>
</tr>
<tr>
<td>6. Hyperemesis gravidarum</td>
<td>17</td>
<td>10.3 ± 3.1</td>
<td></td>
</tr>
</tbody>
</table>

* Calculated,

\[
t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}
\]

where \(\bar{x}_1\) = average blood urea of one group of \(n_1\) subjects, \(\bar{x}_2\) = average blood urea of the other group of \(n_2\) subjects, and \(s\) = average standard deviation of the two groups.

In view of the differences in fasting blood urea levels between the three groups of subjects a further study was made with larger groups of non-pregnant and normal pregnant persons. Table II gives the resultant data. It is again clear that blood urea was decreased during pregnancy; in several cases the change was apparent as early as the 6th week of gestation. Within a few days after the birth of the infant, blood urea rose to the normal non-pregnant level.

In Table III are shown the results of a test load of DL-alanine. A series of observations indicated that the maximum urea value was obtained at the 6th hour after alanine administration and that the blood level returned to normal within 12 hours in non-pregnant and normal pregnant subjects. For this reason the presentation of data was restricted to values prior to
the test dose and those found at the 6th and 12th hours. Ranges of urea clearances are shown also; in all instances urea clearance was normal. It is obvious that patients with hyperemesis gravidarum responded differently to the test load of amino acid than did normal subjects, and the response became normal after the administration of pyridoxine. The normal sequence after the test load is a maximum value for blood urea at the 6th hour and a decrease to the original level by the 12th hour; the abnormal response is a failure to decrease between the 6th and 12th hours.

**Table III**

_Effect of Test Load of Alanine on Blood Urea_

<table>
<thead>
<tr>
<th>Groups</th>
<th>No of subjects</th>
<th>Mean blood urea at 0 hr.</th>
<th>Mean blood urea at 6th hr.</th>
<th>Mean blood urea at 12th hr.</th>
<th>Urea clearance range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal females, non-pregnant</td>
<td>17</td>
<td>23.6</td>
<td>30.6</td>
<td>23.4</td>
<td>70-110</td>
</tr>
<tr>
<td>pregnant, all trimesters</td>
<td>31</td>
<td>16.2</td>
<td>20.8</td>
<td>15.5</td>
<td>70-110</td>
</tr>
<tr>
<td>&quot; 5 days post partum</td>
<td>15</td>
<td>24.0</td>
<td>29.4</td>
<td>24.2</td>
<td>90-140</td>
</tr>
<tr>
<td>Hyperemesis gravidarum admission</td>
<td>14</td>
<td>10.8</td>
<td>16.2</td>
<td>15.1</td>
<td>75-100</td>
</tr>
<tr>
<td>After supportive therapy for 72 hrs.</td>
<td>8</td>
<td>13.8</td>
<td>16.6</td>
<td>16.9</td>
<td>80-110</td>
</tr>
<tr>
<td>&quot; 72 hrs., + 120 mg. pyridoxine</td>
<td>12</td>
<td>16.2</td>
<td>21.4</td>
<td>14.8</td>
<td>80-110</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The investigation of Hawkins, MacFarland, and McHenry (10) showed that an increase in fasting blood urea accompanies the development of pyridoxine insufficiency in rats and that the blood urea response to a test load of alanine is different from that obtained in normal rats. In dogs, however, an elevation in blood urea was not observed, but there was a significant increase in urinary urea. Hawkins and Barsky (4) observed no change in blood or urinary urea in a human subject maintained on a low pyridoxine diet for some weeks; the lack of any significant alteration might indicate that a state of pyridoxine insufficiency was not obtained.

In the present study the administration of pyridoxine appeared to have a significant effect upon fasting urea levels in the blood of patients showing marked nausea and vomiting in the first trimester of pregnancy, but not in that of non-pregnant or normal pregnant women. There are at least two possible explanations of the observed effect. Regardless of the administration of pyridoxine, hospitalization and supportive therapy of the subjects with hyperemesis gravidarum may have made possible a better retention of ingested food with a consequent increased intake of pro-
tein and a resultant rise in blood urea; the supposed effect of pyridoxine might have been a coincidence. An obvious alternative explanation is that pyridoxine produced the observed alteration. The results obtained with a test load of an amino acid do not support the first explanation and definitely conform to the second.

The results reported above may be interpreted as presumptive evidence that in the cases of nausea and vomiting pyridoxine insufficiency was exhibited which was ameliorated by a supply of the vitamin. While the low level of fasting blood urea was opposite to the condition found in pyridoxine-deficient rats (10), the response to a test load of alanine was entirely similar. It might be assumed that the failure of pyridoxine to produce any effect in non-pregnant and normal pregnant subjects was due to the absence of a deficiency of the vitamin. We believe that the data may be most easily explained by the assumption that a pyridoxine insufficiency was present in the cases of hyperemesis gravidarum and that the results supply the first objective evidence of any effect of pyridoxine in humans. Recently Hobson (11) has observed, on the basis of an examination of food intakes, that pregnant women showing toxemia are possibly deficient in pyridoxine and niacin.

The employment of a test load of an amino acid was useful to detect a change in nitrogen metabolism, and the application of this procedure to other types of abnormalities would seem advantageous. Preliminary observations in cases of hepatitis strengthen this view.

It is useful to consider the results obtained recently on the protective action of pyridoxine against untoward effects resulting from deep x-ray treatment. An investigation on mice by Goldfeder et al. (12) showed that pyridoxine had a significant protective value. Two clinical reports (13, 14) have indicated that pyridoxine may have a similar effect in the reduction of nausea after irradiation to that which has been claimed in the nausea and vomiting of pregnancy. The question of whether irradiation induces a state of pyridoxine insufficiency is under investigation in our laboratory.

SUMMARY

In confirmation of the work of others, fasting blood urea was significantly less in normal pregnant than in non-pregnant subjects. The urea level was definitely lower in cases of hyperemesis gravidarum than in normal pregnancy, but was restored to a typical normal value after the administration of pyridoxine. Changes in blood urea after a test load of alanine were similar in normal pregnancy to those observed in non-pregnant persons, whereas subjects with hyperemesis gravidarum showed an abnormal response which was corrected after pyridoxine was given.
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BIBLIOGRAPHY

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