Urinary Excretion of Vanillylmandelic Acid in Normal Korean Adults and in Patients with Primary Hypertension

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(Received for Publication: December 2, 1965)

ABSTRACT

Urinary excretion of vanillylmandelic acid (VMA) during a period of 24 hours was determined in 127 normal Korean adults and in 27 patients suffering from primary hypertension. The diurnal and nocturnal variations of urinary VMA excretion were measured in 30 normal persons and 11 patients with primary hypertension, and the day to day variations of urinary VMA excretion in 12 normal persons. The mean daily output of urinary VMA was fairly constant in each individual but varied widely between individuals. The mean daily output of urinary VMA in normal Korean adults is 1.95±1.15 (S.D.) mg, which is similar to that observed in occidentals. There is no significant difference between the nocturnal and the diurnal excretion of VMA. The mean daily output of urinary VMA in patients with primary hypertension was 2.17±0.76 (S.D.) mg. This means that there is no significant variation in the urinary excretion of VMA between normal adults and patients with primary hypertension. Furthermore, the urinary output of VMA is not influenced by the sex.

In 1940, Henry showed that he could isolate a conjugate of adrenalin from the urine by examining large quantities of adrenalin. Then Armstrong et al. (1957) isolated VMA from human urine. VMA is a major metabolite of norepinephrine and epinephrine. Axelrod (1958) isolated metanephrine and normetanephrine from the rat urine. In the same year, Von Euler (1958) demonstrated 3,4 dihydroxymandelic acid from human urine.

Norepinephrine may undergo O-methylation by the action of O-methyltransferase to form normetanephrine. A portion of normetanephrine produced by this reaction is excreted in the urine either in a conjugated form or as a sulfuric acid conjugate. Another portion of the normetanephrine undergoes oxidative deamination by the action of monoamine oxidase, to form VMA. As an alternative pathway, norepinephrine may be oxidatively deaminated to 3,4 dihydroxymandelic acid. A portion of 3,4 dihydroxymandelic acid is excreted in the urine, but a large fraction undergoes O-methylation to form VMA, which leads to the excretion of free and conjugated VMA and other mandelic derivatives. The metabolic pathways of epinephrine are analogous to those of norepinephrine. It is noteworthy that Kopin and Axelrod (1960) demonstrated in the rat that 3-methoxy-4-hydroxyphenylglycol is an additional metabolite of epinephrine. Kopin (1960) demonstrated that small quantities of 3-methoxy-4-hydroxyphenylglycol might be detected in the urine of normal persons. It was demonstrated, later that normetanephrine and metanephrine may be metabolized to 3-methoxy-4-hydroxymandelic aldehyde, which may be either reduced to 3-methoxy-4-hydroxyphenylglycol or oxidized to 3-methoxy-4-hydroxymandelic acid (VMA).

Many investigators (Armstrong et al. 1957,
Sunderman 1960 Gitlow 1960 and Sato 1963) examined the urinary daily excretion of VMA and agreed that the amount of urinary VMA appears to be relatively constant in each individual but varies considerably between individuals. They suggested that quantitative determination of urinary VMA, the major metabolite of catecholamines, is valuable for detecting the presence of pheochromocytoma and is also a reliable and simple test. In view of high incidence of hypertension among patients suffering from certain forms of pheochromocytoma, the urinary VMA was also determined in patients suffering from primary hypertension.

**METHOD AND MATERIALS**

One hundred and twenty seven normal Korean adults (53 males and 74 females), ranging in age from 16 to 72 years, were selected from the persons who were admitted for complete physical examination in the University hospital. Twenty seven patients suffering from primary hypertension were also included in this study. The diagnosis of primary hypertension was made following a careful workup to rule out any recognized pathologic process which might cause secondary hypertension. Nocturnal and diurnal variations in thirty normal adults and day to day variations of VMA excretion on 2 consecutive days in twelve normal adults were determined. The nocturnal and diurnal variations of VMA excretion were studied in eleven patients with primary hypertension.

Subjects were not allowed any coffee, tea, banana, chocolate, salicylate or antihypertensive drugs for 24 hours prior to and during the collection of urine to determine the VMA. Physical activity and postural stimuli were kept at a minimum. Twenty four hour urine samples were collected from each individual and were immediately brought to a pH of 2 to 4 with 3N-HCl and stored at 10°C, until the time of the chemical determination. The amount of VMA in a 24 hour urine specimen was determined according to the method of Gitlow (1960), and the amount of urinary creatinine by Folin's method (1919).

**RESULTS**

1. Urinary excretion of VMA in normal subjects:

In order to observe the daily variation of the urinary excretion of VMA, the amount of VMA in a 24 hour urine specimen was determined in an individual for 3 consecutive days. The amount of VMA excretion during a period of 24 hours was fairly constant and did not vary more than 0.4 mg per 24 hours or 0.4 mg per mg creatinine (table 1). Day to day VMA excretion in eleven normal adults determined on 2 consecutive days demonstrated that there was no significant mean difference from day to day in normal adults, as shown in table 2.

| Table 1. Daily variation of VMA excretion in a normal individual |
|---|---|---|---|---|
| Consecutive days | Urine volume (ml) | Creatinine mg per 24 hrs | VMA mg/mg Creatinine | VMA mg/24 hrs |
| 1 | 1200 | 744 | 1.85 | 1.38 |
| 2 | 1800 | 468 | 2.29 | 1.08 |
| 3 | 2200 | 546 | 2.27 | 1.24 |

| Table 2. Day to day variation in VMA excretion of 2 consecutive days in 12 normal adults |
|---|---|---|
| Day | 1 | 2 |
| No. of subjects | 12 | 12 |
| VMA mg/mg creatinine Mean±S.D. | 1.77±0.33 | 1.76±0.28 |
| Range | 1.30~2.44 | 0.61~3.20 |
| VMA mg/24 hrs Mean±S.D. | 1.81±0.83 | 1.89±0.76 |
| Range | 1.64~2.95 | 1.08~2.69 |

As shown in table 3, the mean urinary output of VMA during a period of 24 hours for 127 normal Korean adults was 1.95 mg, ranging from 0.57 mg to 7.20 mg. The mean value in
53 male was 2.11 mg per 24 hours, that in 74 females was 1.85 mg per 24 hours. This value was somewhat lower in females, but there was no significant difference in urinary excretion of VMA between females and males (P > 0.2). Two-third of the total number included between 1.0 mg and 3.0 mg per 24 hours.

Table 3. Daily excretion of urinary VMA in normal subjects

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>53</td>
<td>74</td>
<td>127</td>
</tr>
</tbody>
</table>

VMAmg/mg
Mean±S.D. | 2.17±1.49 | 2.61±1.36 | 2.40±1.47 |
Range     | 0.81~8.00 | 0.93~9.38 | 0.81~9.38 |

VMAmg/24hrs
Mean±S.D. | 2.11±1.23 | 1.85±1.01 | 1.95±1.15 |
Range     | 0.60~7.20 | 0.57~5.58 | 0.57~7.20 |

2. Nocturnal and diurnal variations of VMA excretion in normal subjects:

The nocturnal excretion of VMA, during the resting period from 8.00 P.M. to 8.00 A.M., ranged from 0.49 mg to 1.90 mg per 12 hours, with a mean of 0.96 mg per 12 hours. Diurnal excretion of VMA, from 8.00 A.M. to 8.00 P.M., ranged from 0.53 mg to 3.70 mg per 12 hours. In 13 normal subjects the nocturnal value of VMA excretion was somewhat lower than that of diurnal excretion, but there was no significant difference between nocturnal and diurnal value of the VMA excretion (P > 0.2) (table 4).

Table 4. Nocturnal and diurnal excretion of VMA in 30 normal subjects

<table>
<thead>
<tr>
<th></th>
<th>Diurnal</th>
<th>Nocturnal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>30</td>
<td>30</td>
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</tbody>
</table>

VMAmg/mg
Mean±S.D. | 2.53±1.37 | 2.02±0.79 |
Range     | 0.79~6.90 | 0.87~5.13 |

VMAmg/24hrs
Mean±S.D. | 1.25±0.62 | 0.96±0.36 |
Range     | 0.53~3.70 | 0.49~1.90 |

3. Urinary excretion of VMA in patients with primary hypertension

For twenty seven patients with primary hypertension the mean value of VMA excretion during a period of 24 hours was 2.17 mg, with a range of 0.80 mg to 3.78 mg respectively (table 5). There was no significant difference of the urinary excretion of VMA between normal adults and patients with primary hypertension (P > 0.2).

Table 5. Daily excretion of urinary VMA in 27 patients with primary hypertension

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>16</td>
<td>11</td>
<td>27</td>
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</table>

VMAmg/mg
Mean±S.D. | 2.67±2.02 | 1.47±0.35 | 2.50±1.65 |
Range     | 1.22~9.09 | 1.32~3.63 | 1.22~9.09 |

VMAmg/24 hrs
Mean±S.D. | 2.55±0.70 | 1.61±0.73 | 2.17±0.76 |
Range     | 1.30~3.78 | 0.80~2.73 | 2.80~3.78 |

4. Nocturnal and diurnal variations of VMA excretion in patients with primary hypertension

Eleven patients with primary hypertension were also studied using the process as in the normal subjects. The mean value of the diurnal excretion of VMA was 1.37 mg per 12 hours, and that in the nocturnal excretion was 1.05 mg per 12 hours. These findings were similar to

Table 6. Nocturnal and diurnal excretion of VMA in 11 patients with primary hypertension

<table>
<thead>
<tr>
<th></th>
<th>Diurnal</th>
<th>Nocturnal</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

VMAmg/mg
Mean±S.D. | 2.52±1.27 | 2.76±1.51 |
Range     | 1.16~5.56 | 0.89~7.80 |

VMAmg/24 hrs
Mean±S.D. | 1.37±0.61 | 1.05±0.54 |
Range     | 0.52~2.20 | 0.26~1.80 |
those in normal adults. In 5 patients with primary hypertension the value of diurnal excretion of VMA was somewhat higher value than that of the nocturnal excretion. There was no statistically significant difference between the nocturnal and diurnal excretion of VMA in patients with primary hypertension (P > 0.2).

**DISCUSSION**

Following the original report of Armstrong et al. (1957) concerning the urinary excretion of VMA in normal subjects and patients with pheochromocytoma, numerous investigators (Robinson 1959, Sunderman 1960, Gitlow 1960 and Crout 1960) have demonstrated the mean urinary excretion of VMA in occidentals. Sato (1963) has reported that the mean value of VMA excretion in 24 hours in thirteen normal Japanese adults was 3.95 mg per 24 hours. Our value of 1.95 mg ± 1.15 (S.D.) mg per 24 hours, ranging from 0.57 to 7.20 mg, was similar to that found in occidentals. There was no significant sex difference in VMA excretion.

Several investigators have found that the diurnal excretion of catecholamines was influenced both by physical activity and by stress. Sunderman (1960) has reported the mean excretion of catecholamines during the resting hours to be significantly lower than that during the most active working hours. In contrast, Goodal (1957), Sundermann (1960) and Elmanjian et al. (1957) have found that neither stress, physical activity nor rest affected the urinary excretion of VMA, a major metabolite of catecholamines. We also have found no significant difference between the urinary excretion of VMA in the diurnal and nocturnal samples.

Goodal and Bogdonoff (1961) have reported a somewhat higher excretion of noradrenalin in patients with primary hypertension. However, this was not observed by Henry (1957) who, has found higher urinary output of catecholamines only in patients with pheochromocytoma. Gitlow (1960) has demonstrated no significant difference in the urinary excretion of VMA in normal adults and those with primary hypertension, but VMA excretion was markedly increased in the patients with pheochromocytoma. Most studies have shown normal VMA excretion in the urine of patients with primary hypertension (Robison 1957, Gitlow 1959 and Vincent 1965). Furthermore, no correlation could be found between blood pressure level and VMA excretion (Vincent 1965). Brunjes (1964) and Theil (1965) have postulated the presence of a defect in the metabolic conversion of catecholamines in patients with primary hypertension, but Wolf (1965) could not confirm this postulation. In our experiment we found no difference in the amount of urinary VMA detected in normal subjects and in those patients with primary hypertension.

In conclusion, no changes in catecholamine metabolism were found in patients with primary hypertension using quantitative determination of urinary VMA.

**Acknowledgment:** We wish to express our thanks to Drs. C. S. Song and J. H. Kim for their advice and assistance.

**REFERENCES**


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