Metabolic Fate of an Oral Dose of $^{15}$N-labeled Nitrate in Humans: Effect of Diet Supplementation with Ascorbic Acid

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ABSTRACT

The metabolic fate of a p.o. dose of 3.5 mmol $^{15}$N-labeled nitrate has been investigated in 12 healthy young adults. Samples of urine, saliva, plasma, and feces were collected over a period of 48 hr following administration of the dose. Subjects received either 60 mg of ascorbic acid, 2 g of ascorbic acid, or 2 g of sodium ascorbate per day. An average of 60% of the $^{15}$NO$_3^-$ dose appeared in the urine as nitrate within 48 hr. Less than 0.1% appeared in the feces. The $^{15}$N label of nitrate was also found in the urine (3%) and feces (0.2%) in the form of ammonia or urea. The fate of the remaining 35% of the $^{15}$NO$_3^-$ dose administered is unknown. No effect of ascorbic acid or sodium ascorbate on the nitrate and nitrite levels of plasma, saliva, urine, or feces was observed. A one-compartment pharmacokinetic model was used to describe the relationships between intake, plasma concentration, and urinary excretion of nitrate. The half-life of nitrate in the body was found to be approximately 5 hr, and its volume of distribution was about 30% of body weight. Daily endogenous biosynthesis of nitrate was estimated to be about 1 mmol/day.

INTRODUCTION

There is widespread concern over exposure to nitrate from dietary and environmental origins and its potential risk to human health. Several epidemiological studies have suggested an association between exposure to high levels of nitrate and increased incidence of stomach cancer (2, 11, 35). While nitrate is a stable chemical species, it can be converted to nitrite by bacterial reduction in the oral cavity (29) or other areas of the body containing high concentrations of bacteria (23, 27). Salivary nitrite concentration has been reported to be directly proportional to the amount of nitrate ingested (25). The swallowing of saliva exposes the stomach to the nitrite formed in the oral cavity. Considerable evidence suggests that nitrite in the stomach has the potential to nitrosate nitrogenous constituents of food products, drugs, and agricultural chemicals to form N-nitroso compounds (4, 6, 16). Endogenous production of N-nitroso compounds has been demonstrated in humans by a number of investigators (14, 21, 30). The specific involvement of N-nitroso compounds in human disease has not been shown, but it is well established that most N-nitroso compounds are potent carcinogens in laboratory animals (17). Recent studies (7, 8, 15, 26, 34) have confirmed earlier reports (19) that the diet is not the only source of nitrate but that nitrate is synthesized endogenously from reduced nitrogen compounds. Hence, not all of the nitrate excreted in the urine is of dietary origin, although during periods of large nitrate intake, the contribution of endogenous nitrate biosynthesis to urinary nitrate is small. Urinary excretion of nitrate in humans after high nitrate intakes relative to typical dietary levels (1.2 mmol/day for the United States population [33]) range from 50 to 90% (5, 12, 22). The recovery of large p.o. doses of nitrate in laboratory animals has been found to be between 35 and 92% (10, 13, 32). Since urinary recovery is incomplete and fecal excretion of nitrate has been found to be negligible (23), it is clear that nitrate is metabolized to a significant extent in the body.

The administration of $^{15}$N-labeled nitrate allows one to study the metabolic fate of ingested nitrate more directly. Wang et al. (31) administered $^{15}$N-labeled nitrate to rats and recovered approximately 60 to 70% of the $^{15}$N label in the urine, about one-half of which was in the form of nitrate. We reported previously that about one-half of the $^{15}$N-labeled nitrate administered to humans appeared in the urine as nitrate (7); however, the urine or feces was not analyzed for the presence of $^{15}$N label in other nitrogen-containing compounds.

In addition to collections of urine, feces, and saliva, the studies reported in this paper included blood sampling up to 48 hr after ingestion of Na$^{15}$NO$_3$. This permits a comparison of urinary nitrate clearance with total nitrate clearance from the body with the use of a one-compartment pharmacokinetic model and also is helpful in interpreting salivary nitrate and nitrite data. Since supplementing the diet with ascorbic acid has been suggested as a possible means of reducing endogenous N-nitrosation (18), the effect of ascorbic acid on the clearance of nitrate from the body and on the nitrate and nitrite levels of saliva was investigated.

MATERIALS AND METHODS

The protocols for work described were screened by the Committee on the Use of Humans as Experimental Subjects of M. I. T. Subjects were selected for experiments on the basis of a medical history, thorough physical examination, and normal routine blood and urine clinical chemistry analysis. Volunteers on these studies were selected from the M. I. T. student population and participated on an outpatient basis in the M. I. T. Clinical Research Center but consumed their meals in the Department Diet Kitchen.

The first study was conducted on 6 young adult men, ages 20 to 28 years, with a mean body weight of 79 kg. Subjects received a low-nitrate diet for 7 days with complete mineral and vitamin supplements to meet all National Academy of Sciences/National Research Council recommendations, including trace elements. The diet, which has been described previously (7), consisted of a soy protein diet, supplying 0.8 g of protein (N x 6.25) per kg per day, to which egg and milk protein was added to increase protein intake to 1.5 g of protein per kg per day. The remaining calories were derived from protein-free cookies, cornstarch dessert, and carbonated and sucrose beverages. Energy intake to provide energy...

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5 ml of urine with urease in the outer well of a Conway dish (1). After a
enrichment of both ammonia and urea in urine was assayed by treating
of [15N]nitrate in feces was analyzed in an identical manner. The total 15N
cleanup step (23).

A final reverse-phase Sep-Pak (Waters Associates, Inc., Milford, Mass.)
analyzed for nitrate similarly to food samples but with the addition of a
centrifugation for 15 min (2500 x g), the resulting supernatant was
at 50°. After protein precipitation by 10 ml of 1.4 M ZnSO4 and then
diet component (10 g) was extracted for 30 min into an alkaline solution
analyzed by an automated Griess procedure (9). Diet samples were
centrifuged for 30 min at 1000 x g. Plasma was removed and stored at
-20° until analyzed.

Saliva was immediately centrifuged at 10,000 x g for
collecting urine for shorter collection periods. Saliva was collected in
sterile polypropylene centrifuge tubes containing 100 n\l of 1.0 N NaOH
amounts but similar ratios of the preservatives were added to bottles
for 3 days and pooled.

Complete daily 24-hr urine samples were collected in prewashed 2-
liter polypropylene bottles containing the following preservatives: 100 ml
of pure ethyl alcohol, 10 g of NaH2PO4, and 1.5 g of NaH2SO3. Lower
amounts but similar ratios of the preservatives were added to bottles
collecting urine for shorter collection periods. Saliva was collected in
sterile polypropylene centrifuge tubes containing 100 μl of 1.0 N NaOH
as a preservative. Saliva was immediately centrifuged at 10,000 x g for
15 min after collection in order to move any microbiological sediment or
large debris. The supernatant was removed and stored frozen (-20°)
until analyzed. Whole blood was collected in heparinized tubes and
centrifuged for 30 min at 1000 x g. Plasma was removed and stored at
-20° until analyzed.

Nitrates in urine and plasma and nitrates in saliva were measured
by an automated Griess procedure (9). Diet samples were
analyzed for nitrate according to the method of Sen and Lee (24). Each
diet component (10 g) was extracted for 30 min into an alkaline solution
at 50°. After protein precipitation by 10 ml of 1.4 M ZnSO4 and then
centrification for 15 min (2500 x g), the resulting supernatant was
placed on a short (10 cm) anion-exchange column (Dowex 1, 50 to 100
mesh). Nitrate was eluted with 20 ml of 4 M NaCl. Fecal samples were
analyzed for nitrate similarly to food samples but with the addition of a
final reverse-phase Sep-Pak (Waters Associates, Inc., Milford, Mass.)
cleanup step (23).

15N-Labeled nitrate in urine was measured by nitrogen of benzene to
form [15N]nitrobenezene, followed by gas chromatography-mass spec-
trometry (HP5992 system from Hewlett-Packard) with selected ion mon-
itoring at a mass:charge ratio of 123 (M) and 124 (M + 1) (9). The amount
of [15N]nitrate in feces was analyzed in an identical manner. The total 15N
enrichment of both ammonia and urea in urine was assayed by treating
5 m of urine with urease in the outer well of a Conway dish (1). After a
saturated K2CO3 solution is added to liberate gaseous ammonia, the
ammonia is trapped in 1% H2SO4 in the center well of the Conway dish.
The resulting ammonium sulfate solution was analyzed by isotopic ratio

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proline formation in man, manuscript in preparation.

The average fasting nitrate level in plasma was 0.03 mm for
the low-nitrate acid diet period (Table 2). After the administra-
tion of nitrate, the plasma levels rose sharply during the first hr,
a 6-fold increase above fasting levels. Nitrate levels in plasma
did not fully return to initial base-line levels until 24 to 48 hr later.
The average fasting level or rate of decay of nitrate in plasma
was not altered by supplementation of ascorbic acid or sodium
ascorbate (data not shown).

As shown in Table 2, the fasting salivary nitrate and nitrite
concentrations for 12 individuals on the low ascorbic acid diet,
measured before the nitrate dose, averaged 0.20 and 0.09 mm,
respectively. The mean nitrate and nitrite levels in mixed saliva
following the dose are also given in Table 2. Wide variations in
the concentration of nitrate and nitrite in saliva were observed
among individuals. The peak concentration of salivary nitrate
and nitrite occurred in the vicinity of 1 hr. The peak level for
salivary nitrate was roughly 10 times the fasting level, whereas
the nitrite peak was about 5 times that of the fasting salivary
nitrite level. The S:P ratios varied between 12 and 20, the higher
values occurring shortly after the dose (Table 2). The S:P ratio
averaged 17 following the dose, but 2 individuals showed S:P ratios of up to 50. The average ratio of salivary nitrite to salivary
nitrate varied from 0.19 to 0.42 (Table 2). This ratio was highest
at fasting but dropped significantly following the nitrate dose. Ascorbic acid or sodium ascorbate did not alter nitrate and nitrite
levels in saliva.

The recovery of 15N after the 15NO3" dose revealed that
approximately 60% (2.0 mmol) of the 15NO3 appears as unmetab-
ilized nitrate in urine within 48 hr after the dose. Less than
0.1% (0.001 mmol) of the nitrate dose appears in the feces as
15NO3". Three % (0.11 mmol) of the administered 15NO3" ap-

RESULTS

The daily urinary nitrate excretion for 12 subjects on a 5-day
low-nitrate acid diet (60 mg/day) was 0.78 ± 0.22 (S.D.) mmol/
day. No significant effect of ascorbic acid or sodium ascorbate
(bid only at 2 g/day) on daily urinary nitrate excretion was
found; the average daily nitrate excretion for each 5-day diet
period was 0.70 ± 0.26 and 0.68 ± 0.36 mmol/day, respectively.
However, on all 3 diets, more nitrate was excreted in the urine
than was ingested. Since the average daily intake of nitrate from
the diet for all subjects was 0.15 mmol/day, this represents
excretion of about 0.6 mmol nitrate/day in excess of dietary
intake.

The urinary excretion of a 3.5-mmol p.o. dose of 15NO3~ is
shown in Table 1. About 90% of all 15NO3~ appearing in urine
was excreted within 24 hr. Even during elevated nitrate intake,
excess urinary nitrate excretion above dietary intake still occurs,
as shown by the excretion of 15NO3~. A high supplementation of
ascorbic acid (2 g/day) or sodium ascorbate (2 g/day) had no
significant effect on urinary excretion of the 15NO3~ dose (data
not shown).

The average fasting nitrate level in plasma was 0.03 mm for
the low-nitrate acid diet period (Table 2). After the administra-
tion of nitrate, the plasma levels rose sharply during the first hr,
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The abbreviation used is: S:P ratio, the average ratio of the sum of salivary
nitrate and nitrite to plasma nitrate.

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appeared in the urine as either ammonia or urea. The \(^{15}\)N content of Kjeldahl-digested feces was considerably less (only 0.2% of the administered dose). Therefore, approximately 35% of the \(^{15}\)NO\(_3^-\) dose cannot be recovered as either excreted nitrate, ammonia, or urea.

**DISCUSSION**

Nitrate balance studies as presented here and those conducted previously (7, 8, 15, 19, 26, 34) show net urinary nitrate excretion which cannot be attributed to dietary intake. During periods of low dietary nitrate intake (0.15 mmol/day), urinary nitrate excretion in excess of dietary intake is approximately 0.6 mmol/day. We have suggested that endogenous nitrate biosynthesis in man must account for this excess urinary nitrate excretion (7). When a high intake (3.5 mmol) of nitrate, as \(^{15}\)NO\(_3^-\), was administered to subjects, this endogenous production of nitrate still occurred; excretion of \(^{14}\)NO\(_3^-\) averaged 1 mmol/day.

When the diet was supplemented with 2 g of ascorbic acid or sodium ascorbate, there was no significant effect on endogenous production of nitrate. Furthermore, while ascorbic acid effectively competes with nitrogen-containing compounds for nitrosating species derived from nitrate metabolism (18), it appears to have no influence on nitrate excretion. Following the administration of 3.5 mmol of \(^{15}\)NO\(_3^-\), the amount of nitrate appearing in the urine, plasma, or saliva was not different in supplemented and nonsupplemented ascorbic acid diet periods.

Fasting salivary nitrate levels averaged 0.09 mw, as has been reported previously for individuals consuming a low-nitrate diet (25, 29). A wide range of salivary nitrate and nitrite concentrations among the individuals was found following the nitrate dose. The variability found in this study may be associated with individual differences in salivary flow rates, oral cavity flora (25), and the capacity of the active transport mechanism for enriching saliva with nitrate (3). The ratio of nitrite to nitrate in saliva tended to average about 0.33, which is slightly higher than the value of 0.25 reported by Spiegelhalder et al. (25). This ratio appears lower at earlier times following the dose (high salivary nitrate levels) and is high at low salivary nitrate concentrations.

A possible explanation is that the nitrate reductases of the oral bacteria are approaching saturation at the peak salivary nitrate concentrations achieved following the dose (2.0 to 3.0 mmol).

The mean recovery of \(^{15}\)NO\(_3^-\) in urine was 60% of the administered dose. Previously reported recovery of nitrate in urine in human studies is between 50 and 90% (5, 7, 12, 22). The excretion of nitrate in the feces was negligible (less than 0.1%), as was similarly reported by Saul et al. (23). Excretion of nitrate in the feces has also been reported to be low in the rat following administration of nitrate (8, 31). It was found that nitrate undergoes reduction to reduced nitrogen, with 3% of administered nitrate appearing as either ammonia or urea in urine and 0.2% in feces. This is much less than the value of 16% obtained from studies with rats (8). About 35% of the \(^{15}\)NO\(_3^-\) dose cannot be recovered as excreted nitrogen-containing compounds in the urine or feces. This nitrate may undergo metabolism to gaseous products which are exhaled in the breath or appear in flatus.

A one-compartment pharmacokinetic model is a useful tool in analyzing the plasma and urine data obtained in this study. Nitrate entry into the body can occur by 2 routes, namely, dietary intake and endogenous synthesis. Nitrate is removed by urinary excretion and reaction to reduced forms of nitrogen. When the nitrate inputs to the body are taken to be constant and the removal processes are assumed to be first order in nitrate concentration, a one-compartment pharmacokinetic model leads to the following equation to describe the plasma nitrate concentrations:

\[
V_d \frac{dC}{dt} = R - k_T V_d C
\]

where \(V_d\) is the volume of distribution of the body, \(C\) is the plasma nitrate concentration, \(R\) is the net rate of input (primarily endogenous synthesis), and \(k_T\) is the total elimination constant (units of inverse time). The solution to this equation is:

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**Table 1**

<table>
<thead>
<tr>
<th>Time (hr) after dose</th>
<th>Rate of urinary excretion</th>
<th>Cumulative urinary excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (^{15})NO(_3^-) (mmol/hr)</td>
<td>(^{15})NO(_3^-) (mmol/hr)</td>
</tr>
<tr>
<td>0-1</td>
<td>0.39 ± 0.06^e</td>
<td>0.28 ± 0.05</td>
</tr>
<tr>
<td>1-3</td>
<td>0.25 ± 0.05</td>
<td>0.19 ± 0.04</td>
</tr>
<tr>
<td>3-6</td>
<td>0.19 ± 0.04</td>
<td>0.14 ± 0.02</td>
</tr>
<tr>
<td>4-6</td>
<td>0.12 ± 0.02</td>
<td>0.08 ± 0.02</td>
</tr>
<tr>
<td>6-12</td>
<td>0.06 ± 0.01</td>
<td>0.03 ± 0.00</td>
</tr>
<tr>
<td>12-24</td>
<td>0.04 ± 0.02</td>
<td>0.01 ± 0.00</td>
</tr>
<tr>
<td>24-48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2**

<table>
<thead>
<tr>
<th>Time (hr) after dose</th>
<th>Plasma (^{15})NO(_3^-) (mw)</th>
<th>Salivary (^{15})NO(_3^-) (mmol/hr)</th>
<th>Salivary (^{14})NO(_3^-) (mmol/hr)</th>
<th>S:P ratio</th>
<th>Salivary (^{14})NO(_3^-)/NO(_2^-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.03 ± 0.01^e</td>
<td>0.20 ± 0.09</td>
<td>0.09 ± 0.04</td>
<td>13 ± 9</td>
<td>0.42 ± 0.18</td>
</tr>
<tr>
<td>0.5</td>
<td>0.17 ± 0.03</td>
<td>2.3 ± 0.76</td>
<td>0.53 ± 0.22</td>
<td>20 ± 7</td>
<td>0.19 ± 0.08</td>
</tr>
<tr>
<td>2</td>
<td>0.14 ± 0.02</td>
<td>2.3 ± 0.87</td>
<td>0.52 ± 0.27</td>
<td>20 ± 7</td>
<td>0.23 ± 0.11</td>
</tr>
<tr>
<td>6</td>
<td>0.10 ± 0.01</td>
<td>1.9 ± 0.78</td>
<td>0.49 ± 0.20</td>
<td>13 ± 6</td>
<td>0.30 ± 0.14</td>
</tr>
<tr>
<td>12</td>
<td>0.06 ± 0.01</td>
<td>0.81 ± 0.18</td>
<td>0.29 ± 0.16</td>
<td>12 ± 7</td>
<td>0.38 ± 0.17</td>
</tr>
<tr>
<td>24</td>
<td>0.04 ± 0.01</td>
<td>0.43 ± 0.19</td>
<td>0.15 ± 0.06</td>
<td>15 ± 5</td>
<td>0.30 ± 0.15</td>
</tr>
<tr>
<td>48</td>
<td>0.03 ± 0.02</td>
<td>0.28 ± 0.25</td>
<td>0.10 ± 0.08</td>
<td>12 ± 5</td>
<td>0.42 ± 0.25</td>
</tr>
</tbody>
</table>

^e Mean ± S.D.
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\[ C(t) = \frac{R}{k_vV_D} + C_0e^{-kt} \]

\( C_0 \) is equal to the size of the dose divided by \( V_D \). \( \frac{R}{k_vV_D} \) is seen to be the steady-state plasma nitrate concentration, \( C_{ss} \). The above equation predicts that plotting \( [C(t) - C_u] \) versus time semi-logarithmically should yield a straight line with slope \(-k_t\) and intercept \( C_0\).

From the data in Table 2, it appears that the steady-state concentration of nitrate in plasma has a mean value of about 0.03 mm. This value was subtracted from the mean plasma concentration following ingestion of the nitrate dose and plotted versus time on semilog coordinates. It was found that the removal of nitrate from the body was, indeed, primarily first order in plasma nitrate concentration (data not shown). \( k_t \) was found to be 0.14 per hr, corresponding to a half-life for nitrate in the body of 5 hr. \( C_0 \) was determined by extrapolating the semilog plot to time 0 and was found to be 0.135 mm, indicating a volume of distribution for nitrate of 21.1 liters (\( V_D = \text{dose}/C_0 \)). Since the mean weight of all 12 subjects was 71.4 kg, the nitrate space in humans is thus about 30% of body weight. The data of Ellen et al. (5), who administered a dose of up to 130 mmol of nitrate, also shows an exponential decay in plasma nitrate concentration following ingestion and suggests a similar volume of distribution of about 30% of body weight.

The total clearance of nitrate from the body can be estimated by multiplying \( k_t \) and \( V_D \), which yields 2.9 liters/hr for the subjects of this study. Urinary clearance was calculated by dividing the average rate of urinary excretion by the log mean plasma nitrate concentration for each urine collection period, which yielded a mean value of 1.6 liters/hr. This ratio of renal to total clearance (1.6/2.9), determined from the data for total nitrate \( ^{14+15}N \), provides an independent prediction of the fraction of the nitrate presented to the body which will appear unmetabolized in urine. The urinary clearance was calculated to be 55% of total clearance, which is in good agreement with the recovery of 60% of the administered \( ^{15}NO_3^- \) in urine as nitrate.

The daily nitrate excretion in the urine was found to be in the range of 0.50 to 0.90 mmol/day. However, this only represents 60% of the total daily exposure to nitrate. Since the mean consumption of dietary nitrate was 0.15 mmol/day in this study, the amount of endogenous nitrate biosynthesis in humans can be estimated to be 0.60 to 1.4 mmol/day.

A one-compartment model is inadequate for addressing questions concerning such matters as the generation of nitrite in the oral cavity and the fate of nitrite presented to the stomach. However, since the nitrate concentration of the blood is a major factor in determining the nitrite and nitrate levels of the rest of the body, the simple analysis presented here is an important step toward developing models which will yield insight into these issues.

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Fate of $^{15}$NO$_3^-$ in Humans


Metabolic Fate of an Oral Dose of $^{15}\text{N}$-labeled Nitrate in Humans: Effect of Diet Supplementation with Ascorbic Acid


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