The Effect of Garlic Extract on Human Metabolism of Acetaminophen

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Introduction

There are a number of reports in the literature supporting the role of garlic in the prevention of cancer. Proposed mechanisms by which the sulfur constituents of garlic (e.g., diallyl sulfide) cause chemoprevention include modification of the activation of procarcinogens to corresponding electrophilic forms, stimulation of glutathione S-transferase activity, direct influence on the electrophilic metabolites, and inhibition of cellular proliferation.

Research in animals continues to evaluate the mechanisms by which garlic constituents inhibit carcinogenesis. However, clarification of the role of garlic in the chemoprevention of human cancer eventually will require studies in man. A number of commonly used drugs share some of the metabolic pathways by which carcinogens undergo bio-transformation. Furthermore, a small number of drugs also are known to produce electrophilic, reactive, intermediate metabolites at therapeutic doses, in an analogous fashion to carcinogens. Therefore, such compounds could serve as model substrates for an examination of the effects of garlic on metabolic pathways similar to those involved in carcinogenesis.

One of the most widely used compounds possessing these characteristics is acetaminophen. In addition to glucuronide and sulfate formation, a minor but significant fraction of the drug undergoes cytochrome P-450 oxidation. Metabolism by this route produces a highly active, short-lived metabolite, N-acetyl-p-benzoquinonimine. At toxic doses of acetaminophen, the concentration of this metabolite is high enough to covalently bind to proteins and DNA. At therapeutic doses, the intermediate is inactivated promptly by conjugation with glutathione and is excreted subsequently as the cysteine, mercapturate, and methylthio products. It should be emphasized that there is no evidence that acetaminophen is associated with carcinogenesis. However, the parallel between oxidative metabolism of the drug and the activation of various carcinogens is clear.

To evaluate the potential effects of garlic on the activation and deactivation of carcinogens in man, the metabolism of acetaminophen was studied in healthy volunteers before, during, and after chronic, daily administration of garlic in the form of a garlic extract.

Materials and Methods

Study Design

The overall plan of the study was to administer garlic in the form of an extract to each subject, daily, for 3 months. One gram of acetaminophen, in the form of Tylenol Caplets (500 mg/caplet; McNeil Laboratories Inc., Fort Washington, PA) was administered to each subject on five separate occasions: immediately before garlic treatment; at the end of the first, second, and third month of garlic treatment; and finally at one month after cessation of garlic treatment.

Subjects

Sixteen male nonsmokers aged (mean ± SD), 25.75 ± 3.96 years and weighing 79.1 ± 11.4 kg participated in the study. The subjects comprised 15 caucasians and 1 Asian/Pacific islander. Before entering the study, subjects received a physical examination and routine laboratory work, including complete blood cell count, electrolytes, creatinine, blood urea nitrogen, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, and total bilirubin. All values were found to be in the normal range. The study was conducted from December to May. One week before the
study began, a registered dietitian instructed the subjects on food, beverage, and medication restrictions; the daily garlic consumption; and recording dietary intake.

**Dietary and Medical Restrictions.** Subjects were encouraged to maintain normal eating habits throughout the study but to avoid vegetables in the allium family: onions, garlic, chives, shallots, and leeks. Instruction included how to read labels on food products and how to order foods at restaurants to avoid these vegetables. Alcohol consumption was limited to two drinks/day with no alcohol consumed 24 h before each acetaminophen administration. Caffeinated foods and beverages also were restricted before acetaminophen administration and during the subsequent 24 h of blood and urine collection. Medication restrictions included acetaminophen and vitamins, as well as mineral supplements at all times. Ibuprofen and aspirin were restricted before acetaminophen administration and during the subsequent 24 h of blood and urine collection. Dietary and medication restrictions began 1 week before the garlic dosing and continued for the following 16 weeks.

**Garlic Consumption.** By popular vote, the subjects chose orange juice as the vehicle for garlic consumption. Subjects were instructed to drink 10 ml of aged garlic extract (Wakunaga of America, Ltd., Mission Viejo, CA) mixed with 120 ml of orange juice each day between 6 p.m. and 10 p.m. for 12 weeks. Measuring utensils were provided and proper measuring technique was demonstrated. Juice and garlic were provided to each subject throughout the study. Garlic consumption began the day after baseline blood and urine samples were collected after the initial acetaminophen test dose.

**Recording Dietary Intake.** The subjects completed 72-h food records on three occasions: baseline, week 4, and week 12 of the study. They were asked to record food and beverage consumption on the 3 days before acetaminophen administration. The reason for assigning these days was to enhance the record-keeping compliance and to assess actual intake before sample collection. A dietitian reviewed the completed food records with each subject to assure accuracy in recording. The records were analyzed on CompuTrition software (CompuTrition, Chatsworth, CA) for total calories, protein, carbohydrate, fat, alcohol, vitamin, and mineral content.

**Compliance and Weight Monitoring.** To monitor adherence to the protocol, each subject received a dietary exception form (i.e., "whoops sheet") on which any deviation from the protocol was recorded. Each subject’s weight was measured weekly on a balance beam scale and recorded to the nearest 0.1 kg. At the time of the weight measurements, the whoops sheet was collected and compliance was encouraged.

**Garlic Extract Composition**

The constituents of the aged garlic extract were analyzed by Southwest Research Institute, San Antonio, TX under a National Cancer Institute contract and will be published in detail elsewhere. The composition of the garlic extract was reported (mean ± SD, µg/ml) as follows: diallyl sulfide, 6.91 ± 2.37; diallyl disulfide, 52.9 ± 9.40; methyl allyl disulfide, 4.33 ± 1.25; and S-allyl-cysteine, 1890 ± 305. The method of production and composition of hydroalcoholic garlic extracts have been discussed by Lawson et al. (9). Minced garlic is incubated in 15–20% alcohol for 8–20 months. These authors cite allyl (diallyl thiosulfinate) as the most prominent sulfur-containing compound in crushed or homogenized garlic. However, as is the case in this report, they were unable to detect this compound or its degradation products in a commercially available aged garlic extract. This was attributed to the volatility of the compounds and the time required for aging of the extract.

**Acetaminophen Blood and Urine Studies**

After an overnight fast, subjects entered the University of Nebraska Medical Center Cancer Clinic. Predose urine and blood were obtained for blank purposes. One gram of acetaminophen in the form of two Tylenol caplets (McNeil Laboratories) was ingested with 250 ml of water. A butterfly was inserted in a vein in the back of the hand. Five-ml blood samples were obtained at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, and 24 h in heparinized tubes. Blood was centrifuged immediately and the plasma was frozen. Urine was collected before dose administration (void) and over periods of 0–1, 1–3, 3–6, 6–12, and 12–24 h after dose administration. The urine was frozen initially. At a later date it was thawed, the volume was recorded and an aliquot of each urine sample was frozen at −70°C until assay. Subjects were allowed to be ambulatory during the collection period and could eat after the 4-hr blood sample.

**Acetaminophen Assay**

Acetaminophen and its glucuronide and sulfate conjugates were measured in plasma by the method of Slattery et al. (10). The same compounds plus 3-cysteinyl acetaminophen, acetaminophen 3-mercapturate, and 3-methylthioacetaminophen were measured in urine by the method of Wilson et al. (8).

Acetaminophen was obtained from Sigma Chemical Co. (Lot #60H0801, St. Louis, MO). Acetaminophen glucuronide and acetaminophen sulfate were kindly supplied by McNeil Laboratories Inc, Fort Washington, PA. The 3-cysteinyl acetaminophen, acetaminophen 3-mercapturate and 3-methylthioacetaminophen were generously donated by Sterling-Winthrop Production Division, Newcastle upon Tyne, England.

Chromatography was performed using a Shimadzu LC-6A solvent delivery module and SIL-6B autoinjector linked to an SCL-6B system controller (Shimadzu Corp., Kyoto, Japan). Separations were carried out on a Phenomenex 300 × 3.9-mm ID stainless steel tube packed with 10-µm Bondclone 10 C18 packing (Phenomenex, Torrance, CA). The mobile phase consisted of 7% methanol and 0.75% glacial acetic acid in 0.1 M KH2PO4. Flow rate was 2 ml/min. The detector used was an Isco V4 variable wavelength detector, set at 248 nm (lsco, Lincoln, NE) with output to a Shimadzu C-R4A data processor. In the case of the urine measurements, the UV detector was linked in series to a Shimadzu electrochemical detector (Shimadzu, L-ECD-6A) at +0.6 V, which is required to achieve the necessary sensitivity to assay the products of oxidative metabolism.

**Plasma Assay.** Plasma samples were allowed to thaw at room temperature. A 0.7-ml aliquot was transferred to a 1.5-ml microcentrifuge tube containing 0.7 ml of a 1.0 M perchloric acid (HC1O4) solution. The tube was vortexed and then placed in a microcentrifuge and centrifuged at 3000...
rpm for 4 min. A 0.8-ml portion of the resulting supernatant was transferred to another tube and 0.4 ml of a 1.0 M K$_2$HPO$_4$ solution was added. The tube was vortexed again and centrifuged at 3000 rpm for 2 min. The supernatant was transferred to an autosampler vial and 20 μl was injected onto the high pressure liquid chromatograph.

**Urine Assay.** Two aliquots (1 ml) were removed from each urine sample and transferred to vials each containing 4 ml of 2 M acetate buffer, pH 5.0. To one vial was added 50 μl of β-glucuronidase-sulfatase (Sigma). This step was necessary because most of the oxidative metabolites were conjugated further and standards of the conjugates are unavailable. The urine sample with the glucuronidase was incubated overnight at 37°C to hydrolyze the conjugates. Two hundred μl were removed and centrifuged. Twenty μl from each urine preparation was injected onto the column.

**Pharmacokinetic and Statistical Analysis**

The areas under the plasma concentration-time curves of acetaminophen, glucuronide, and sulfate were estimated up to the last sampling time by numerical integration using the Lagrange cubic polynomial method with the program LAGRAN (11). The remaining area from the last sampling time to time infinity was calculated by $C_t/k$, where $C_t$ is the concentration at the last sampling time and $k$ is the slope of the logarithm of the terminal concentrations versus time plot. The maximum peak concentration and the time to the maximum peak concentration of acetaminophen, glucuronide, and sulfate corresponded to the highest concentration observed and the time this concentration was observed after dose administration. The half-life was estimated as 0.693/k.

The apparent clearance of acetaminophen was estimated by the dose (1000 mg) divided by the area under the acetaminophen plasma concentration-time curve. Renal clearance was estimated by dividing the amount of drug or metabolite recovered in the urine by the corresponding area under the plasma concentration-time curve. Partial (formation) clearances of each metabolite was estimated by multiplying the fraction of the dose recovered in the urine as the respective metabolite and the apparent acetaminophen clearance. For this calculation, both acetaminophen dose and the urinary recovery of the metabolite were expressed in molar quantities. Pharmacokinetic parameters obtained after each acetaminophen administration were compared using repeated measures analysis of variance (SAS Institute, Inc., Cary, NC). Significance was ascertained at the 5% level ($P < 0.05$).

**Results**

The subjects seemed to tolerate the chronic administration of garlic extract well. Five individuals (not included with the 16 subjects described here) withdrew from the study. These subjects exhibited the following toxicities, rated in accordance with National Cancer Institute Toxicity Criteria: Subject 1, vomiting (grade I); subject 2, vomiting and diarrhea (grade II); subject 3, diarrhea (grade II); subject 4, nose bleed (grade I); and subject 5, gas with distention (not severe enough to achieve a grade). Two other subjects experienced flatus but did not withdraw from the study. Surprisingly, body odor was not noticeable during the 3 months of daily ingestion of garlic extract.

The participants who completed the study maintained base-line weight (± 3%) over the study. Mean caloric intake also was reasonably constant during the study with mean values of 2210, 2563, and 2388 Kcal at baseline, week 4, and week 12. Based on diet records and whoops sheets, subjects were remarkably compliant with regard to diet, alcohol, and drug restrictions.

A typical plasma concentration profile of acetaminophen and its glucuronide and sulfate conjugates is shown in Fig. 1. The associated urinary excretion rate plots of acetaminophen, 3-cysteiny1-acetaminophen and acetaminophen-3-mercapturate are presented in Fig. 2. The individual values for the pharmacokinetic parameters are summarized in Tables 1 and 2. The mean values for half-lives, renal clearance, and partial clearance of metabolites compare well with those found by others (8, 10). All values were compared statistically using repeated measures analysis of variance. The SEs in the tables reflect the considerable intersubject variability. In the repeated measures analysis of variance this variability is partitioned out leaving the variability due to the experimental condition under study (i.e., garlic treatment). In this way, greater precision is attained and even seemingly small differences in mean values are detectable.

There were several differences seen among the treatments. The area under the plasma concentration-time curve for acetaminophen at 2 months of garlic extract treatment (Table 1) was significantly increased. A significant increase in the area under the plasma concentration-time curve for acetaminophen glucuronide was found after 3 months of garlic extract treatment. A significant increase in the peak plasma concentration of acetaminophen was observed after 1 month of garlic extract treatment and was associated with the lowest time of occurrence of the peak plasma acetaminophen concentration (Table 2). Finally, a significant increase was seen in the peak concentration of acetaminophen and a decrease was seen in the sulfate peak concentration 1 month after garlic extract administration had ended. A similar decrease was noted with the glucuronide conjugate but just failed statistical significance ($P = 0.0575$). All other parameters did not appear to be affected by garlic extract treatment.

**Discussion**

Garlic has been suggested as a chemopreventive agent for cancer. Several mechanisms have been proposed to explain
Effect of Garlic Extract on Acetaminophen Metabolism

Fig. 2. Excretion rates of acetaminophen, 3-cysteinyl-acetaminophen and acetaminophen-3-mercapturate plotted against the time of the midpoint ($T_{mid}$) of each urine collection. Data was collected from the same individual as in Fig. 1.

how garlic exerts its chemopreventive effects. One component of garlic, diallyl sulfide, has been shown to inhibit the carcinogenic effect of agents requiring metabolic activation, such as dimethylhydrazine and dimethylnitrosamine (1–3). Suppression of cytochrome P450IIE1 in hepatic microsomes also was observed (1).

Another potential mechanism for the chemopreventive action of garlic is stimulation of glutathione $\mathbf{S}$-transferase activity (4). Allyl methyl trisulfide and diallyl sulfide have been found to enhance glutathione $\mathbf{S}$-transferase activity in a variety of tissues in animals (4, 5). Elevated glutathione activity would result in increased conjugation and therefore more efficient detoxification of reactive electrophilic metabolites.

In light of these postulated mechanisms, the use of acetaminophen as a model substrate seems most appropriate. Acetaminophen is metabolized by three principal routes. The greatest fraction of the dose is converted to the glucuronide and sulfate conjugates, which are excreted by the kidneys. A much smaller fraction is oxidized by cytochrome P-450, yielding a reactive intermediate metabolite, N-acetyl-p-benzoquinonimine. At therapeutic doses, this intermediate is detoxified efficiently by glutathione conjugation. Subsequent modification of the conjugate results in the formation of 3-cysteinyl-acetaminophen, acetaminophen-3-mercaptopurate, and 3-methylthioacetaminophen. Thus, evaluation of the effects of chronic garlic administration on acetaminophen metabolism could aid understanding of a possible mechanism of garlic chemoprevention in man.

Our results indicate that the oxidative pathway that leads to the reactive metabolite is not affected by the garlic treatment. Mean values of the partial clearance of the cysteinyl, mercapturate, and methylthio conjugates of acetaminophen were similar for all treatment groups, and no statistical differences were found. There are several reasons that might explain this apparent lack of effect. First, the diallyl sulfide concentrations in the garlic extract were considerably lower than those used in animal experiments demonstrating inhibition of metabolic activation (1). Second, although the isozyme P450IIE1, which was suppressed in the animal experiments, is involved in the formation of the reactive acetaminophen metabolite, other isozymes, including P450IA2, are also capable of the metabolic conversion (12). The effect of diallyl sulfide on these isozymes is not known. Furthermore, it should be noted that in the animal experiment cited, suppression of the IIIE1 was accompanied by elevation of IIB1 (1).

The second mechanism by which garlic may exert its chemopreventive action is stimulation of glutathione $\mathbf{S}$-transferase activity. Again, our studies show no change in the partial clearances of the three metabolites arising from conjugation of the reactive intermediate with glutathione. Furthermore, there were no significant differences in the excretion rate plots for the cysteinyl and mercapturate metabolites. That this lack of effect should be found is consistent with one animal study demonstrating that following diallyl sulfide administration to female CD-1 mice, glutathione $\mathbf{S}$-transferase activity increased in various tissues but no change in the level of hepatic glutathione $\mathbf{S}$-transferase activity was observed (13). However, in another study, A/14 and C57B1/1 mice were treated similarly and hepatic glutathione $\mathbf{S}$-transferase activity was increased (14).

In addition to the fairly low levels of diallyl sulfide, a major component of the garlic extract was $\mathbf{S}$-allyl-$\mathbf{l}$-cysteine. Experiments by Slattery et al. (10) have shown that at doses of 3 gm acetaminophen, glutathione conjugation is saturable. Furthermore, in subjects taking this relatively high acetaminophen dose, administration of a single, 10-gm N-acetylcysteine dose apparently enhanced glutathione conjugation. Because our studies were performed using therapeutic doses of acetaminophen, that is 1 gm, it is likely that sufficient glutathione is available for efficient conjugation of the reactive metabolite. Thus, at this dose, the effects of increases in glutathione activity as a result of chronic administration of $\mathbf{S}$-allyl-$\mathbf{l}$-cysteine may not be discernible.

Also, in agreement with the studies of Slattery et al. (10) investigating the influence of N-acetylcysteine on acetaminophen disposition, there appears to be an elevation in the formation of the sulfate conjugate of acetaminophen. A slight (average 8.6%) but not statistically significant increase in the area under the sulfate plasma concentration-time curves during garlic administration compared with both pretreatment controls was seen. No statistically significant changes in the renal clearance or the partial or formation clearance of the sulfate was found. Furthermore evaluation of the effect of garlic extract on sulfate formation was performed by fitting the acetaminophen sulfate plasma concentrations to a pharmacokinetic model with a first order formation rate constant and either a one- or two-compartment model for sulfate disposition. This analysis revealed that the mean formation rate constant for the sulfate metabolite was higher on months 1 ($P < 0.022$) and 3 ($P < 0.011$), but not for month 2 ($P > 0.225$) of garlic extract administration compared with pretreatment controls. Sulfation requires inorganic sulfate as a precursor to 3'-phosphoadenosine 5'-phosphosulfate, the co-factor required for sulfoconjugation. Sulfate can be supplied as inorganic sulfate or a thiol-containing amino acid. Thus, it would appear that the $\mathbf{S}$-allyl-$\mathbf{l}$-cysteine is a likely candidate for enhancement of sulfate conjugation. For many compounds, such as phenols (15), sulfation is a primary route of inactivation. Thus, enhancement of sulfoconjugation by garlic extract administration for such compounds could represent a mechanism of chemoprevention.
The increase in the peak plasma concentration of acetaminophen after 1 month of garlic extract administration, accompanied by a decrease in the time to peak, but no change in area under the plasma concentration-time curve argues strongly for an increase in the absorption rate of the drug. However, such changes were not observed at later times. Acetaminophen frequently has been used as a marker for esophageal and gastric emptying rates (16, 17). These findings suggest that the gastrointestinal distress noted in the subjects may be associated with increased gastrointestinal motility. However, this change diminishes with time because the gut apparently adapts to the chronic garlic extract administration.

Two other observations were made in this study that are less easy to explain. The first is that there appears to be an increase in the area under the glucuronide plasma concentration-time curve. The value at the end of the first month of garlic administration is almost identical to the pretreatment control value. At the end of the second month it is higher, but not significantly so. However, by the third month the increase is statistically significant. A slight trend toward lower renal clearance of the glucuronide conjugate was seen, but it was not statistically significant. Similarly, a trend toward increased glucuronide partial clearance was seen, although again it was not statistically significant. The only other report in the literature of a vegetable-based diet-enhancing glucuronidation is that of Pantuck et al. (18). After a 10-day diet fortified with brussels sprouts and cabbage, acetaminophen glucuronidation, but not sulfation, was increased significantly. The possibility that garlic treatment might increase both conjugation pathways is interesting but cannot be substantiated from the present data.

Secondly, the peak concentration of acetaminophen was statistically higher in the post-treatment compared with pretreatment control. Also, the peak plasma concentrations of both the glucuronide and the sulfate were lower 1 month after the end of garlic treatment, although the glucuronide just fails to be statistically significant (P < 0.057). Many factors influence the peak concentration of a compound in the body, including the rate of formation, the rate of elimination, and the volume of distribution of the substance. The lowest mean values of the area under the plasma concentration-time curve of both glucuronide and sulfate were observed in the post-treatment study, which would suggest increased clearance or a reduced fraction of drug being metabolized by this route. However, the renal clearance of these conjugates does not show such increases. Therefore, the decreased peak concentrations and areas may reflect decreases in the rate of glucuronidation and sulfation. Whatever the reason for the changes, it is interesting that in this study, chronic garlic administration exerted an effect that appeared to influence the disposition of acetaminophen metabolites 1 month after the treatment stopped.

### Table 1 Summary of mean values of primary acetaminophen pharmacokinetic variables in humans consuming garlic extract for 3 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under plasma curve (mg/l/h)</td>
<td>28.6 ± 2.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29.7 ± 2.7</td>
<td>30.4 ± 2.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29.0 ± 2.1</td>
<td>31.7 ± 2.7</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>108.3 ± 6.0</td>
<td>108.6 ± 7.3</td>
<td>114.4 ± 5.4</td>
<td>118.6 ± 6.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>106.5 ± 6.5</td>
</tr>
<tr>
<td>Glucuronide</td>
<td>35.0 ± 2.6</td>
<td>37.2 ± 2.4</td>
<td>36.7 ± 2.2</td>
<td>37.6 ± 5.4</td>
<td>30.6 ± 2.3</td>
</tr>
<tr>
<td>Renal clearance (l/h)</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.2</td>
<td>0.7 ± 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>8.1 ± 0.8</td>
<td>9.1 ± 0.8</td>
<td>8.1 ± 0.4</td>
<td>8.0 ± 0.5</td>
<td>9.3 ± 0.8</td>
</tr>
<tr>
<td>Glucuronide</td>
<td>11.2 ± 0.7</td>
<td>13.9 ± 2.3</td>
<td>14.0 ± 2.8</td>
<td>12.0 ± 1.3</td>
<td>12.7 ± 1.2</td>
</tr>
<tr>
<td>Sulfate</td>
<td>13.2 ± 1.6</td>
<td>15.2 ± 1.6</td>
<td>14.1 ± 1.4</td>
<td>14.6 ± 1.1</td>
<td>13.9 ± 2.2</td>
</tr>
<tr>
<td>Partial clearance (l/h)</td>
<td>8.7 ± 1.0</td>
<td>11.5 ± 1.4</td>
<td>13.2 ± 3.3</td>
<td>11.1 ± 1.6</td>
<td>10.0 ± 1.9</td>
</tr>
<tr>
<td>Cysteine</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Mercapturate</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.0</td>
<td>0.5 ± 0.0</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Methylthio</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> SE of the mean.

<sup>b</sup> Significantly different from pretreatment controls (P < 0.05).

### Table 2 Summary of mean values of secondary acetaminophen pharmacokinetic variables in humans consuming garlic extract for 3 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak plasma concentration (mg/l)</td>
<td>8.1 ± 0.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.1 ± 0.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10.1 ± 1.3</td>
<td>10.1 ± 1.0</td>
<td>11.1 ± 1.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>14.4 ± 1.1</td>
<td>14.7 ± 1.2</td>
<td>14.2 ± 0.7</td>
<td>15.2 ± 1.0</td>
<td>12.6 ± 0.8</td>
</tr>
<tr>
<td>Glucuronide</td>
<td>5.1 ± 0.3</td>
<td>5.2 ± 0.4</td>
<td>5.4 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>4.5 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Time to peak plasma concentration (hour)</td>
<td>1.1 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>3.1 ± 0.3</td>
<td>3.4 ± 0.2</td>
<td>3.2 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>Glucuronide</td>
<td>1.8 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>1.5 ± 0.1</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Sulfate</td>
<td>2.8 ± 0.02</td>
<td>2.9 ± 0.2</td>
<td>2.9 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>3.4 ± 0.2</td>
</tr>
<tr>
<td>Half-life (hour)</td>
<td>3.8 ± 0.02</td>
<td>3.8 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>3.9 ± 0.2</td>
<td>3.9 ± 0.2</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>3.6 ± 0.2</td>
<td>3.5 ± 0.2</td>
<td>3.9 ± 0.3</td>
<td>3.2 ± 0.2</td>
<td>3.3 ± 0.3</td>
</tr>
<tr>
<td>Glucuronide</td>
<td>3.3 ± 0.3</td>
<td>3.5 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>3.2 ± 0.2</td>
<td>3.3 ± 0.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> SE of the mean.

<sup>b</sup> Significantly different from pretreatment control (P < 0.05).
In conclusion, chronic garlic extract administration appears to have little effect on the metabolism of acetaminophen. No change was observed in the oxidative metabolism of the drug, nor in glutathione conjugation of the reactive metabolite. A very slight increase in glucuronidation occurred after long-term administration of the extract. Some evidence of enhanced sulfate conjugation was observed. These findings suggest that garlic extract has limited potential as a chemopreventive agent.

References
The effect of garlic extract on human metabolism of acetaminophen.

P R Gwilt, C L Lear, M A Tempero, et al.