Pharmacokinetics and Pharmacodynamics of Oltipraz as a Chemopreventive Agent¹


ABSTRACT

Oral oltipraz, as a single-dose treatment, was evaluated as a chemopreventive agent in 31 normal subjects. In a subset of subjects, the relationship between plasma oltipraz concentrations and the induction of lymphocyte glutathione (GSH) and glutathione S-transferase (GST) enzyme levels was evaluated. Pharmacokinetic analysis revealed nonlinear disposition of oltipraz with disproportionate 40-fold increase and 9.5-fold decrease in peak plasma concentrations (Cmax) and p.o. clearance, respectively, over the dose range of 100–500 mg. There was no correlation between the oltipraz dose and the absorption rate or the time to reach Cmax. Since oltipraz undergoes extensive metabolism, saturable first-pass elimination could be one of the sources of nonlinearity. Pharmacodynamic evaluation was conducted based on the percentage of elevation of GSH and GST levels over baseline in lymphocytes of subjects receiving 100 mg and 125 mg oltipraz. Induction was observed in both dose groups with a time lag between the maximum concentrations of oltipraz and that of GSH or GST. We also observed a linear correlation between oltipraz Cmax and the corresponding GST and GSH elevations. Subjects with higher Cmax values showed a greater increase over baseline in the GSH and GST levels. Mild toxicities were observed at all dose levels. The most common were flatulence, hunger, fatigue, and headache. These preliminary results indicate that oltipraz may be effective in inducing GSH and GST, an enzyme capable of carcinogen elimination.

INTRODUCTION

Chemoprevention refers to the administration of agents to inhibit various stages of carcinogenesis (1). Oltipraz³ belongs to the class of 1,2-dithiole-3-thiones found in cruciferous vegetables. Epidemiological data suggest that consumption of cruciferous vegetables such as cabbage, broccoli, and brussel sprouts, which are a source of 1,2-dithiole-3-thiones, results in decreased cancer risk in humans (2, 3). Animal studies suggest that cabbage-supplemented diets protect against carcinogens by an increase in the activities of a number of Phase II enzymes including GST in conjunction with the elevation of intracellular GSH levels (4–6). GSTs comprise a family of enzymes that can conjugate potential carcinogens with GSH, resulting in increased water solubility and elimination of the xenobiotics (7–9). GSH is an important cellular nonprotein thiol, which has been shown to serve as a protector against oxidants, free radicals, and electrophilic intermediates or certain chemicals including drugs (10). Owing to its ability to induce GSH and GST enzyme levels, oltipraz has shown efficacy as an inhibitor of experimental carcinogenesis in breast, bladder, liver, forestomach, colon, trachea, lung, and skin cancer in rodents (reviewed in Ref. 11). Thus, based on available data, oltipraz appears to be a potential chemopreventive agent. However, there is limited information on effective daily doses and toxicities of oltipraz in humans.

Modulation of GST activity has been identified as a drug effect marker of oltipraz administration. Additionally, if modulation of GST activity is found to relate to cancer incidence in a particular target tissue, this may very well represent the primary mechanism of oltipraz’s chemopreventive effect in that target (12). Rao et al. (13) have demonstrated enzyme induction in the tissues of rats treated with oltipraz. Elevation of Phase II enzymes has also been reported in murine hepatoma cells and in human peripheral blood lymphocytes following oltipraz exposure (14, 15). Lymphocytes are considered to be a reliable surrogate tissue for detecting liver GST polymorphisms in humans (16). Elevation of GST and GSH levels in lymphocytes may serve as surrogate markers for relevant chemopreventive pharmacodynamic activities of oltipraz in other target organs, if modulation in lymphocytes is predictive of modulation in other relevant target organs, and is validated in future trials addressing this issue.

The goals of this study were to: (a) characterize the pharmacokinetics of oltipraz following single p.o. doses, (b) inves-

¹ The abbreviations used are: Oltipraz, 5-(2-pyrazinyl)-4-methyl-1,2-dithiole-3-thione; GST, glutathione S-transferase; GSH, glutathione; NIST, National Institute of Standards and Technology; AUC, area under the plasma concentration time curve; Cmax, maximum concentration; Tmax, time to reach maximum concentration; CLp.o, apparent p.o. clearance; CV, coefficient of variation.

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² To whom requests for reprints should be addressed, at Section of Hematology/Oncology, The University of Chicago, 5841 South Maryland Avenue, MC 2115, Chicago, IL 60637.
tigate the induction of GSH and GST in lymphocytes, and (c) evaluate toxicity associated with a single p.o. dose of oltipraz.

**PATIENTS AND METHODS**

**Subjects.** Normal subjects from the University of Chicago volunteer program were chosen. The subjects had no previous chemotherapy, immunotherapy, or radiation therapy, were at least 20 years of age, and had an Eastern Cooperative Oncology Group performance status of 0. The subjects had no serious renal, pulmonary, hepatic, or cardiac problems and were not glucose-6-phosphate dehydrogenase deficient. Pregnant women were excluded from the study. Informed written consent was obtained from all subjects in accordance with institutional and federal guidelines.

**Treatment.** A pilot study to determine pharmacokinetics following p.o. administration of oltipraz involved 15 patients at dose levels of 125–500 mg. A more thorough investigation followed which included 16 patients at a dose of 20–125 mg, and both pharmacokinetics and pharmacodynamics were evaluated. Oltipraz capsules (RP 35972) were formulated by Rhône-Poulenc (Paris, France) and were supplied by Ogden Bioservices (in 20, 50, 100, and 125 mg strengths). Subjects were admitted to the University of Chicago Clinical Research Center for the duration of the study. Oltipraz was administered as a single p.o. dose following a high-fat breakfast. This was done because the bioavailability of oltipraz is markedly enhanced by the coadministration of food, and a high-fat meal could further improve the systemic availability (17–19).

Blood samples (7–10 ml each) were collected before drug administration and at 1, 2, 3, 4, 5, 6, 8, 12, 18, and 24 h after dosing. For the second investigation, additional blood samples (20–30 ml) were collected at predose and at 6, 10, and 24 h after drug administration to measure GSH and GST levels.

**Sample Analysis.** To quantitate oltipraz in plasma samples, a modification of the extraction method published by Bennett et al. (20) was used. One hundred µl plasma were spiked with 50 µl internal standard (ethyl oltipraz, 4 µg/ml; Rhône-Poulenc) and extracted twice with 3 ml heptane. After centrifugation, the supernatant (~5.5 ml) was evaporated to dryness under nitrogen. The samples were reconstituted with 40% methanol and analyzed by reversed phase HPLC using a µNovapak C18 column (10 µm, 3.9 × 300 mm; Waters Associates, Milford, MA). The mobile phase consisted of 60% methanol:40% 50 mM ammonium acetate. The amount of oltipraz in the samples was quantitated by monitoring absorbance at 448 nm. Adequate measures were taken during sample extraction procedures to prevent exposure to light. Extraction efficiency was determined to be >90%, and all samples were analyzed in duplicate. Standards from the NIST were also analyzed. There was less than 5% deviation between the actual concentrations versus those determined by our methods, which were acceptable by NIST.

For the quantitation of GSH, lymphocytes were isolated by adding 30 ml blood to an equal volume of RPMI 1640 medium and layered on Ficoll-Paque as described (21). After centrifugation at 400 × g for 30 min, the layer containing lymphocytes was removed and resuspended in 15 ml PBS and centrifuged at 400 × g for 10 min at room temperature. Resuspension in PBS and centrifugation were repeated twice. Final pellets were suspended in 0.1 mM potassium phosphate buffer (pH 6.65). GSH was measured using the glutathione disulfide reductase methods of Tietze (22) and Griffith (23). Following two repeated 10-s sonications of the lymphocytes in phosphate buffer, separated by 30 s, sulfosalicylic acid (1.7%; Sigma Chemical Co., St. Louis, MO) was added. The samples were placed on ice for 10 min and centrifuged at 500 × g for 5 min at 4°C. The supernatant was incubated with NADPH, 5,5’-dithiobis(2-nitrobenzoic acid), and glutathione reductase (Sigma Chemical Co.) in sodium phosphate/EDTA buffer (pH 7.5). Glutathione reductase was added immediately prior to reading at 412 nm. Results were compared to standard curves constructed using increasing concentrations of GSH in place of lymphocyte extract in the reaction mixture. Protein estimations were done according to the method of Bradford (24).

Total GST in the lymphocytes was determined using a kinetic spectrophotometric assay (25). Frozen lymphocyte pellets were rapidly thawed, resuspended, and sonicated twice at 15-s intervals. Supernatant was obtained following centrifugation at 10,000 × g at 4°C for 30 min. Reaction mixtures contained 500 µM GSH, cytosolic extract (300 µg total protein), and 3.2 mM 1-chloro-2,4-dinitrobenzene (Eastman Organic Chemicals, Rochester, NY) in 0.01 M potassium phosphate buffer (pH 6.65). The reaction was performed in a cuvette, and the increase in absorbance was monitored at 0.25-min intervals for 2.5 min. GST activity was determined as the linear rate of formation of substrate. Protein estimation was performed according to the method of Bradford (24).

**Pharmacokinetic Analysis.** Plasma concentration-time data of oltipraz were analyzed by noncompartmental methods using PCNONLIN (SCI Software, Lexington, KY). Estimates of $C_{\text{max}}$ and $T_{\text{max}}$ were obtained from visual evaluation of the plasma profile. AUC from time 0 to the last sampling time point (AUC$_0$) was calculated using the trapezoidal rule. The AUC extrapolated to time infinity (AUC$_\infty$) was estimated by dividing the last quantifiable concentration by the terminal rate constant ($K_t$) obtained by log linear regression of the terminal phase. The total AUC was the sum of both the AUC estimations. The terminal $t_{1/2}$ was determined as the ratio of 0.693 to $K_t$. $Cl_{\text{tot}}$ was calculated as the ratio of the dose to the total AUC. $K_t$ was determined by stripping the plasma concentration time profile using RSTRIP (Micromath Scientific Software, Salt Lake City, UT).

**Pharmacodynamic Analysis.** GSH $C_{\text{max}}$ and GST $C_{\text{max}}$ and the corresponding GSH $T_{\text{max}}$ and GST $T_{\text{max}}$ were determined by visual evaluation of the lymphocyte GSH/GST concentration-time profile. The percentage of elevations at 6, 10, and 24 h following p.o. oltipraz were determined using the following equation:

$$\% \text{ Elevation} = \frac{\text{Postdose level} - \text{Baseline}}{\text{Baseline}} \times 100$$

Due to nondetectable plasma levels of oltipraz following 20- and 50-mg doses, pharmacokinetic-pharmacodynamic analyses were performed for the dose levels of 100 mg and 125 mg only.
The concentrations resulting from all doses greater than 50 mg were below the limit of quantitation (−5 ng/ml). The observed concentrations resulting from all doses greater than 50 mg were higher than that reported in another investigation (19).

Nonlinearity was observed in the disposition of oltipraz. The C_{max} values showed a disproportionate 40-fold increase over the 5-fold dose range, suggesting increased p.o. bioavailability of oltipraz with increasing doses (Table 1). Accordingly, there was a 44-fold increase in the AUC estimates (data not shown), which resulted in a 9.5-fold decrease in the Cl_{ao} estimates over the dose range. K_{e} and T_{max} values were unrelated to the dose. While the K_{e} values ranged from 0.19 to 4.5 h⁻¹, the T_{max} values ranged from 0.5 to 8 h. Within each dose level, there was a considerable amount of interpatient variability as measured by the CV percentage in the estimates of C_{max} (CV, 40–92%) and Cl_{ao} (CV, 31–71%).

Data from six patients, three from the 100-mg and three from the 125-mg dose group, were obtained for pharmacodynamic evaluation. For one patient receiving 125 mg oltipraz, the enzyme levels at the 24-h time point could not be accurately estimated. We observed intrapatient variability in the baseline levels of GSH and GST. Since induction was measured relative to baseline levels, we determined the extent of variability 1 week before and on the day of dosing (prior to oltipraz administration). The intrasubject CV in the GSH and GST levels ranged from 2 to 9% and 1 to 29%, respectively, in the 100-mg dose group and from 17 to 19% and 16 to 36%, respectively, in the 125-mg dose group (Table 2).

Elevation of GSH or GST levels over baseline was observed in both dose groups. Subjects showing elevation of GST levels also tended to show induction of GSH levels. There appeared to be a time lag between the plasma C_{max} of oltipraz and the lymphocyte C_{max} of GSH or GST. The plasma and lymphocyte profiles in a subject exhibiting the highest degree of enzyme induction (subject 1, receiving 125 mg oltipraz) is shown in Fig. 2. Overall, peak elevations in GSH levels and GST activity in lymphocytes occurred as early as 6 h after dosing, although in many instances, peak levels/activities were noted at the final sampling time (24 h), indicating that the T_{max} associated with these parameters may not have been realized in this trial (Table 2). The response was dose dependent, with the maximum induction of GSH levels in the 100-mg (subject 2) and 125-mg (subject 1) dose groups being 27 and 81%, respectively, while that observed in the GST levels was 60 and 101%, respectively.

We investigated the correlation between the oltipraz C_{max} estimates and the corresponding GSH or GST percentage of change. This was done because GSH and GST induction correlated better with oltipraz C_{max} than AUC estimates (data not shown). As apparent from Fig. 3, subjects with higher oltipraz C_{max} values had a greater induction of GSH and GST. The intrapatient variability (% CV) in the subject with the maximum induction (patient 1, 125-mg dose) was 18% for GSH and 36% for GST. In comparison, the maximum enhancement in GSH was 81% whereas GST increased to 101%, indicating that it is unlikely that these increases were due to variability in the data.

Toxicities observed were minimal and resolved without any intervention. As shown in Table 3, side effects were not dose related. In the first study, there were no toxicities at the 125-mg and 500-mg dose. In the second study, toxicities were not observed at the 20-mg dose but were noted at 50, 100, and 125 mg. Most common toxicities were flatulence, hunger, fatigue, and headache.

**DISCUSSION**

There have been a few studies reporting the dose-effect relationship of oltipraz in humans (19, 26). The current investigation was designed to ascertain the pharmacokinetics of oltipraz following a single p.o. dose and its enzyme induction effect using lymphocyte GSH and GST as drug effect markers.

Oltipraz concentrations reported in this investigation have been validated against NIST standards. The difference in values compared to other studies could be due to variations in formulation, diet, or subject characteristics (gender, body mass index, metabolic capacity, etc.). Oltipraz exhibited nonlinear disposition, which could be partly due to saturation of its metabolic pathway. This drug has been shown to undergo extensive metabolism. About 13 metabolites have been identified in the urine of mice, monkeys, and humans (27, 28). In humans, oltipraz has been shown to form a desulfurated metabolite, and two pheno-
Clinical Evaluation of Oltipraz as a Chemopreventive Agent

Table 1 Pharmacokinetic parameters following p.o. administration of oltipraz

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>K&lt;sub&gt;a&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>Terminal t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>CL&lt;sub&gt;0&lt;/sub&gt; (liter/h/m&lt;sup&gt;2&lt;/sup&gt;)</th>
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<tbody>
<tr>
<td>20 (n = 4)</td>
<td>nd&lt;sup&gt;a&lt;/sup&gt;</td>
<td>nd</td>
<td>nd</td>
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<td>nd</td>
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<tr>
<td>50 (n = 4)</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>100 (n = 4)</td>
<td>125 ± 50</td>
<td>5.50 ± 1.91</td>
<td>0.57 ± 0.33</td>
<td>4.16 ± 1.69</td>
<td>119 ± 45.8</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>(67-189)</td>
<td>(4.0-8.0)</td>
<td>(0.19-0.92)</td>
<td>(2.51-6.53)</td>
<td>(82.7-178)</td>
</tr>
<tr>
<td>125 (n = 4)</td>
<td>267 ± 139</td>
<td>1.88 ± 1.13</td>
<td>1.37 ± 0.82</td>
<td>6.95 ± 3.94</td>
<td>99.7 ± 46.5</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>(50-546)</td>
<td>(1.0-4.0)</td>
<td>(0.54-2.82)</td>
<td>(2.32-15.1)</td>
<td>(60.4-192)</td>
</tr>
<tr>
<td>250 (n = 4)</td>
<td>1062 ± 827</td>
<td>2.0 ± 1.16</td>
<td>0.96 ± 0.86</td>
<td>6.45 ± 3.60</td>
<td>47.6 ± 34.5</td>
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<td>(n = 4)</td>
<td>(288-2084)</td>
<td>(1.0-3.0)</td>
<td>(0.36-2.22)</td>
<td>(3.33-11.7)</td>
<td>(16.6-92.8)</td>
</tr>
<tr>
<td>375 (n = 3)</td>
<td>2608 ± 2387</td>
<td>3.33 ± 2.52</td>
<td>1.84 ± 2.29</td>
<td>9.01 ± 4.89</td>
<td>14.6 ± 4.53</td>
</tr>
<tr>
<td>500 (n = 4)</td>
<td>4970 ± 551</td>
<td>2.63 ± 1.70</td>
<td>0.55 ± 0.21</td>
<td>11.1 ± 2.59</td>
<td>12.6 ± 7.53</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>(1952-9493)</td>
<td>(0.5-4.0)</td>
<td>(0.25-0.70)</td>
<td>(8.89-14.6)</td>
<td>(3.63-19.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are mean ± SD with the range indicated in parentheses.
<sup>b</sup> nd, not detectable.

Table 2 Pharmacodynamic parameter estimates following oltipraz administration<sup>a</sup>

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline (nmol/mg) %CV</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (nmol/mg)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>Baseline (nmol/min/mg) %CV</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (nmol/min/mg)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
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</thead>
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<tr>
<td>100 mg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15.64 3</td>
<td>15.88 10</td>
<td></td>
<td>191.2 1</td>
<td>180.2 24</td>
<td></td>
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<tr>
<td>2</td>
<td>11.75 9</td>
<td>14.86 24</td>
<td></td>
<td>165.8 29</td>
<td>264.8 10</td>
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<tr>
<td>3</td>
<td>11.54 2</td>
<td>13.85 6</td>
<td></td>
<td>130.4 15</td>
<td>184.0 24</td>
<td></td>
</tr>
<tr>
<td>125 mg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.18 18</td>
<td>14.77 10</td>
<td></td>
<td>52.08 36</td>
<td>104.7 10</td>
<td></td>
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<tr>
<td>2</td>
<td>10.77 17</td>
<td>11.58 24</td>
<td></td>
<td>144.3 16</td>
<td>155.7 6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>14.47 19</td>
<td>19.29 10</td>
<td></td>
<td>144.8 16</td>
<td>204.9 10</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> GSH and GST levels in lymphocytes were quantitated at predose and at 6, 10, and 24 h after oltipraz dose. % CV, intrasubject CV percentage of two baseline levels determined 1 week before and on the day treatment began.

different types of oltipraz metabolizers have been identified (26). High-saturable metabolic clearance of oltipraz suggests appreciable first-pass elimination of the drug and may result in reduced systemic bioavailability from p.o. dosing while attaining enhanced hepatic delivery above that anticipated from i.v. drug administration.

Analysis of the plasma concentration-time data indicated wide variability in the K<sub>a</sub> and T<sub>max</sub> estimates, which was in agreement with a previous report (19). Since K<sub>a</sub> values were not dose dependent, transport of oltipraz across the gastrointestinal mucosa probably does not involve any active transport mechanism. The rate of gastric emptying determines the time taken for a p.o. administered drug to reach the absorption site and the rate of absorption (29). Various foodstuffs influence the secretion of gastrointestinal hormones and thereby affect gastric motility, which in turn could control formulation disintegration and subsequent dissolution of the drug (30). In the present study where oltipraz capsules were administered in the presence of food, individual differences in gastric emptying and gastric motility could have contributed to the variable K<sub>a</sub> and T<sub>max</sub> values.

Pharmacodynamic analysis of the present data demonstrated that oltipraz induced GSH as well as GST levels in the lymphocytes with the induction of GST being more pronounced than that of GSH. An elevation of GSH and GST correlated better with the C<sub>max</sub> of oltipraz compared to the systemic availability, suggesting the requirement of a minimum effective concentration for oltipraz activity. It is unknown what magnitude of increase in GSH or GST constitutes a clinical response and what duration of increase is required. The pharmacodynamic observations of the present data must be made cautiously since they are derived from only six patients distributed among two dose levels. In addition, baseline levels of GSH and GST display significant inter- and intraindividual variability which could be due to the assay as well as differences in dietary conditions between the two level assessments. Therefore, if the pharmacodynamic interpretations offered in this trial are accurate, in that lymphocyte levels of GSH and GST activity are consistently modulated by oltipraz, maintenance of a sustained increase in GST activity and GSH levels might be achieved by repeated p.o. dosing of 125 mg oltipraz. Of course, the impact of this modulation on cancer risk remains to be validated.

None of the toxicities observed in this study were dose limiting. The most frequent toxicities included flatulence, headache, fatigue, and hunger, suggesting that oltipraz is well tolerated as a single p.o. dose. Although this is consistent with previous animal as well as human studies (reviewed in Ref. 12),
the exacerbation of the toxicities on repeated dosing remains to be determined.

Chemoprevention may be a useful alternative in the control of cancer in tissues for which therapeutic intervention is relatively ineffective. Key concepts related to the development of cancer chemopreventive agents include (a) long-term administration, (b) p.o. route of administration, and (c) matching of toxic side effects to degree of cancer risk (31). Following repeated p.o. doses at 125 mg/day for 6 months, oltipraz was well tolerated with major toxicities being grade 2 rash, grade 1 headache and vision change, and grade 1 fatigue, none of which were dose limiting (32). Mean plasma concentrations obtained in this chronic dosing study were 282 ng/ml, which were higher than the plasma concentrations that resulted in maximum elevations in GSH and GST in the current study. If this dosing schedule results in sufficient increase in GSH and GST to potentially protect against carcinogenesis, then oltipraz may meet the criteria required for an effective chemopreventive agent. Additional clinical investigations are warranted.

ACKNOWLEDGMENTS

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REFERENCES

4. Wattenberg, L. W., and Bueding, E. Inhibitory effects of 5-(2-pyrazinyl)-4-methyl-1,2-dithiole-3-thione (oltipraz) on carcinogenesis.

Fig. 2 Representative profiles of the effect of oltipraz on GSH levels (A) and GST levels (B) in lymphocytes in a subject receiving a dose of 125 mg (subject I). Oltipraz plasma levels peaked 4 h after dosing while GSH and GST levels peaked at 10 h.

Fig. 3 Correlation of oltipraz Cmax values and GSH and GST percentage of change in subjects treated with a single dose of either 100 mg or 125 mg. Subjects with high Cmax values tended to have greater induction of GSH and GST.

Table 3 Toxicties associated with a single dose of oltipraz

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of patients</th>
<th>Dose (mg)</th>
<th>Grade</th>
</tr>
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<tbody>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>250</td>
<td>1</td>
</tr>
<tr>
<td>Bloating</td>
<td>1</td>
<td>250</td>
<td>2</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>Hunger</td>
<td>1</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>250</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Metallic taste</td>
<td>1</td>
<td>375</td>
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</tr>
<tr>
<td>Hives</td>
<td>1</td>
<td>125</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
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<td>125</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>250</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
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</tr>
<tr>
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