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ORIGINAL ARTICLE

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In vivo inhibition of human CYP1A2 activity by oltipraz

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Abstract *Purpose*: Oltipraz is currently undergoing clinical evaluation as a cancer chemopreventive agent, especially with respect to aflatoxin-associated hepatocarcinogenesis. The agent's ability to induce phase II xenobiotic enzymes that detoxify the ultimate carcinogen formed in vivo is thought to be an important mechanism by which disease risk may be attenuated. However, an additional mechanism could be a reduction in the activation of environmental procarcinogens by certain cytochrome P450 (CYP) isoforms. This hypothesis was tested with respect to CYP1A2, by using the clearance of caffeine by *N*-demethylation as a phenotypic trait measurement of the isoform's catalytic activity. *Methods*: Subjects received a single oral dose of caffeine (200 mg) on five separate occasions: on the day prior to oltipraz administration (day 0), 2 h after the first (day 1) of eight daily oral doses of oltipraz (125 mg) and 2 h after the last dose (day 8). In addition, CYP1A2 activity was also measured 2 and 14 days (days 10 and 22, respectively) after discontinuation of oltipraz administration. Plasma concentrations of caffeine and its *N*-demethylated metabolite, paraxanthine, over 24 h after drug administration, were determined by HPLC. *Results*: A single 125-mg dose of oltipraz markedly reduced CYP1A2 activity by 75 ± 13% in nine healthy subjects, resulting in a higher caffeine plasma level and prolongation of the in vivo probe's elimination half-life. Daily administration of 125 mg oltipraz for 8 days resulted in further inhibition so that only 19 ± 13% of the original baseline level of activity was present. However, 2 days after discontinuation of oltipraz treatment, CYP1A2 activity had returned to 66 ± 33% of its original level and complete recovery was achieved within 14 days of the chemopreventive agent being stopped. *Conclusions*: These results demonstrate that oltipraz is a potent, in vivo inhibitor of CYP1A2 in humans and, because this isoform is importantly involved in procarcinogen activation, they also indicate that such inhibition probably contributes to oltipraz's cancer-chemopreventive effect. In addition, the findings also suggest the likelihood of significant drug interactions between oltipraz and drugs whose metabolism is mediated by CYP1A2.

Keywords Caffeine metabolism · CYP1A2 · Drug interaction · Oltipraz

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Introduction

In recent years, cancer chemoprevention – the administration of agents to inhibit various stages of carcinogenesis – has received increased interest as a means to reduce the risk of developing the disease. An increasingly large number of such putative agents are under investigation, some of which have reached the stage of clinical study in humans [11, 12]. Oltipraz (4-methyl-5-(2-pyrazinyl)-3*H*-1,2-dithiol-3-thione) is one such drug [1, 5, 14, 15] and is currently undergoing phase 2 evaluation in intervention trials targeted to aflatoxin-associated hepatocarcinoma in the People's Republic of China [10, 14, 26, 29]. Although the mechanism of cancer chemoprevention, in general, is not fully understood, and is likely to be multifactorial, a determinant that is often considered to be important is a beneficial modulation in the balance of phase I xenobiotic metabolizing enzymes which activate procarcinogens, for example, cytochromes P450 (CYP), and phase II enzymes that detoxify the generated carcinogens, for example, glutathione-*S*-transferases, NAD(P)H:quinone oxidoreductase, epoxide hydrolase, and UDP-glucuronosyl transferases

[27, 28]. A number of investigations in both animals [5, 14, 15] and more recently humans [9, 20] have shown that oltipraz induces a battery of these phase II enzymes, and this is thought to be important in the drug's overall cancer chemopreventive activity. Fewer studies, however, have addressed oltipraz's potential interaction with the CYP family of enzymes and their results are somewhat contradictory. For example, oltipraz inhibited CYP1A2 and CYP3A activity in primary cultured human [16] and rat [18] hepatocytes and a similar but transient effect was also noted in vivo in the rat with respect to CYP1A [18]. On the other hand, low dietary levels of oltipraz were found to selectively induce a number of rat CYPs [13] and increases in CYP1A and CYP3A isoforms were also present after pretreatment with higher pharmacologic dosages [2, 3, 18].

Possible in vivo effects of oltipraz on CYP isoforms in humans are, however, not known. Such interactions, resulting in either inhibition or induction of specific isoforms, would not only have potential significance from the cancer chemopreventive perspective, but could also be important with respect to interactions that might arise during the therapeutic use of drugs in subjects already receiving oltipraz. Accordingly, an investigation was undertaken to determine the effect of oltipraz administration on the in vivo activity of CYP1A2, an isoform importantly involved in the activation of not only aflatoxin B_1, but also various arylamines and heterocyclic amines including food mutagens, and also the elimination of several important drugs [8].

Patients and methods

Studies were undertaken in eight healthy men and one woman of European-American ancestry, aged 24 to 35 years and weighing 51 to 104 kg. All were judged to be healthy on the basis of medical history, physical examination, and routine biochemical tests reflecting hepatic and renal function. None of the subjects were tobacco smokers and all were medication-free, including ethanol, for at least 7 days prior to each study period. In addition, caffeine-containing foodstuffs were not permitted within 3 days of a study period. The study was approved by the Vanderbilt University Institutional Review Board and all subjects provided written informed consent.

The *N*-demethylation of caffeine was used as an in vivo probe to measure the overall CYP1A2 catalytic activity of each individual subject [19]. The experimental protocol involved the oral administration of 200 mg caffeine (NoDoze, Bristol Myers Squibb) and collection of serial EDTA–blood samples (10 ml) through an indwelling intravenous cannula at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h after drug administration. CYP1A2 activity was determined on several occasions related temporally to the administration of oltipraz: initially, prior to oltipraz administration (day 0), then 2 h after the first (day 1) of eight daily oral doses of oltipraz (125 mg) and after the last dose (day 8) of treatment. In addition, the isoform's activity was also measured 2 and 14 days after oltipraz administration was discontinued (days 10 and 22, respectively). Oltipraz was administered along with a standardized high-fat breakfast to reduce the likelihood of gastro-intestinal side effects and to increase absorption [1].

The plasma concentrations of caffeine and its *N*-demethylated metabolite, paraxanthine, were determined by a solid-phase extraction, HPLC-based procedure [4, 22]. Briefly, this involved extraction of 1 ml plasma, to which 5 μg 7-(β-hydroxypropyl)theophylline had been added as an internal standard, and by using a 3 ml/500 mg column (C-18 Bond Elut, Varian Associates, Walnut Creek, Calif.), eluted with 2 × 1 ml methanol. The eluant was evaporated to dryness under nitrogen at 40 °C and the residue was reconstituted in 200 μl distilled water. An aliquot of the latter was injected onto a 5-μm (4.6 mm × 25 cm) reverse-phase C-18 column (UltraSphere, Beckman Instruments, Fullerton, Calif.) with a mobile phase of 1% tetrahydrofuran, 20% methanol, and 79% 10 mM KH_2PO_4 buffer (pH 3.5) at a flow rate of 0.8 ml/min. Caffeine and paraxanthine were measured by an ultraviolet detector set at 273 nm. The coefficient of variation for repeated determinations was less than 2.5% and the interday variability was between 10% and 15% across the concentration range of 0.5 to 5 μg/ml.

The first-order elimination rate constant (k) of caffeine was determined from the post-absorption decline in plasma levels by logarithmic linear regression, which allowed estimation of the drug's elimination half-life ($t_{1/2} = 0.693/k$). Caffeine's oral clearance (C_0) was estimated by the relationship $C_0 =$ dose/AUC, where the total area under the drug's plasma concentration vs time curve (AUC) was determined by the trapezoidal rule with extrapolation to infinite time by use of conventional formulae. Other parameters were obtained directly from the data. Comparative analysis of the pharmacokinetic parameters on the various study days used restricted/residual maximum likelihood (REML) based mixed-effect models (SAS version 7.0; SAS Institute, Cary, N.C.); this permitted adjustment for any intracorrelation effect. All tests of significance were two-sided and differences were considered significant when the P value was less than 0.05.

Results

Caffeine was rapidly absorbed following oral administration and its subsequent elimination was exponential with a half-life between about 4 and 13 h in the nine subjects. Administration of a single 125-mg dose of oltipraz, 2 h prior to caffeine administration (day 1), resulted in pronounced changes in the plasma concentration–time profiles of both caffeine and its *N*-demethylated metabolite, paraxanthine (Fig. 1). The maxi-mum plasma level of caffeine was modestly increased and its elimination half-life prolonged in all subjects (Table 1, Fig. 1). In one subject, the elimination half-life could not be determined because of an insufficient decline in the plasma levels over the sampling period; accordingly, a clearance value could not be determined. By contrast, paraxanthine plasma levels were markedly reduced (Fig. 1). These changes reflected a 2.5 to 11-fold reduction in caffeine's oral elimination clearance rather than a change in the drug's distribution, and elimination was further impaired in most subjects following 8 days of daily administration of oltipraz (Table 1, Fig. 2). After this period of treatment, the estimated CYP1A2 activity was reduced by 52–92% from its baseline activity. Two days after oltipraz administration was discontinued, caffeine's clearance had returned to 26–122% of its baseline value, and 14 days after use of the drug was stopped, this parameter had returned to its pretreatment value, or greater (Table 1, Fig. 2). Similar findings were also noted in the plasma concentration ratio of paraxanthine to caffeine estimated 6 h after caffeine administration, although this

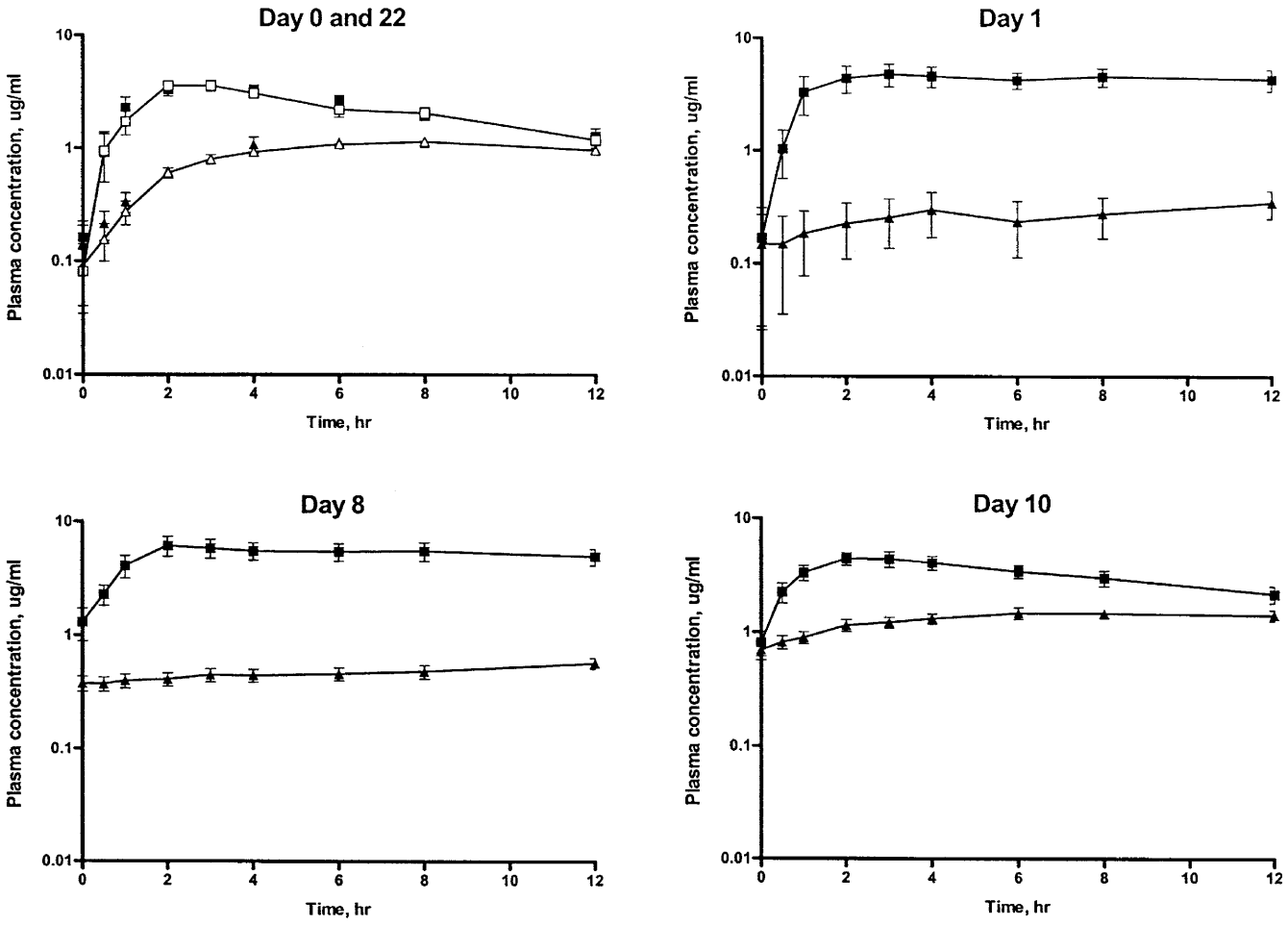

Fig. 1 Effect of oltipraz (125 mg/daily) on the plasma concentration–time curves of caffeine (■, *upper curves*) and paraxanthine (▲, *lower curves*). Data represent the mean ± SD in nine subjects, after oral administration of 200 mg caffeine. Day 0 is prior to oltipraz administration (*open symbols*, *top left graph*); day 1 is after a single oltipraz dose; day 8 is after eight daily doses of oltipraz; day 10 is 2 days after discontinuation of oltipraz administration, and day 22 (*closed symbols*, *top left graph*) is 14 days after discontinuation of oltipraz administration

alternative phenotypic measure of CYP1A2 activity did not exhibit a further reduction in its value on day 8 following 7 days of oltipraz treatment compared to that following a single dose (day 1).

Discussion

Oltipraz is undergoing a phase 2 clinical investigation in China as a cancer chemopreventive agent especially targeted towards hepatocarcinogenesis [10, 14, 26, 29]. A major mechanism of oltipraz's efficacy is, generally, considered to involve its marked induction of phase II metabolizing enzymes such as glutathione-*S*-transferases [5, 9, 14, 15, 20]. This presumably results in reduced exposure to carcinogenic species previously formed by phase I activation of environmental procarcinogens. In the case of hepatocarcinogenesis, ingestion of foodstuffs containing aflatoxin B_1 is considered to be a causative

Table 1 Effect of oltipraz (125 mg/day), given on days 1 through 8, on the pharmacokinetic parameters (mean ± SD) of caffeine in eight subjects

	Day 0	Day 1	Day 8	Day 10	Day 22
Oral clearance, ml/min	91.2 ± 28.5	23.2 ± 10.5*	16.8 ± 12.6*	60.7 ± 34.5*·**	98.1 ± 36.0
Elimination half-life, h	7.0 ± 3.1	24.2 ± 15.4	33.4 ± 22.9*	10.7 ± .9.6**	5.64 ± 1.2
Maximum plasma level, μg/ml	4.1 ± 0.9	5.3 ± 1.8*	6.8 ± 3.8*	5.3 ± 1.8*	3.9 ± 1.3
Paraxanthine:caffeine in plasma at 6 h	0.55 ± 0.16	0.06 ± 0.06*	0.10 ± 0.07*	0.47 ± 0.17**	0.47 ± 0.18

*$P < 0.05$ day 1 compared to day 0
**$P < 0.05$ day 10 compared to day 8

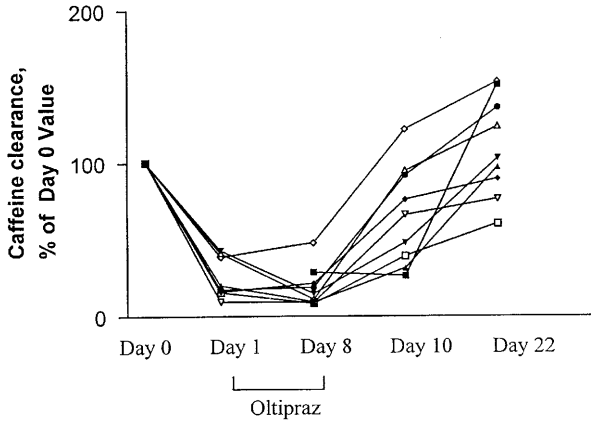

Fig. 2 Inhibition of CYP1A2 activity, measured by caffeine's oral clearance, by oltipraz (125 mg daily) in nine healthy subjects

factor because, at dietary levels, this contaminant is metabolized by CYP1A2 [7] to the ultimate carcinogen (aflatoxin-8,9-oxide) that is subsequently detoxified by phase II enzymes [14]. However, in vitro [18] and in vivo [23] studies in animals, and in vitro investigation with human liver preparation and enzymes [7, 16, 17] suggest that oltipraz's cancer chemopreventive activity might also involve inhibition of phase I activating enzymes, in particular CYP1A2. On the other hand, other studies have demonstrated that oltipraz causes induction of CYP-mediated metabolism including that involving CYP1A2 [2, 3, 15, 18]. The situation in humans receiving putative chemopreventive doses of oltipraz is similarly unclear, since previous studies have not directly addressed the issue, rather, they have used secondary measures of CYP1A2 activity that were incidental to the primary goals of clinical investigation [26] and provided no indication of the extent of any putative modulation. By contrast, the present study was designed to directly assess the nature and magnitude of any interaction in humans between CYP1A2 and oltipraz administered according to a clinically relevant dosage regimen.

The metabolism of caffeine in humans is essentially complete and the primary steps are almost solely mediated by CYP1A2 [19]. Accordingly, its plasma clearance following oral administration is considered the gold standard for estimating CYP1A2's overall activity, which in nonsmoking, healthy subjects reflects hepatic metabolism [19]. An alternative phenotypic measure appears to be the plasma concentration ratio of the metabolite paraxanthine to unchanged drug, measured 3 to 10 h after caffeine administration [6]. Both trait measures are sensitive to changes in CYP1A2 activity and have been used to temporally monitor the enzyme's modulation by drugs and other factors [19, 24]. Accordingly, the observed changes in caffeine's metabolism may be interpreted as reflecting alterations in hepatic CYP1A2 activity. It is noteworthy, however, that the change in the 6-h paraxanthine:caffeine ratio did not precisely mirror the change in caffeine clearance between days 1 and 8. This probably reflects inhibition by accumulating levels of oltipraz or metabolite(s) of paraxanthine's metabolism by CYP isoforms other than CYP1A2. Supportive evidence for this is that the paraxanthine plasma levels were higher on day 8 than on day 1.

A single 125-mg dose of oltipraz given 2 h before the dose of caffeine had a marked effect on CYP1A2: its activity was inhibited by $75 \pm 13\%$ compared to its value in the control period. Moreover, such inhibition was further increased by continued oltipraz administration, so that at the end of eight daily doses only $19 \pm 13\%$ of the baseline activity remained. This inhibitory effect is consistent with in vitro data in both rat [18] and human [16, 17] preparations; which indicates competitive and, to a lesser extent, irreversible inhibition by oltipraz of CYP1A2-mediated metabolism. However, the apparent K_i value (10 μM) of oltipraz for this interaction with yeast expressed, human recombinant enzyme [16, 17] is over an order of magnitude greater than the peak plasma level (0.5 to 1 μM) observed in subjects receiving a single 125-mg dose of oltipraz administered after a high-fat breakfast [9]. While oltipraz's concentration in the portal vein following absorption, and probably in the liver, would be expected to be somewhat higher than that in systemic plasma, this discordancy between in vitro and in vivo inhibition could reflect the mechanism-based inhibition of CYP1A2 by oltipraz or, alternatively, a role for one or more of the numerous metabolites of oltipraz [17]. Such an effect would also explain the increase in inhibition noted after repeated oltipraz doses – an observation that is not consistent with the drug's relatively short elimination half-life of about 7 ± 4 h following single-dose administration of 125 mg, since significant accumulation of the drug would not be expected when it is given every 24 h. Given such pronounced CYP1A2 inhibition after administration of 125 mg oltipraz per day for 8 days to Caucasians, it is unclear why the same daily dose in Chinese subjects did not produce a statistically significant reduction in AFM_1 excretion [26], since formation of this hydroxylated metabolite of aflatoxin B_1 is mediated by CYP1A2. One possibility is that the urine-sampling procedure in the phase 2a study was not optimally designed to detect such an effect. However, interracial differences in oltipraz's disposition resulting in lower oltipraz concentrations in the Chinese subjects might be an alternative explanation, although supportive data to this effect is not currently available.

Many drugs that inhibit CYP activity also result in induction when administered over a prolonged period; moreover, in vivo data in rats [2, 3, 13, 18] suggest that this may be the case with oltipraz. With such drugs, induction in vivo is only demonstrable after the drug level in the body has fallen below that producing inhibition, which for rapidly eliminated drugs ($t_{1/2}$ ca. 8 h) would be expected to be present 2 days after dosing has been discontinued. For example, the induction of CYP2E1 by isoniazid was clearly demonstrable at this time, even though marked inhibition was present at the

end of a multiple-dose 14-day treatment period [21]. In the case of oltipraz, CYP1A2 inhibition was still observable 2 days after administration of oltipraz was stopped, although this was substantially less than during the dosing period. Also, complete recovery had occurred 14 days after discontinuation of the treatment. Thus, it does not appear as if prolonged oltipraz administration to humans at a daily dose of 125 mg leads to the induction of CYP1A2 in vivo; moreover, the inhibitory effect is fully reversible and occurs within several days. It is, therefore, likely that even intermittent dosing at infrequent intervals, for example, one dose per week, which may be a clinically efficacious [14], could cause CYP1A2 inhibition for a considerable period of time. This would explain the observation that 500 mg oltipraz given weekly for 4 weeks resulted in a 50% reduction in AFM_1 excretion in Chinese subjects participating in a phase 2a clinical trial [26].

The demonstration that oltipraz profoundly inhibits CYP1A2 activity strongly suggests that this effect does, in fact, contribute importantly to the agent's putative cancer chemopreventive activity against chemical-induced carcinogenesis involving procarcinogen activation by the isoform. This would include arylamines like aflatoxin B_1 as well as heterocyclic amines found in cigarette smoke and formed by certain types of food processing, for example, charcoal broiling [8]. Such inhibition, therefore, beneficially complements the previously established induction of phase II enzymes to reduce the body's overall exposure to the carcinogenic species. On the other hand, CYP1A2 is importantly involved in the metabolism of a number of drugs including acetaminophen, caffeine, clozapine, theophylline, tacrine, and tamoxifen [8]. Accordingly, it would be expected that coadministration of oltipraz along with such drugs would significantly enhance their plasma drug concentration following usual doses, with the associated likelihood of increased risk of adverse effects. Considering that the therapeutic usefulness of a cancer chemopreventive agent such as oltipraz may require continuous administration over many years, it is not unreasonable to predict that such drug interactions will occur. Of particular concern in this regard is the possible situation with caffeine, the most widely and frequently consumed xenobiotic throughout the world because of its presence in the diet and in certain pharmaceutical products. None of the study subjects suffered caffeine-associated adverse effects, because caffeine-containing foodstuffs and drugs were excluded before and during the study period. On the other hand, an unacceptable level of side effects was observed as a result of the inhibition of CYP1A2 by the potent inhibitor furafylline and the unexpected accumulation of caffeine from normal dietary constituents [25]. If a similar situation occurs with oltipraz, individuals in whom CYP1A2 activity is most extensively inhibited and who ingest large amounts of dietary caffeine would be at particular risk for developing adverse effects during therapy with the chemopreventive agent.

In summary, the experimental findings clearly demonstrate that oltipraz is a potent in vivo inhibitor of CYP1A2 activity in humans. As such, this effect provides, in part, a mechanistic explanation to account for the agent's cancer chemopreventive activity. In addition, it is probable that the concomitant administration of oltipraz with drugs whose metabolism is importantly determined by CYP1A2 will result in a drug interaction that could result in unanticipated adverse effects. Whether oltipraz interacts similarly with other CYP isoforms remains to be determined.

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