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Oltipraz: Clinical Opportunities for Cancer Chemoprevention

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Abstract Oltipraz [4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione], originally developed as an antischistosomal agent, protects against chemical carcinogenesis in lung, trachea, forestomach, small intestine, colon, breast, skin, liver and urinary bladder in rodents. Oltipraz induces electrophile detoxication enzymes, resulting in diminished carcinogen-DNA adduct formation and reduced cytotoxicity, an important component of anticarcinogenic actions. Phase I trials of this drug have been recently conducted in the United States and indicate that the maximum tolerated dose is about 125 mg/day over a six-month period. Grade I/II dose-limiting toxicities included photosensitivity/heat intolerance, gastrointestinal, and neurologic toxicities. Ongoing studies are monitoring relationships between dose scheduling, drug plasma concentrations and pharmacodynamic action. Subsequent trials with this agent might most appropriately target individuals at high risk for occupational or environmental exposures to genotoxic carcinogens. Towards this end, a randomized, placebo-controlled Phase II study is planned for people at high risk for exposure to aflatoxins and development of hepatocellular carcinoma. Modulation of biomarkers reflecting the biologically effective dose of aflatoxin will serve as study endpoints.

Key words: Aflatoxin B_1, antischistosomiasis, carcinogen detoxication, enzyme induction, glutathione *S*-transferases, hepatocellular carcinoma

Oltipraz [4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione] was extensively evaluated as a treatment for schistosomiasis in the early 1980s [1]. Single doses of oltipraz have achieved cure rates of greater than 90% in field trials. While studying oltipraz's mechanisms of antischistosomal activity, Bueding *et al.* [2] initially noted that giving the drug to mice infected with *Schistosoma mansoni* caused a reduction in the glutathione stores of the parasite; however, this agent increased levels of glutathione in many tissues of the host [3]. Subsequent studies demonstrated that oltipraz and related 1,2-dithiole-3-thiones were potent inducers of enzymes concerned with the maintenance of reduced glutathione pools, as well as enzymes important to electrophile detoxication in tissues of rats and mice. The elevation of carcinogen detoxication enzymes has been recognized as characteristic of the action of many chemopreventive agents [4]. These results prompted Bueding to predict that oltipraz might have cancer chemopreventive properties; it has now been shown to be an effective chemopreventive agent in nearly a dozen different models of experimental carcinogenesis. Its broad range of anticarcinogenic activity coupled with apparently low mammalian toxicity has fostered the continued development of this drug as a potential human chemopreventive agent. Oltipraz has recently undergone Phase I trials in the United States to determine its pharmacokinetics and dose-limiting side effects during chronic admini-

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stration to humans [5,6]. This review highlights strategies, based upon pharmacokinetic and mechanistic considerations, for the efficient and effective evaluation of oltipraz in clinical chemoprotection trials with populations at high risk for exposure to genotoxic carcinogens.

CHEMOPREVENTION IN EXPERIMENTAL MODELS

Predicted chemopreventive activity was demonstrated when pretreatment of mice with oltipraz protected against the hepatotoxicity of carbon tetrachloride and acetaminophen [7]. Ensuing studies have demonstrated protection by oltipraz against the acute hepatotoxicities of allyl alcohol and acetaminophen in the hamster [8,9] and aflatoxin B_1 (AFB_1) in the rat [10]. Toxin-induced elevations in liver function tests were blunted in all cases. Pretreatment with oltipraz also substantially reduced the mortality produced by either single or chronic exposure to AFB_1 [10].

To directly test the cancer chemoprotective activity of oltipraz, Wattenberg and Bueding [11] examined the capacity of oltipraz to inhibit carcinogen-induced neoplasia in mice. Oltipraz was administered either 24 or 48 hours before treatment with each of three chemically diverse carcinogens: diethylnitrosamine, uracil mustard, and benzo[*a*]pyrene. This sequence of oltipraz and carcinogen administration was repeated once a week for 4–5 weeks. Oltipraz reduced by nearly 70% the number of both pulmonary adenomas and tumors of the forestomach induced by benzo[*a*]pyrene. Pulmonary adenoma formation induced by uracil mustard or diethylnitrosamine was also significantly reduced by oltipraz pretreatment, but to a lesser extent. As summarized in Table I, oltipraz has now also shown chemopreventive activity against different classes of carcinogens targeting the small intestine [12], colon [13,14], urinary bladder [15], trachea [16], liver [17], mammary glands [18] and skin [19]. The most dramatic actions of oltipraz occur in the colon and liver, where dietary administration results in significant reductions in both tumor incidence and multiplicity. Pharmacokinetic studies indicate that these two organs have amongst the highest tissue concentrations following oral administration of the drug [20]. Complete protection against AFB_1-induced hepatocarcinogenesis is achieved when oltipraz is fed before and during carcinogen administration; however, such an exposure-intervention paradigm is not directly relevant to most human populations. Bolton *et al.* [21] observed that a delayed and transient intervention with oltipraz relative to the period of aflatoxin administration affords significant protection against the formation of presumptive preneoplastic lesions in the liver. These results are consistent with observations that oltipraz protects against both the genotoxic and cytotoxic actions of AFB_1. However, administration of oltipraz after exposure to AFB_1 is without any protective effect [22]. By contrast, Reddy *et al.* [14] observed that the protective effects of oltipraz against azoxymethane-induced colon carcinogenesis in rats is nearly equi-effective, regardless of whether oltipraz is administered during or after carcinogen administration.

The role of oltipraz in combination chemoprotection is also under investigation. When fed at 40 and 80% of the maximum tolerated dose (MTD) to mice, oltipraz had no effect in preventing urinary bladder carcinogenesis induced by *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; however, when combined with α-difluoromethylornithine, significant dose-dependent inhibition was observed [10]. Oltipraz in combination with either the retinoid *N*-(4-hydroxyphenyl)retinamide or β-carotene was also very effective against diethylnitrosamine-induced respiratory carcinogenesis [11]. Thus, the use of oltipraz in combination with agents exhibiting different mechanisms of action appears promising.

MECHANISMS OF CHEMOPREVENTION

Most of the chemoprevention protocols tested to date have involved concomitant exposure to both carcinogen and oltipraz. In these instances, oltipraz likely affects the metabolism and/or disposition of carcinogens. In the case of aflatoxin, alterations in the balance of competing pathways of the ultimate carcinogen, aflatoxin-8,9-oxide, directly modulate the availability of the epoxide for binding to DNA. Anticarcinogenic concentrations of oltipraz in the diet markedly induce the activities of glutathione *S*-transferases (GSTs) in rat tissues to facilitate conjugation of glutathione to aflatoxin-8,9-oxide, thereby enhancing its elimination and coordinately diminishing DNA adduct formation [23]. Feeding oltipraz for 1 week

TABLE I. Chemoprevention Studies with Oltipraz in Animals

Target Organ	Species	Dose and Route of Oltipraz	Carcinogen[a]	Outcome	Reference
Forestomach	Mouse	500 mg/kg/wk, po, for 4 weeks	B[*a*]P	↓ tumor multiplicity	[11]
Small Intestines	Rat	200, 400 ppm in diet	AOM	↓ tumor incidence	[12]
Colon	Mouse	960 ppm in diet	MAM acetate	↓ tumor multiplicity	[13]
Colon	Rat	200 ppm in diet	AOM	↓ tumor multiplicity	[14]
Urinary Bladder	Mouse	500 ppm in diet	OH-BBN	↓ tumor incidence	[15]
Trachea	Hamster	300 ppm in diet	MNU	↓ tumor incidence	[16]
Lung	Mouse	500 mg/kg/wk, po, for 4 weeks	B[*a*]P	↓ tumor multiplicity	[11]
Lung	Mouse	500 mg/kg/wk, po, for 4 weeks	DEN	↓ tumor multiplicity	[11]
Lung	Mouse	500 mg/kg/wk, po, for 5 weeks	uracil mustard	↓ tumor multiplicity	[11]
Lung	Mouse	250 ppm in diet	NNK	no effect	[20]
Liver	Rat	750 ppm in diet	AFB_1	↓ tumor incidence	[17]
Mammary Glands	Rat	250 ppm in diet	DMBA	↓ tumor latency	[18]
Skin	Mouse	200 ppm in diet	DMBA→TPA	↓ tumor multiplicity	[19]

[a]B[*a*]P, benzo[*a*]pyrene; AOM, azoxymethane; MAM acetate, methylazoxymethanol acetate; OH-BBN, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; DEN, diethylnitrosamine; NNK, 4-[methylnitroso-amino-1-(3-pyridyl)]-1-butanone; DMBA, 7,12-dimethylbenz-[*a*]anthracene; TPA, 12-*O*-tetradecanoyl-phorbol-13-acetate.

before exposure to AFB_1 increases the initial rate of biliary elimination of the aflatoxin-glutathione conjugate by nearly three-fold. Concordantly, feeding oltipraz led to three- to four-fold increases in the specific activity of rat liver GST and elevations in the levels of some α-, μ-, and π- class subunits [24]. Molecular studies indicate that initial increases in hepatic GST mRNA and protein levels in response to oltipraz were mediated through transcriptional activation of GST genes [25]. Several regulatory elements control the expression and inducibility of rat GST subunits [26]. A 41 bp element in the 5'-flanking region of the rat GST Ya gene, termed the "antioxidant response element", appears likely to mediate induction by oltipraz [27]. Induction of GSTs by oltipraz in primary cultures of human hepatocytes has also been observed [28]. While the role of GSTs as determinants of AFB_1 hepatocarcinogenesis sensitivity appears reasonable, other phase II enzymes, notably UDP-glucuronosyltransferases and NAD(P)H:quinone reductase, are likely to exert important effects on the detoxification of other carcinogens and need to be explored in greater detail. A significant attribute of oltipraz is the responsiveness of many tissues to its enzyme inductive actions. A practical outcome of this mechanism of action arises from the long biological half-life of the enzyme inductive response. Although the half-life of oltipraz in rodents and man is about 6–8 hours, the inductive effects on some phase II enzymes persist for over one week. Thus, intermittent dosing schedules may offer advantages (fewer side effects, greater compliance) while maintaining efficacy (enhanced carcinogen detoxication). With this view in mind, the effect of dose scheduling on inhibiting aflatoxin-induced tumorigenesis has been recently evaluated. Rats were treated with AFB_1 daily for 28 consecutive days and received oltipraz daily, twice-weekly, once-weekly, or not at all throughout this period. Daily treatment with oltipraz engendered >99% reduction in hepatic tumor burden; remarkably, the twice- and once-weekly regimens reduced tumor burden by 97 and 95%, respectively. While transient micro-

molar concentrations of oltipraz appear to be required to trigger the induction of protective enzymes, sustained elevation of plasma levels of the drug are not necessary to achieve chemoprevention.

CLINICAL INVESTIGATIONS

Antischistosomiasis Trials

Oltipraz has been reported to have good antischistosomal activity in mice and monkeys infected with *Schistosoma mansoni* and in man infected with *S. mansoni, S. haematobium* or *S. intercalatum.* Clinical trials conducted in Mali, Gaboon, and France demonstrated a 90% cure using 2.0–7.5 g oltipraz (over 1–5 days) in 86 patients infected with *S. haematobium,* an 87% cure using 1.25–4.5 g over 3 days in 72 patients infected with *S. intercalatum,* and 100% cure in 47 patients infected with *S. mansoni* following treatment with a total dose of 3.0–5.0 g over 2–5 days [29]. At least 18 schistosomiasis studies have been conducted [30]. The most frequent side effects among the 1,284 patients exposed to oltipraz were related to the digestive system, namely, nausea (14.4%), abdominal pain/distress (10.4%), vomiting (9.0%) and diarrhea (1.2%). Headaches (12.5%), dizziness (10.8%), and paresthesia and fingertip pain (7.5%) were also frequently reported [30]. The latter two effects appeared to increase after exposure to sunlight. Most of these effects were reported to be mild, subsided within 1–2 days, and did not require discontinuation of the drug. No significant changes were noted in blood chemistry and hematology. Because of concerns about photosensitivity, oltipraz is no longer used to treat schistosomiasis.

Phase I Chemoprevention Trials

As summarized in Table II, two Phase I chemoprevention trials with oltipraz have been completed. In a trial conducted by the Illinois Cancer Council [6,31], 14 healthy female subjects with breast cancer relatives and 10 patients with resected colon polyps received 125 mg or 250 mg oltipraz, respectively, for six months. Nine of 14 subjects completed the six-month course of 125 mg/day and 4 of 10 subjects completed six months at 250 mg/day. Although not all dropouts were drug-related, toxicity was frequent at

TABLE II. Phase I Chemoprevention Clinical Studies with Oltipraz

Number of Subjects	Daily Oral Dose	Study Duration	Remarks	Reference
9	1, 2, 3 mg/kg	1 dose	PCS[a]: 16, 61, 205 ng/ml	[5]
1	2 mg/kg	10 days	no steady state reached	[5]
3	2 mg/kg	4 days	high-fat diet ↑ PSC; no effect on steady state	[5]
6	1.5, 3 mg/kg	10 days	received loading dose; 4 ng/ml steady state	[5]
6	1.5, 2 mg/kg	28 days	received loading dose; 3–4 ng/ml steady state	[5]
16	125, 250, 375, 500 mg	1 dose	PSC: 348, 1,049, 3,145, 4,921 ng/ml	[6,31]
14	125 mg	6 months	9 of 14 completed six-month course	[6,31]
10	250 mg	6 months	4 of 10 completed six-month course	[6,31]

[a]PSC, peak serum concentration

the 250 mg/day dose while 125 mg/day of oltipraz appeared to be near the MTD for chronic administration. Like earlier experiences in antischistosomiasis trials, toxicities were generally mild and reversible. Gastrointestinal discomfort was most common; sensitivity of the hands to sunlight and heat most significant. An earlier study conducted at Michigan State University [5] demonstrated that daily administration of 1.5–2.0 mg/kg/day for up to 4 weeks was well tolerated. Introduction of a loading dose during the first day produced a steady state which was maintained by daily doses thereafter. No steady state was obtained in the absence of a loading dose. The pharmacokinetics of oltipraz as determined in the antischistosomiasis and chemoprevention trials has been recently reviewed [31]. Although the steady-state concentrations of oltipraz are rather low, reflecting the rapid clearance of oltipraz from the body, the peak concentrations following administration of 125–500 mg oltipraz/day are comparable to those required to trigger the expression of phase II enzymes in rodent and human cell culture models. As discussed earlier, the functional half-life of these alterations in enzyme activity may approach one week.

Additional studies in progress will further define the MTD during acute and chronic administrations of the drug. In addition to pharmacokinetic analyses, these studies will assess the effects of the pharmacodynamic actions of oltipraz in study participants. Glutathione levels and activities of phase 2 detoxication enzymes will be assayed in surrogate (lymphocytes) and potential target tissues (bowel mucosa).

Prevention of Hepatocarcinogenesis in High-Risk Populations

A Phase II clinical trial with oltipraz is being developed in Qidong, Jiangsu Province, People's Republic of China under the auspices of the Shanghai Cancer Institute and the Qidong Liver Cancer Institute. Qidong County is located north of Shanghai at the mouth of the Yangtze River and has a population of greater than one million. Hepatocellular carcinoma is the leading cause of cancer death in Qidong with a mortality rate of 55/100,000 per year [32]. Major risk factors for liver cancer include infection with hepatitis B virus and exposure to aflatoxins. Approximately 10% of the population in Qidong are HBsAg-positive. Aflatoxins are consistent contaminants of the food supply; the prevalence of residents testing positive for aflatoxin biomarkers in their blood and/or urine exceeds 50% [33]. Characterization of the mutational spectra in the p53 tumor suppressor gene in hepatocellular carcinomas from Qidong demonstrate a high frequency (>50%) of AGG→AGT transversion mutations on the noncoding strand at codon 249 [34]. These mutations are not observed in liver cancers from low aflatoxin exposure regions of China. GC→TA transversions are the most common base substitutions produced by AFB_1 in experimental systems. Using a nested case-control study design, Qian *et al.* [35] recently reported highly significant associations between the presence of urinary aflatoxins, serum HBsAg positivity and risk of hepatocellular carcinoma. Particularly striking was a marked synergistic interaction between viral and chemical risk factors. Collectively, these studies highlight the importance of both large-scale hepatitis B vaccination programs and limitation of exposures and toxicities from aflatoxins as important strategies to decrease the incidence of liver cancer.

The randomized, placebo-controlled trial in Qidong will examine the effects of daily (125 mg) and weekly (500 mg) doses of oltipraz on levels of two independent intermediate biomarkers: aflatoxin-N^7-guanine adducts excreted into urine, and aflatoxin-albumin adducts in serum. These two biomarkers have been extensively validated in experimental chemoprevention models and through ecological and prospective epidemiological studies [35-37]. While these biomarkers reflect exposures to aflatoxins, their presence also signals increased risk for liver cancer. Levels of these biomarkers can be markedly attenuated in rats by intervention with oltipraz during periods of AFB_1 exposure. Aflatoxin-N^7-guanine has a short biological half-life (~8 hr) and reflects genetic damage from recent exposures to AFB_1. By contrast, aflatoxin-albumin adducts have a longer half-life (~21 days) and reflect cumulative exposures to the mycotoxin. As a consequence, blood and urine samples will be collected throughout a two-month intervention period as well as during a two-month post-intervention follow-up period to fully define the dynamics of potential changes in biomarker levels. With 80 participants in each of 3 arms, the clinical trial will have the

power to determine decreases in the levels of the urinary and/or serum aflatoxin biomarkers of at least 25%. Although the doses have been defined as the MTD from completed Phase I trials, a major element of the Qidong trial will be monitoring participants for potential adverse effects. Objective evaluation of adverse events will be greatly facilitated by including a placebo arm in the study design.

The availability of intermediate markers reflecting the modulation of the biologically effective dose of environmental carcinogens as study endpoints allows the design and conduct of efficient clinical trials. Hopefully, results from such trials with oltipraz will provide rapid insights into the means to achieve large-scale reductions in the incidence of hepatocellular carcinoma in populations at high risk for unavoidable exposures to aflatoxins. Further, such studies may serve as templates for chemopreventive interventions targeting individuals at high risk for other environmentally induced diseases.

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