Ketoconazole as a Possible Universal Inhibitor of Cytochrome P-450 Dependent Enzymes: Its Mode of Inhibition

YOTSUO HIGASHI, MASAKO OMURA, KEIKO SUZUKI*, HIROSHI INANO* AND HIROYUKI OSHIMA

Department of Urology, Tokyo Medical and Dental University School of Medicine, Bunkyo-ku, Tokyo 113 and National Institute of Radiological Sciences, Chiba 260*, Japan

Abstract

Modes of inhibition and binding of ketoconazole, an orally antimycotic agent, to NADPH-cytochrome P-450 dependent enzymes were investigated using subcellular fractions of human and rat testes, human adrenocortical adenoma tissue and rat adrenals and livers. Ketoconazole competitively inhibited the activities of steroid 17α-hydroxylase and C17-20 lyase in rat and human testes, 16α-hydroxylase in human testes and 21-hydroxylase in rat adrenal glands. Ki values were in the order of $10^{-8}$ M for human testicular enzymes, while the order was $10^{-7}-10^{-8}$ M for rat adrenal and testicular enzymes. Kinetic studies indicated that ketoconazole bound to cytochrome P-450 and not to other components of monooxygenase systems. Spectrophotometric studies also revealed direct binding of ketoconazole to cytochrome P-450 component by inducing type II difference spectra in all tissue preparations examined, indicating that ketoconazole is possibly a universal inhibitor of NADPH-cytochrome P-450 dependent monooxygenases which are involved in metabolism of many substances including steroids, toxins, carcinogens and others.

An imidazole agent, ketoconazole (cis-1-acetyl-4-{4-[[2-(2, 4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1, 3-dioxalan-4-yl]methoxy]phenyl]piperazine) is an orally active broad-spectrum antifungal drug. It inhibits production of ergosterol in yeast cell by blocking the 14α-demethylation of lanosterol (Van den Bossche et al., 1980). However, gynecomastia, impotence or adrenal insufficiency has occurred during clinical use of this agent (De Felice et al., 1981; Tucker et al., 1985), as a result of interference of steroid biosynthesis in both testes and adrenal glands (Pont et al., 1982a, b; Shurmeyer and Nieschlag, 1982). Steroid synthetic reactions documented to be inhibited by the agent are 17α-hydroxylation and side chain cleavage at C17-20 in the rat testis (Sikka et al., 1985) and side chain cleavage of cholesterol and 11β-hydroxylation of deoxycorticosterone in the adrenal gland (Loose et al., 1983; Kowal, 1983). These reactions are catalyzed by cytochrome
P-450 dependent monoxygenases, and in fact, the binding of an imidazole agent, miconazole (1-[2, 4-Dichloro-β-][2, 4-dichlorobenzyl]oxy|phenethyl|imidazole) to cytochrome P-450 component of human placental microsome aromatizing enzyme has been proved by a spectrophotometric study (Mason et al., 1983).

These data suggest that ketoconazole is a universal inhibitor of cytochrome P-450 dependent monoxygenases which catalyze hydroxylation of many compounds in the process of biosynthesis and catabolism. Up to the present, however, the mechanism of inhibition by ketoconazole has not been well elucidated. Therefore, the present study was designed to clarify the inhibition mode and binding site of ketoconazole to the NADPH-cytochrome P-450 monooxygenase system using human and rat tissues.

Materials and Methods

Chemicals

[4-14C]Progesterone (SA, 57 Ci/mmol), [4-14C]-17α-hydroxy-progesterone (SA, 50 Ci/mmol) and Econofluor were purchased from New England Nuclear Corp. (Boston, MA). Non-radioactive steroids and NADPH were products of Sigma Chemical Co. (St. Louis, MO). Ketoconazole was supplied by Kyowa Hakko Co. (Tokyo, Japan). Emulgen 913 was a gift from Kao-Atlas Co. (Tokyo, Japan). All other reagents were of analytical grade and all organic solvents were redistilled.

Tissue preparations

Human testicular tissue: Testicular tissue was obtained from patients at orchiectomy as the treatment of prostatic carcinoma. None had received any prior hormonal treatment.

The removed tissue was immediately frozen in liquid nitrogen and stored at −70°C until use. The frozen tissue was allowed to thaw at 4°C, and then homogenized with an Ultra-Turrax homogenizer (Ika-Werk Co., West Germany) in 5 volumes of 0.25 M sucrose solution (pH 7.4).

The mitochondrial and microsome fractions were prepared by conventional differential centrifugation at 800–10,000×g for 20 min. and 10,000–105,000×g for 60 min., respectively (Shikita and Tamaoki, 1965). The precipitates were resuspended in fresh ice cold 0.25 M sucrose solution and recentrifuged as above to obtain washed mitochondrial and microsome fractions. All procedures were performed at 0–4°C.

Human adrenal gland: Adrenal tissue was obtained at adrenalectomy of a patient with adrenal adenoma manifesting Cushing's syndrome. The removed adrenal adenoma was immediately frozen and stored at −70°C until use. The frozen tissue was homogenized with an Ultra-Turrax homogenizer in approximately 5 volumes of 0.33 M sucrose solution (pH 7.4). The mitochondrial and microsome fractions were prepared by differential centrifugation as described above.

Rat liver, adrenal gland and testis: Adult male Wistar rats, aged 12 weeks with a body weight of 250–280 g were sacrificed by decapsulation. Livers, adrenal glands and testes were immediately removed and homogenized with an Ultra-Turrax homogenizer in approximately 4 volumes of 0.13 M potassium-phosphate buffer (pH 7.4), 10 volumes of 0.33 M sucrose (pH 7.4) and 4 volumes of 0.25 M sucrose (pH 7.4) solutions, respectively. Mitochondrial and microsome fractions were prepared from each homogenate by differential centrifugation.

Verification of tissue preparations: Isocitrate dehydrogenase (E. C. 1.1.1.42) (Nordlie and Arion, 1966) and glucose-6-phosphate phosphohydrolase (E. C. 3.1.3.9) (Bachmann et al., 1966) were measured as a marker enzyme of the mitochondrial and microsome fractions, respectively, to verify the purity of the tissue preparations.

Assay of enzymes related to steroid biosynthesis

Incubations: All incubations were carried out in duplicate. The incubation medium contained the microsome fraction, one of 14C-labeled steroid substrates, 0.25 M sucrose, 17 mM Tris (pH 7.4), 1.7 mM MgCl2 and 0.2 mM NADPH in the presence or absence of ketoconazole. The concentration of steroid substrates and ketoconazole is indicated in the legends to figures. The final volume of incubation medium was 3 ml. The specific radioactivity of each steroid sub-
strate was adjusted with corresponding authentic non-radioactive steroids to obtain the desired substrate concentrations. Incubations were carried out at 37°C for 20 min. under an atmosphere of 95% O₂ and 5% CO₂ (v/v). The enzyme reaction was started by adding the microsome fraction and terminated by vigorous shaking of the incubation flask after adding 10 ml methylene dichloride.

Extraction, separation and identification of steroids: After adding non-radioactive carrier steroids (100 µg, each), extraction was repeated three times with 10 ml methylene dichloride. The combined extracts were dried over anhydrous sodium sulfate and concentrated at 40°C under reduced pressure. The residue was applied to ascending thin layer chromatography of silica gel G and GF 254 (4:1, w/w) with the benzene and acetone solvent system (4:1, v/v). Carrier and radioactive steroids on the thin layer plate were each detected under UV light (254 nm) and autoradiography, and exhaustively eluted from silica gel with a mixture of chloroform and ethanol (1:1, v/v). 16α-Hydroxyprogesterone was identified by chromatographic mobilities combined with chemical derivative formations (Oshima et al., 1967).

Identification of other metabolites was accomplished by demonstrating constant specific radioactivities during repeated recrystallization with corresponding authentic steroid preparations (Higashi et al., 1984). Once identification and purity of the products were established as above the metabolites obtained in subsequent experiments under similar conditions were identified using a combined method of derivative formation and chromatographic mobilities.

Expression of enzyme activities: Enzyme activities were expressed as the sum of metabolites produced by the enzyme action on the substrate. When progesterone was used as a substrate, the metabolites detected on the autoradiogram were 16α-hydroxy-progesterone, 17α-hydroxyprogesterone and 20α-hydroxy-4-pregnene-3-one. The radioactivities in fractions which coincided with androstenedione and testosterone on the thin layer plate were examined but were too limited for quantitation. Therefore, activities of 16α-hydroxylase (steroid, hydrogen donor: oxygen oxydoreductase (16α-hydroxylating)) and 17α-hydroxylase (E. C. 1.14.99.9) were expressed as the amount of 16α-hydroxyprogesterone and the amount of 17α-hydroxyprogesterone produced from progesterone, respectively. The sum of androstenedione and testosterone produced from 17α-hydroxyprogesterone indicated the activity of C17-20 lyase (E. C. 4.1.2.30) for 17α-hydroxy-progesterone. Since deoxycorticosterone was the only detectable metabolite produced from progesterone in rat adrenal microsome fraction, its amount was employed as the activity of 21-hydroxylase (E. C. 1.14.99.10).

Enzyme activities expressed as above showed linear relationships with either incubation time up to 30 min. or the amounts of tissue preparations added under the conditions employed in the present study.

Quantitation of steroids and protein
The radioactivity of each steroid fraction was measured with a liquid scintillation spectrometer (Packard, TRI-CARB 460) in the scintillation cocktail Econofluor. The amount of each metabolite was calculated from its percent yield and the specific radioactivity of the substrate. Over 90% of the initial radioactivity was recovered.

The protein content in each tissue preparation was determined by the methods of Lowry et al. (1951).

Analysis of CO-binding and substrate-induced difference spectra of cytochrome P-450
CO-binding spectrum of mitochondrial cytochrome P-450 of rat adrenal gland was obtained by the modified method of Omura et al. (1964). Briefly, mitochondrial fraction suspended in 6 ml of 100 mM potassium-phosphate buffer (pH 7.25) containing 0.07% Emulgen 913 was prepared and after adding a few mg sodium dithionite, the mixture was divided and put into sample and reference cuvettes. The CO gas was slowly bubbled in the sample cuvette for 1 min. The difference spectrum of cytochrome P-450 was obtained with a spectrophotometer (Hitachi 200-20, Japan) with cuvettes having a 1 cm optical path.

Substrate-induced difference spectra of cytochrome P-450 were analyzed using mitochondrial and microsome fractions. Each tissue preparation was adjusted to 6 ml with 100 mM potassium-phosphate buffer containing 0.07% Emulgen 913. The suspension was divided into two equal portion and poured into cuvettes. The sample cuvette was titrated with an ethanol solution of various concentrations of ketoconazole as a sub-
strate, and the corresponding volume of ethanol was added to the reference cuvette. The final concentration of ethanol was less than 2.5%. The difference spectra were measured from 350 to 500 nm (Suzuki and Tamaoki, 1983). Other conditions were described in legends to figures.

**Effect of ketoconazole on NADPH-cytochrome c (P-450) reductase activity**

Purification of NADPH-cytochrome c (P-450) reductase (E. C. 1.6.2.4) from rat liver and testes and measurement of the activity was carried out according to the method of Omura and Takesue (1970) with slight modifications. The reaction mixture in the microcuvette contained 20 nmol horse heart cytochrome c and 100 nmol NADPH in 1 ml of 100 mM phosphate buffer (pH 7.4). The enzyme reaction was initiated by adding purified NADPH-cytochrome c reductase. The spectrum obtained by the reduction of cytochrome c was followed at 550 nm for 3 min. at ambient temperature. To determine the effect of ketoconazole, the spectrum was measured in the same manner in the presence of 85 μM ketoconazole.

**Results**

**Effect of ketoconazole on enzyme activities of the human testicular microsome cytochrome P-450 dependent monoxygenases**

As shown in Fig. 1, ketoconazole dose-dependently inhibited cytochrome P-450 dependent monoxygenases including C17–20 lyase for 17α-hydroxyprogesterone, 16α- and 17α-hydroxylases for progesterone.

Fig. 2 shows the mode of inhibition by ketoconazole of C17–20 lyase, 16α- and 17α-hydroxylases with the Lineweaver-Burk plot. As shown in Table 1, the inhibition was competitive to all of enzymes examined and Ki values ranged from approximately one twentieth to one sixtieth of the corresponding Kms, indicating high affinity of ketoconazole with human testicular monoxygenases.

**Mode of inhibition of microsome monoxygenases in rat testes and adrenal gland by ketoconazole**

![Graph](image)

Symbols show the mean for each duplicate experiment. Microsome fractions contained 10.8 mg protein/flask in one and 9.8 mg protein/flask in the other.

●; C17–20 lyase for 17α-hydroxyprogesterone, ▲; 17α-hydroxylase for progesterone and ■; 16α-hydroxylase for progesterone.

---

Fig. 1. Dose-related inhibition of activities of cytochrome P-450 dependent monoxygenases in human testicular microsome fractions by ketoconazole. Microsome fractions were incubated with 10.6 μM progesterone or 5.0 μM 17α-hydroxyprogesterone in the presence of 0, 0.31, 3.1 or 31.3 μM ketoconazole. Two separate duplicated experiments were carried out using different tissues obtained from patients with prostatic cancer.
Fig. 2. Mode of inhibition of cytochrome P-450 dependent monooxygenases in the human testis by ketoconazole.

Microsome fractions containing 4.5 mg protein/flask for A and B, and 5.6 mg protein/flask for C were incubated in the absence (●) or presence (▲) of ketoconazole. Ketoconazole concentrations were 0.63 μM for A and B, and 0.31 μM for C. v; amount of product in nmol/mg protein/20 min. and s; substrate concentration in μM.

Table 1. Mode of inhibition by ketoconazole of microsome monooxygenases in human testis.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Km (μM)</th>
<th>Inhibition by ketoconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>17α-hydroxylase</td>
<td>progesterone</td>
<td>2.5</td>
<td>0.09</td>
</tr>
<tr>
<td>16α-hydroxylase</td>
<td>progesterone</td>
<td>1.5</td>
<td>0.08</td>
</tr>
<tr>
<td>C17-20 lyase</td>
<td>17α-hydroxyprogesterone</td>
<td>2.5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are calculated from Fig. 2.

Enzymes in microsome fractions of rat adrenal glands and testes were also studied under similar conditions. As shown in Fig. 3, the Lineweaver-Burk plot of the kinetic study revealed competitive inhibition by ketoconazole of 17α-hydroxylase for progesterone and C17-20 lyase for 17α-hydroxyprogesterone in rat testes, and 21-hydroxylase for progesterone in rat adrenal glands. The Ki value of ketoconazole for each enzyme was determined and shown in Table 2, and found rather higher than those for human testicular ones, indicating the different affinities of ketoconazole with rat and human cytochrome P-450 dependent monooxygenases.

Ketoconazole was a non-competitive inhibitor of 17α-hydroxylase for NADPH as demonstrated in Fig. 4.

To evaluate the interaction between ketoconazole and NADPH-cytochrome c (P-450) reductase, activities of NADPH-cytochrome c reductase purified from rat liver and testes were examined by the spectral method. The results indicated that NADPH-cytochrome c reductase activity was not influenced by ketoconazole at the concentration examined (85 μM), although the concentration was sufficient to inhibit the microsome cytochrome P-450 dependent monooxygenases, i.e. C17-20 lyase, 16α- and 17α-hydroxylases.

Effect of ketoconazole on 17α-hydroxylase for NADPH and NADPH-cytochrome c (P-450) reductase activity

Mode of ketoconazole and deoxycorticosterone binding to rat mitochondrial cytochrome P-450

A typical CO-binding spectrum of reduced
Fig. 3. Mode of inhibition by ketoconazole of cytochrome P-450 dependent monooxygenases in rat testes and adrenal glands. Microsome fractions containing 3.4 mg protein/flask for A and B, and 0.07 mg protein/flask for C were incubated in the absence (●) or presence (▲) of ketoconazole. Ketoconazole concentrations were 3.1 μM for A, and 0.63 μM for B and C.

Table 2. Mode of inhibition by ketoconazole of microsome monooxygenases in rat testes and adrenal gland.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Organ</th>
<th>Substrate</th>
<th>Km (μM)</th>
<th>Inhibition by ketoconazole</th>
<th>type</th>
</tr>
</thead>
<tbody>
<tr>
<td>17α-hydroxylase</td>
<td>Testis</td>
<td>progesterone</td>
<td>1.2</td>
<td>1.6</td>
<td>competitive</td>
</tr>
<tr>
<td>C17-20 lyase</td>
<td>(Testis)</td>
<td>17α-hydroxyprogesterone</td>
<td>1.4</td>
<td>0.4</td>
<td>competitive</td>
</tr>
<tr>
<td>21-hydroxylase</td>
<td>(Adrenal)</td>
<td>progesterone</td>
<td>2.5</td>
<td>5.0</td>
<td>competitive</td>
</tr>
</tbody>
</table>

Values are calculated from Fig. 3

Fig. 4. Mode of inhibition by ketoconazole of rat testicular 17α-hydroxylase for NADPH. Microsome fraction containing 3.6 mg protein/flask was incubated with 10.6 μM progesterone in the absence (●) or presence (▲) of 31.3 μM ketoconazole. Details are described in the legend to Fig. 2.
Ketoconazole and Cytochrome P-450

Fig. 5. The CO-binding spectrum of reduced cytochrome P-450 in the rat adrenal mitochondria (left panel) and substrate-induced difference spectra for rat adrenal mitochondrial cytochrome P-450 with 60 μM ketoconazole and 18.2 μM deoxycorticosterone (right panel).

Fig. 6. Ketoconazole-induced difference spectra for cytochrome P-450 in adrenal glands and testes.

Ketoconazole concentrations are indicated in the figure. Total protein concentrations were as follows: 0.07 mg/ml for human adrenal Ms, 0.04 mg/ml for human adrenal Mt, 0.61 mg/ml for rat adrenal Ms, 0.39 mg/ml for adrenal Mt and 0.74 mg/ml for rat testicular Ms. Ms; microsome fraction and Mt; mitochondrial fraction.

cytochrome P-450 in rat mitochondrial fraction was obtained as shown in Fig. 5 (left panel). In contrast to type I substrate-induced difference spectra of cytochrome P-450 in the same tissue preparation with deoxycorticosterone, ketoconazole induced type II spectrum characterized by a peak at 432 nm and a trough at 412 nm with zero crossing at 423 nm (Jefcoate, 1978) (Fig. 5, right panel).
Comparison of ketoconazole-induced difference spectra of cytochrome P-450 in rat and human adrenal glands and rat testes

As shown in Fig. 6, cytochrome P-450 in all tissue preparations examined revealed type II spectral change due to the addition of ketoconazole. Though the difference spectrum of cytochrome P-450 in rat testicular microsome was rather obscure, the peak at 432 nm and the trough at 405 nm indicated a type II spectrum. We failed to show a binding difference spectrum of rat testicular mitochondrial cytochrome P-450 with ketoconazole. It may be due to the high turbidity and small amount of cytochrome P-450 in the testicular preparation.

Substrate-induced difference spectra of cytochrome P-450 in rat liver

To investigate whether ketoconazole bound to liver cytochrome P-450 in a similar fashion to that mentioned above, spectral binding studies were performed using rat liver microsomal and mitochondrial fractions. As shown in Fig. 7, ketoconazole induced dose-related type II difference spectra to cytochrome P-450 in the rat liver.

Discussion

The present study shows that ketoconazole competitively inhibits the monooxygenase activities for steroid substrates in testes and adrenal glands of rats as well as human testes. Monooxygenases examined include 17α-hydroxylase and C17–20 lyase in rat and human testes, 16α-hydroxylase in human testes and 21-hydroxylase in rat adrenal glands. The findings are consistent with adrenal suppression during high dose administration of ketoconazole to humans (Tucker et al., 1985) and rats (Bhasin et al., 1986), in vitro inhibition of steroidogenesis in cultured mouse adrenal cortex tumor cells (Kowal, 1983), in vivo inhibition of testosterone production in male rats (Pont et al., 1982 b; Trachtenberg, 1984 b) and in men (Santen et al., 1983; Schurmeyer and Nieschlag, 1984). Further, ketoconazole has been reported to inhibit monooxygenases such as 17α-hydroxylase and C17–20 lyase in the rat testis (Sikka et al., 1985) and also side-chain cleavage of cholesterol and 11β-hydroxylase in the rat adrenal gland (Loose et al., 1983). Ketoconazole has been also
found to inhibit the hydroxylation of deoxy-
corticosterone at the 11β and 18-positions
in reconstituted steroid monooxygenase sys-
tems (Nagai et al., 1986). On the other
hand, ketoconazole has been reported not
to inhibit rat testicular 17α-hydroxylation
of progesterone (Kanei et al., 1985). How-
ever, the substrate concentration used was
too low to saturate the enzyme. Ki values
of ketoconazole to monooxygenases for
steroid substrates determined in the present
study are definitely greater in rats than in
men, while Km values of the enzymes to
the corresponding steroid substrates are
similar in both species. The results indicate
that the affinity of ketoconazole with testi-
cular monooxygenases examined is higher
in men than in rats.

Since the enzymes mentioned above be-
long to the species of cytochrome P-450
dependent monooxygenases coupled with an
electron transport system from NADPH, the
component which binds ketoconazole is im-
portant in obtaining an insight into the
mechanism of inhibiting effects of ketocona-
zole on monooxygenase and was therefore
investigated in the present study. As a
result, ketoconazole reveals no effect on the
activity of cytochrome c (P-450) reductase
purified from the rat testis and liver, the
type II difference spectrum change of cyto-
chrome P-450 and non-competitive inhibi-
tion of 17α-hydroxylase activity for sub-
strate NADPH in the rat testis. The
former two findings indicate that ketocona-
zole binds to cytochrome P-450 and not
to cytochrome c (P-450) reductase. The
last finding of the non-competitive in-
hibition of 17α-hydroxylase for NADPH can
be explained as follows by assuming that
ketoconazole binds only to the active site
on cytochrome P-450 for steroid substrates.
Since ketoconazole inhibits the same 17α-
hydroxylase for progesterone competitively,
it occupies quantitatively the progesterone
of fixed concentrations of both ketoconazole
and progesterone, resulting in non-competi-
tive inhibition of 17α-hydroxylase for
NADPH. Thus the results are consistent
and indicate the binding of ketoconazole to
the active site of 17α-hydroxylase, in another
words to cytochrome P-450.

Furthermore, the spectral analysis in the
present study reveals that ketoconazole in-
duces type II difference spectra not only
in cytochrome P-450 in microsome fractions
of rat testes and adrenal glands of which
monooxygenases are inhibited by ketocona-
zole competitively, but also in cytochrome
P-450 in mitochondrial fraction of rat
adrenal glands and microsome and mito-
chondrial fractions of a human adrenocortical
adenoma and rat livers. Steroid substrates
induce type I spectral changes in testicular
cytochrome P-450 (Nakajin et al., 1981) as
observed in the present study using deoxy-
corticosterone. In contrast, the nitrogenous
bases such as SU8000, SU10603 and mety-
rapone induce type II difference spectra and
competitively inhibit 17α-hydroxylase and
C17–20 lyase activities on the cytochrome
P-450 purified from neonatal porcine testis
(Nakajin et al., 1981). Another imidazole
agent, miconazole, also induce type II dif-
ference spectra in human placental aro-
matase (Mason et al., 1985). These facts
also support the assumption of a direct
interaction of a nitrogenous ligand of
ketoconazole with the heme iron of cyto-
chrome P-450 (Meredith et al., 1985).

The present results indicate that keto-
conazole is a potent competitive inhibior of
cytochrome P-450 dependent monooxygenases
in the adrenal gland and testis examined
and further binds to cytochrome P-450
universally. Ketoconazole is also a potent
inhibitor of 25-hydroxyvitamin D 24-hydroxy-
lase of cultured porcine kidney cells (Kan
et al., 1985) and ergosterol biosynthesis in
candida albicans as an antimycotic agent.
The latter inhibition is attributable to inter-
ference with reactions involved in demethy-
lation at C14 of lanosterol. The demeth-
ylation is also catalyzed by monooxygenases.
Therefore, it appears most likely that ketoconazole is a universal inhibitor of cytochrome P-450 dependent monooxygenases. Adverse effects of ketoconazole on liver function can also be attributed at least in part to its inhibitory action on liver cytochrome P-450 dependent monooxygenases.

One of the reactions catalyzed in vivo by cytochrome P-450 dependent monooxygenases plays major roles in activation as well as inactivation of either mutagenic or tumor-promoting agents. Up to the present, however, it is not known whether carcinogenic and tumor-promoting agents might be activated or inactivated in the tissue of humans as a result of the inhibition of cytochrome P-450 dependent monooxygenases caused by the administration of ketoconazole. Therefore, great caution should be paid in prolonged administration of ketoconazole as a clinical therapeutic method including antiandrogenic therapy for prostatic cancer, even though recently such clinical trials have been carried out with favorable results (Trachtenberg, 1984 a; Heyns et al., 1985).

References


