

CLINICAL INVESTIGATION STUDY PROPOSAL

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Activity: NRMCM, San Diego, CA.

Title : Ketoconazole Treatment of Systemic Mycoses

Investigators:

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Evaluation of Ketoconazole in the
Treatment of Systemic Mycoses

1. FACILITIES WHERE STUDY WILL BE CARRIED OUT: NRMCM, San Diego
 - A. Hospital days per year. In this project we plan to study 40 patients with systemic mycoses; Part I, Double-Blind Trial of Ketoconazole in the Treatment of Coccidioidomycosis, 20 patients; Part II, Evaluation of Ketoconazole in the Treatment of Systemic Coccidioidomycosis, 10 patients; Part III, Evaluation of Ketoconazole in the Treatment of Systemic Mycoses, 10 patients. Depending on the severity of disease, patients may require 1-6 weeks in the hospital.
 - B. Outpatient studies per year. Patients listed above will require therapy during the outpatient period, and indicated studies at an interval of approximately every 4 weeks.
 - C. Major laboratory determinations. As listed in attached protocol.
 - D. X-rays or other procedures required as part of protocol. Also listed in attached protocol.
 - E. Special equipment. None.
 - F. Special diets. None.

2. ESTIMATED DURATION OF STUDY: 2 years.

3. SUBJECT POPULATION: Subjects with systemic mycoses.

4. PURPOSE OF PROJECT AND BACKGROUND:

A. Discussion of Problem.

Systemic mycoses cause significant morbidity and mortality. During the past 20 years the growing use of antibiotics, cytotoxic and immunosuppressive therapy has increased the number and severity of mycotic infection. In this community coccidioidomycosis is a major problem. The therapy of coccidioidomycosis as well as various other mycotic infections is rather limited and toxic. In this setting, the potential of a new nontoxic antifungal agent which is effective in animals has significant appeal.

Ketoconazole is an imidazole with antifungal activity synthesized by Janssen Pharmaceutica. It is a potent inhibitor of ergosterol biosynthesis. Ergosterol is the major sterol found in most yeast and fungi. Accumulation of this sterol with a methyl group at C₁₄ results in permeability changes in the membrane. Mammalian cells utilize exogenous cholesterol which compensates for the temporary effects of ketoconazole on sterol synthesis. Toxicological studies have been done and apparently satisfy the FDA as to its safety for trials in humans. Various species have been used to study the acute, subacute, and chronic toxicity, as

well as effects on reproduction and mutagenesis. LD50, 7 days after oral or intravenous administration, range from 160-900mg/kg. Subacute and chronic studies at high levels show no hematological, biochemical or histopathologic abnormalities except for some minor observations at 40mg/kg where some changes in the histologic appearance of the adrenal gland, and possibly decreased potassium levels, were observed. There was also some pseudopregnancy and fragile limb bones noted. Chronic studies for 12 months show no adverse effects up to 40mg/kg, where some reduction in appetite and emesis was noted for the first 3 months. SGPT was intermittently elevated and alkaline phosphatase continuously elevated at 40mg/kg level. Females did show some teratogenic effects at 80mg/kg. The pharmacokinetics of ketoconazole show significant levels in the blood after oral ingestion (.08-4.6ug/ml following 2.5mg/kg oral dose). The apparent half-life is approximately 2 hours, with 13% of the dose recovered in the urine and 66% in the feces. About 99% of the drug is bound to plasma proteins. Spinal fluid levels are detectable between 1 and 8 hours and reach antifungal range only in the animals treated with 40mg/kg. In humans, a single 200mg dose results in a plasma concentration of 1-6ug/ml during the first 8 hours, with a mean concentration of 1.2ug/ml persisting for 24 hours.

Studies in animals suggest that the minimal inhibitory concentration for endospores of Coccidioides immitis range between 0.3-0.4ug/ml. In an animal model of acute coccidioidomycosis the effects of orally administered ketoconazole were rather dramatic, resulting in the prevention of death uniformly at doses of 40mg/kg per day, as well as eradicating the fungus from all tissues.

Ketoconazole has also demonstrated activity in vivo and in vitro against Candida, Paracoccidioidomycosis, Histoplasmosis, Nocardiosis, Sporotrichosis, Chromomycosis, and Mycetoma. On the basis of this, the drug company has suggested for clinical studies, and the FDA accepted, plans to treat coccidioidomycosis, candidosis, aspergillosis, blastomycosis, paracoccidioidomycosis, histoplasmosis, and sporotrichosis, as well as chronic mucocutaneous candidiasis and other candidal infections.

B. Specific Objectives.

The objective of this protocol is to evaluate the clinical usefulness of ketoconazole in the treatment of systemic mycoses.

5. PROJECT PROTOCOL:

This protocol is divided into 3 separate parts:

Part I - Double-Blind Trial of Ketoconazole in the Treatment of Coccidioidomycosis.

This is a phase II safety and efficacy trial of the use of ketoconazole (R 41,400/Janssen R&D, Inc.) in the treatment of coccidioidomycosis. We will identify patients with severe disease but who may not have a clear-cut indication for treatment with the standard drug, amphotericin-B.

When the diagnosis of coccidioidomycosis is made there is often a period of evaluation or consolidation of clinical data, including the effect of waiting, prior to a decision to start amphotericin. During this time patients will be offered the opportunity to enter this study, a randomized, controlled study of the effect of ketoconazole versus placebo. Patients will be treated for 3 months or until there is evidence of a treatment failure, as defined below.

I. Criteria For Entry.

A. Pulmonary Only.

1. Necrotizing pneumonia or persistent pneumonia; stable or increasing infiltrate present for 6 weeks or more.
2. Positive culture for C. immitis from pulmonary tissue for secretion.
3. Exclusions:
 - a. isolated thin-walled cavity.
 - b. isolated pulmonary nodule.
 - c. miliary disease.
 - d. CF titer \geq 1:628

B. Limited Dissemination.

1. A single coccidioidal lesion or cluster of lesions outside the lung.
2. Positive culture from that lesion of C. immitis.
3. Exclusions:
 - a. highly symptomatic patients.
 - b. high-risk patients:
 1. non-Caucasian.
 2. negative skin test to coccidioidin (CDN) 1:100.
 3. complement fixation (CF) titer \geq 1:64.
 4. cytotoxic drug therapy.
 5. meningitis.
 - c. Abdomino-peritoneal infection

II. Treatment.

- A. Randomization. Patients accepted into the study will be assigned to treatment or placebo group by random number table, by the Clinical Research Center (CRC), University of California, San Diego.
- B. Patients will not know which group they have been assigned to.
- C. The physician in charge of the patient will not know which group the patient is assigned to.
- D. We plan to enter 20 patients into this study.

III. Monitoring.

- A. Monitoring of Coccidioidal Infection.
 1. Clinical examination weekly:

- a. general status, weight change, fever, sputum.
 - b. signs of dissemination, skin lesions, masses, bone pain, CNS Sx with follow-up of localizing Sx.
2. X-ray chest or bone lesion (every 6 weeks).
 3. CF titer for cocci (every 4 weeks).
 4. Skin test (to be repeated every 4 weeks if < 15mm):
CDN 1:100, spherulin, Trichophyton, and Candida.
 5. Bone scan (and gallium scan if positive before treatment) at outset and every 3 months.
 6. Ultrasound of lesion to measure size, before treatment if possible, and every 3 months.
 7. Photographs of skin lesion every 1 month.
 8. CAT scan (if a lesion is seen on CAT scan at outset, it should be repeated every 3 months).
- B. Monitoring of Drug Safety.
1. Initial studies: Complete blood count (CBC), sedimentation rate, blood glucose, urea nitrogen, creatinine, SGOT, alkaline phosphatase, calcium, total bilirubin, electrolytes, total protein, phosphorus, cholesterol, complete urinalysis (UA), EKG, audiogram (pure tones), slit-lamp eye exam.
 2. Repeat studies: CBC, UA, and blood chemistry monthly; slit-lamp eye exam, audiogram and EKG at beginning and conclusion of study.
 3. Mycology: An initial culture and follow-up once each month will be sent to Dr. H.B. Levine for in vitro sensitivity testing.
 4. Drug absorption: Within the first week of therapy the patient will have a drug absorption study. Blood will be drawn for determination of drug level after the ingestion of a dose, at $\frac{1}{2}$, 1, 2, 4, 6, 12 and 24 hours. In addition, at 2 hours will do level in CSF (if patient has a clinical indication for a lumbar puncture), sputum, and urine.

IV. Evaluation of Response to Therapy.

- A. Evaluation of each case will be done jointly by the investigators. Each case will be presented preferably by the physician in charge of the patient. Evaluation will be made of the following criteria:
1. Size of lesion.
 - a. an X-ray (chest or bone).
 - b. scan (bone or gallium).
 - c. photograph (skin lesion).
 - d. ultrasound (abscess or mass-like lesion).

Evaluation will be made to determine if lesion is growing in size or number (treatment failure), getting smaller, or cleared completely.