

SESSION III: New Drug Development and Use

Itraconazole - A New Antifungal Drug

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The first effective antifungal drug against systemic mycotic infections was amphotericin B. Amphotericin B remains the gold standard for efficacy of antifungal therapy. In spite of the drug's efficacy against many systemic fungal organisms, its renal toxicosis and the need for intravenous administration prompted the search for better antifungal agents. Ketoconazole was the first widely accepted azole. Ketoconazole given orally is reasonably effective and has less toxicity than amphotericin B. Response to ketoconazole is slower than amphotericin B. Ketoconazole may produce significant hepatic toxicosis.

The second generation of the azole drugs, the triazoles, has advantages over ketoconazole. They appear to be more effective at smaller doses thereby reducing toxicity. They have a longer half life and don't interfere with the production of steroid hormones. Fluconazole and itraconazole are the main triazoles in clinical use. Itraconazole is not yet licensed in the US or Canada.

Itraconazole was synthesized in 1980 by Janssen Laboratories and is available in Europe and Mexico under the brand name of SPORANOX. FDA licensing in the US is expected soon. Like the other azoles, it inhibits ergosterol synthesis of the fungal cell wall by interference with the cytochrome P-450 enzyme. It is well absorbed after oral administration. Depending on the fungal organism, *in vitro* it is 5 to 100 times more effective on a weight basis than ketoconazole. It does not suppress testosterone or cortisol production and is effective against a broader spectrum of fungal organisms. It is more lipophilic than ketoconazole which results in greater tissue concentrations of the itraconazole. The greater efficacy is noteworthy for *Aspergillus fumigatus* where many isolates require serum concentrations of ketoconazole that are not clinically achievable.

Itraconazole is best absorbed when given with food containing fat. When given at a dose of 5 mg/kg per dose twice a day, a steady serum concentration is achieved between 1 and 2 weeks. We evaluated the efficacy of itraconazole in dogs with systemic blastomycosis. These were client owned dogs that developed blastomycosis by environmental exposure. Blastomycosis is a good model for systemic fungal infections

because it produces lung, eye, bone, skin and other sites of infection. We also have data on the response of blastomycosis to amphotericin B to compare efficacy.

Minimum inhibitory concentrations (MIC) of *Blastomyces dermatitidis* for itraconazole were approximately one tenth the concentration for ketoconazole. When fungal isolates were obtained from dogs that had a recurrence of blastomycosis after therapy with ketoconazole or itraconazole, there was no increase in the MIC. This suggests that drug resistance is not common. A total of 112 dogs with blastomycosis were treated with itraconazole. Seventy dogs were treated with 10 mg/kg/day and 42 dogs received 5 mg/kg/day. The efficacy of itraconazole was similar to treatment with amphotericin B. There was no significant difference in cure or relapse rates between the two dosage schemes. Serum concentration of the itraconazole varied markedly among individual dogs given the same dosage of drug. The mean serum concentration was greater for dogs given 10 mg/kg/day than dogs given 5 mg/kg/day, but there was considerable overlap in drug concentration between the two groups. Intersubject variations in serum drug concentration is also common in people given itraconazole. Dogs that had serum drug concentrations over 10 µg/mL appeared to have fewer relapses than dogs with concentrations under 10 µg/ml.

The adverse effects of itraconazole therapy were principally anorexia associated with hepatic toxicosis. Toxic effects were more common with the larger drug dose, but some toxic effects were seen at the 5 mg/kg/day dose. Another adverse effect was vasculitis producing areas of ulcerative dermatitis. There was the suspicion of possible cardiac toxicity. The incidence of severe adverse effects were minimal and toxicity resolved with discontinuation of the drug. Anorexia was usually associated with an increase in serum ALT activity. Hepatic toxicosis was more likely to occur in dogs with greater serum concentrations of itraconazole. This suggests that the itraconazole dose can be decreased in dogs with hepatic effects while maintaining therapeutic itraconazole concentrations. The variability in serum itraconazole concentrations was also seen in cats as was the correlation between serum concentration and hepatic toxicosis.

Itraconazole is effective in dogs with blastomycosis involving the bones. It appears to penetrate the eye with good responses, especially when the posterior segment of the eye is involved. Itraconazole is a superior drug in mycotic infections of the cat. The drug can be mixed in the food without affecting the cat's appetite. It is less likely to produce anorexia in cats than ketoconazole. Cryptococcosis and histoplasmosis in cats were responsive to therapy. Itraconazole is effective against nasal aspergillosis in dogs and even has some efficacy against systemic aspergillosis. A number of the saprophytic pigmented fungi which occasionally produce disease can be controlled or cured with itraconazole therapy. A limited number of dogs with *Prototheca* infections responded to itraconazole treatment. Our studies suggest efficacy against many of the fungal pathogens of dogs and cats. Limited studies in the horse suggest itraconazole is effective and has minimal toxicity.

Approval of itraconazole for use in people in the United States is expected this year. More extensive use in veterinary patients will determine the effectiveness and toxicity of this new drug.