5a. Bioavailability

Benznidazole has high oral bioavailability (> 90%) and is widely distributed throughout the body. Over 40% of the drug is bound to plasma proteins (Raaflaub and Ziegler, 1979).

5b. Drug distribution

After oral administration of benznidazole to healthy volunteers, peak concentrations are seen after 3–4 hours. The mean peak plasma concentration after a 100-mg dose was 2.54 μg/ml (Raaflaub and Ziegler, 1979). The half-life of benznidazole is approximately 12 hours in healthy adult volunteers (Raaflaub and Ziegler, 1979), however may be as long as 36 hours in *T. cruzi*–infected adults (Soy *et al.*, 2015).

5c. Clinically important pharmacokinetic and pharmacodynamic features

There are no data yet available correlating the clinical efficacy of benznidazole with the drug's pharmacokinetic/pharmacodynamic parameters.

5d. Excretion

Preclinical studies demonstrated that benznidazole is primarily metabolized in the liver, with approximately 5% of the drug excreted unchanged in the urine (Workman *et al.*, 1984).

5e. Drug interactions

Data from a rat model suggests that concurrent alcohol consumption with benznidazole may induce nitroreductive enzyme activity in liver microsomes, potentially enhancing the toxicity of benznidazole (de Mecca *et al.*, 2013; Castro *et al.*, 2006). There are few other data currently available regarding possible drug interactions with benznidazole.

6. ADVERSE REACTIONS AND TOXICITY

The likelihood of developing adverse drug reactions to benznidazole appears to increase with age. Children treated with benznidazole (especially those under the age of 7) tolerate the drug well and any reactions that occur are generally mild and do not necessitate treatment interruption (Altcheh *et al.*, 2011).

In adults, dermatologic side effects are the most commonly reported adverse effects of benznidazole. Cutaneous reactions appear to be idiosyncratic rather than dose related and are thought to be mainly Th2-mediated delayed hypersensitivity phenomena (Salvador *et al.*, 2015). Approximately 30% of patients develop a photosensitive rash, usually during the first 2 weeks of treatment. The rash is usually mild and generally does not require treatment interruption. Rarely, a hypersensitivity dermatitis can develop leading to exfoliative skin eruptions, generalized edema, fever, lymphadenopathy, myalgia, and arthralgia (Castro *et al.*, 2006). In these instances, temporary cessation of treatment is recommended. The HLA-B*3505 allele may be associated with more severe skin toxicity (Salvador *et al.*, 2015).

Gastrointestinal upset, most frequently nausea, can occur in the initial phase of treatment. These symptoms almost always resolve spontaneously without a need for dose reduction.

Arthralgia and inflammatory arthritis (often polyarticular) have been described, usually occurring 4–5 weeks after the initiation of therapy. The arthritis may be severe enough to result in treatment interruption or cessation (Aldasoro *et al.*, 2015).

Benznidazole can cause bone marrow suppression, resulting in agranulocytosis and thrombocytopenic purpura. These side effects increase in frequency with the cumulative dose administered (Prata, 2001). Cessation of treatment is recommended if these toxic effects occur.

Paresthesia and peripheral neuropathy have also been described with the use of benznidazole (Castro *et al.*, 2006). Again, these adverse effects appear to be dose dependent and are usually reversible, but may take many months to resolve (Cançado, 2002; Bern *et al.*, 2007).

6a. Fertility and carcinogenesis

In animal models, the administration of high-dose benznidazole (100 mg/kg per day) has been observed to cause gonadal toxicity. Inhibition of spermatogenesis and degenerative changes in the ovaries is thought to be due to covalent binding of reduced benznidazole metabolites to proteins and phospholipids within the gonads (Bernacchi *et al.*, 1986; De Castro *et al.*, 1989). Like nifurtimox (see Chapter 193, Nifurtimox), benznidazole has been associated with carcinogenic effects in animals. However, benznidazole use has not been linked to an increased risk of malignancy in humans (Coura and de Castro, 2002).

6b. Risks in pregnancy

When administered to pregnant rats, benznidazole rapidly crosses the placenta. Its reactive metabolites covalently bind not only to maternal but also to fetal proteins, raising concerns of possible teratogenicity. As a result, the use of benznidazole is not recommended during pregnancy (Castro *et al.*, 2006).

Benznidazole readily passes into the breast milk of lactating animals (Castro *et al.*, 2006). An Argentinian study of 12 lactating women with chronic Chagas disease treated with benznidazole 5–8 mg/kg/day (median 5.65 mg/kg/day) and their breastfed infants (all younger than 8 months), found a median benznidazole breastmilk:plasma ratio of 0.52. The breastfed infants were estimated to have received 0.65 mg/kg/day of benznidazole (approximately 12% of the maternal dose). Despite a high incidence of maternal adverse drug reactions, none were observed in the breastfed infants. All infants were followed up for at least 6 months and were not found to have any change in their behavior, weight progress, or any other effects potentially attributable to benznidazole (Garcia-Bournissen *et al.*, 2015).