Clinical Pharmacokinetics of Clofazimine
A Review
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Summary

Clofazimine is useful in the treatment of Hansen’s disease (leprosy) and some dermatological disorders, and is currently being used in drug regimens for patients with human immunodeficiency viral infections who are also infected with Mycobacterium avium complex.

After an oral dose, absorption is variable, but when given in an oil-wax suspension is approximately 70%. Administration with food appears to increase the peak plasma drug concentration and reduce the time to peak level. Data on the volume of distribution and percentage or type of protein binding are not available; however, the drug undergoes extensive tissue distribution. Clofazimine does not cross the blood-brain barrier, but does cross the placenta, and is found in human breast milk.

To date 3 urinary metabolites have been identified in man, but their biological activity is unknown. A substantial portion of the unchanged drug is excreted in faeces. The elimination half-life is variable, with values as long as 70 days being quoted in the literature.

Frequently reported side effects of clofazimine are hyperpigmentation of the skin and conjunctiva, and abdominal pain. These resolve upon cessation of therapy. Biochemical and haematological adverse effects have been reported, but are generally not clinically
Pharmacokinetics of Clofazimine

Clofazimine [3-(p-chloroanilino)-10-(p-chlorophenyl)-2, 10-dihydro-2-isopropyliminophenazine] is an antimycobacterial agent which has been in use since 1962 for the treatment of *Mycobacterium leprae* (Browne & Hogerzeil 1962). Due to the development of primary resistance to monotherapy with dapsone (World Health Organization 1977; Zuidema et al. 1986), it is now recommended that combination drug therapy be used for all cases of Hansen’s disease (leprosy) [World Health Organization 1982]. Clofazimine is also recommended in the treatment of *Mycobacterium avium* complex which is increasingly observed in individuals with human immunodeficiency virus (HIV) infections (Centers for Disease Control 1986; Woods & Washington 1987; Young 1988). Clofazimine is useful in a number of dermatological disorders such as pyoderma gangrenosum (Holdiness 1985a; Rosmusen 1983), lupus erythematosus (Mackey 1976), prurigo nodularis (Belaube et al. 1983) and pustular psoriasis (Chuaprapcislis & Piamphongsant 1978). However, its efficacy in the treatment of *Mycobacterium ulcerans* is questionable (de-Bergeyck et al. 1980; Revill et al. 1973). The mechanism of action of clofazimine in each of the above disorders has not yet been fully elucidated.

Based upon estimates by Sansirricq (1983), approximately 10 to 12 million individuals in the world are infected with the *Mycobacterium leprae* organism. Asia has highest incidence (62% of the total number of cases), followed by Africa (34%), South America (3%), with the rest of the world accounting for about 1%. Thus, about 1 billion people live in areas where the prevalence of Hansen’s disease is approximately one per thousand of the population (Noorden 1985).

By March 1988 a total of 55,315 adults with HIV infections had been reported in the United States alone (Centers for Disease Control 1988). *Mycobacterium avium* complex, a frequent pathogen in these patients, has been observed to occur in up to 40% of those individuals autopsied at the National Institutes of Health (Masur et al. 1987). Thus, the potential number of patients who can benefit from clofazimine treatment is quite large.

Primary drugs available for treatment of Hansen’s disease include dapsone, rifampicin, clofazimine and a combination of ethionamide/prothionamide. Secondary drugs consist of thioacetazone (amithiozone), thiambutosine, long acting sulphonamides such as sulphamethoxypyridazine and certain aminoglycosides, especially streptomycin and kanamycin (Jacobson 1985). Most of these agents are also suitable for use against *Mycobacterium tuberculosis*.

This article deals with the clinical pharmacokinetics, therapeutic use, drug interactions and side effects of clofazimine. In addition, a review of the analytical techniques used to measure the drug in biological tissues is also presented.

### 1. Analytical Methods

Table I contains a list of analytical methods and their limits of detection. Early non-chromatographic procedures used spectrophotometric determination for clofazimine, at its wavelength of maximum absorption (530nm) [Barry et al. 1960]. Production of a fluorescent derivative by reduction with titanous chloride has also been performed (Dill et al. 1970).

Chromatographic procedures have also been used to analyse clofazimine. Lanyi and Dubois (1982) developed a thin layer chromatographic technique with densitometric detection. Using high performance liquid chromatography (HPLC), with ultraviolet detection, Gidoh and Tsutsumi (1981) separated clofazimine from dapsone, and rifampicin on a reversed phase column. However, the procedure involves a complicated extraction scheme, with the switching of 2 different mobile phases in order to allow complete resolution of clo-