33.5.2 Beta-Adrenoceptor Antagonists

Propranolol is a widely prescribed, highly lipophilic beta-adrenoceptor antagonist. As it is lipophilic, having a partition coefficient of 5.39 at pH 7.0, the topical route of administration may theoretically achieve a steady drug release and plasma concentration. Oral propranolol is subject to first-pass metabolism, leading to variable adsorption and low systemic bioavailability.

Ademola et al. (14), studying percutaneous absorption and metabolism of propranolol *in vitro* using intact human skin and microsomal preparations, found that between 10.4% and 36.6% of the drug was absorbed, but only 4.1% to 16.1% of the drug penetrated the skin. Some propranolol was retained in the skin, and metabolites of propranolol were found. Naphthoxyacetic acid, 4-hydroxypropanolol, and *N*-desisopropyl propranolol were formed by intact human skin. The concentration of these metabolites was lower compared with hepatic metabolism, suggesting less enzymatic activity in the skin compared to the liver. These metabolites were also formed by the skin microsomes in a greater concentration than in intact skin. This may be the result of the greater surface area that the microsomes (everted endoplasmic reticulum) had to react with the drug. Additionally, the microsomes biotransformed propranolol to norpropranolol, which the intact skin did not form.

Ademola and Maibach (13) took this study further, using human, LSE, and keratinocyte models. Propranolol does indeed accumulate in human skin, which may be responsible for its irritant or toxic effects. They suggest that the differences between the metabolism of propranolol in skin and liver may explain the accumulation of the drug in the skin. This difference could not be attributed to the degree of enzyme activity, as the enzyme saturation points in the metabolism of propranolol in liver and skin were similarly high.

Ademola and Maibach postulated that the difference in metabolism may lie in the stereoisomeric structure. Using racemic propranolol, they demonstrated that the S-enantiomer was eliminated more efficiently by the skin than the R-enantiomer. This is in contrast to hepatocytes, which are more efficient at removing the R-enantiomer (15). Therefore, the irritation caused by the topical application of propranolol may be the result of accumulation of the R-enantiomer (16).

These studies therefore suggest that propranolol is metabolized by human skin and that its metabolism may be stereoselective. This metabolism and the retention of propranolol in the skin may explain both the low plasma concentration and irritant dermatitis after topical application.

33.5.3 Topical Nitrates

Higo et al. (9) used intact skin and homogenates from hairless mice to study the metabolism of nitroglycerin. In the homogenate study, GTN was incubated with homogenized tissue. After two hours of incubation, 30% of the GTN had been metabolized to the breakdown products 1,2- and 1,3-GDN. This metabolism was shown to be heavily dependent on the presence of glutathione (see earlier). Using the intact skin model, the investigators compared the extent of metabolism using different formulations of the GTN: a 1-mg/mL aqueous solution, a 2% ointment, and a transdermal delivery system. The percentage of metabolites formed was greatest with the aqueous solution (61%), followed by the patch (49%), and least of all with the ointment (35%). This difference is thought to be explained by the greater transdermal flux with the patch and ointment compared to the solution: The smaller the flux, the greater the relative level of skin metabolism.

33.5.4 Theophylline

Theophylline is a xanthine derivative that is used as a bronchodilator. Ademola et al. (5) studied the effect of cutaneous metabolism on its topical administration. This drug has a narrow therapeutic index at which optimal bronchodilation is maintained with minimal adverse effects occurring. Considering this, topical administration may give theoretical advantage over the oral route, as the latter results in variable plasma concentrations and is subject to altered absorption with the presence