International Journal of Pharmaceutics, 27 (1985) 361–362
Elsevier

IJP 00929

Short Communication

Permeation of digoxin through skin in vitro

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(Received July 22nd, 1985)
(Accepted August 21st, 1985)

Key words: permeation – digoxin – skin – in vitro

Digoxin is still one of the most widely used forms of digitalis in the treatment of congestive heart failure and supraventricular tachyarrhythmias (Smith, 1973). However, its narrow therapeutic index has been the reason for toxicity in 35% of patients and a 21% incidence of mortality in intoxicated patients according to Smith and Haber (1973). The toxicity will be lessened if a dosage form that releases digoxin at a steady rate can be developed. The transdermal route seems to be a possibility if digoxin will permeate the skin in a therapeutically significant quantity from a transdermal dosage form. The present experiments were undertaken to determine the permeability of silastic, hairless mouse skin and human skin to digoxin in vitro as a preliminary study to the development of a transdermal dosage form.

Silastic, whole human skin from the upper thigh and ventral forearm and abdominal hairless mouse skin, removed of all subcutaneous fat, were mounted in closed diffusion cells as described by Dürrheim et al. (1980). The epidermal side of the skin, or donor cell, having an available diffusion area of 0.754 cm^2 contained 1.2 ml [21,22-^{3}H]digoxin in 0.9% (w/v) sodium chloride solution (normal saline) with concentration 3.23 μCi/ml. The dermal side, or receiver cell was bathed in 1.2 ml of normal saline. The medium of each cell was stirred and kept at 37°C. At appropriate times, up to 10 h, samples were withdrawn from the cells and replenished accordingly with fresh medium. The amount of digoxin penetrating the skin from the epidermal side to the normal saline in the receiver cell was determined by measuring the radioactivity by a liquid scintillation counter.

The results are presented in Table 1. According to these results, the percutaneous absorption of digoxin is more than 3 times higher in human skin than in hairless mouse skin. These values are of the same order as those obtained by Dürrheim et al. (1980) for methanol (2.6×10^{-3} cm/h) and by Smith (1982) for hydrocortisone (1.6×10^{-3} cm/h), both using hairless mouse skin and of Asche (1984) using human

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TABLE 1
PERMEABILITY COEFFICIENTS OF DIGOXIN THROUGH VARIOUS MEMBRANES IN VITRO

Membrane	Permeability coefficient $\times 10^{-3}$ (cm/h)
Silastic	0.75 ± 0.1 (n = 4)
Nude mouse skin	1.00 ± 0.6 (n = 4)
Human thigh skin	4.70 ± 2.9 (n = 3)
Human forearm skin	9.24 ± 6.0 (n = 4)

Values are means $\pm$ S.D. with number of determinations in parentheses.

skin, who obtained a permeability coefficient of 10.5×10^{-3} cm/h for scopolamine in vitro. Scopolamine is used successfully in the clinical situation in the form of a transdermal therapeutic system.

The results obtained with the in vitro percutaneous absorption of digoxin indicate that it may be very possible to develop a clinically efficient transdermal therapeutic system. In vivo studies are in progress in this laboratory. The preliminary results are very promising and will be reported soon.

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