Regional Variation in Oral Mucosal Drug Absorption: Permeability and Degree of Keratinization in Hamster Oral Cavity

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The regional permeability of oral mucosa to salicylic acid was investigated in vivo in hamsters along with histological variations, especially the degree of keratinization. Histological sections from six regions, i.e., sublingual mucosa, buccal mucosa, dorsum of tongue, ventral surface of tongue, labial mucosa, and cheek pouch mucosa, were prepared to assess the degree of keratinization. The area under the plasma concentration-time curve of salicylic acid following the administration of salicylic acid to the oral mucosa with a film dosage form and the thickness of stratum corneum of each site were in inverse proportion to each other, suggesting that the stratum corneum layer represents the principle barrier to drug absorption.

KEY WORDS: oral mucosa; permeability; histological variation; stratum corneum; hamster; salicylic acid.

INTRODUCTION

Drugs absorbed via the oral–mucosal route avoid both intraalimentary canal and hepatic first-pass eliminations (1–3). However, the oral mucosa was not well characterized in terms of permeability. We have investigated the absorption characteristics from keratinized oral mucosa using a hamster cheek pouch mucosa (4–8). Regionally different oral mucosae exhibit marked variations in degree of keratinization or thickness of stratum corneum layer (9). Squier and Hall reported that the keratinized porcine oral mucosa was significantly less permeable to water and horseradish peroxidase than the non-keratinized one (10). However, the role of the stratum corneum layer in barrier property has not previously been studied with simultaneous morphological assessment of each mucosa.

In this study, the relationship between the in vivo permeability barrier characteristics of oral mucosae from different regions to salicylic acid and the degree of keratinization was investigated in the hamster.

MATERIALS AND METHODS

Chemicals

Salicylic acid was purchased from Nacalai Tesque Co. (Kyoto, Japan). Hydroxypropylcellulose (HPC; HPC-L) was supplied from Nippon Soda Co. (Tokyo). All other chemicals used were of the finest grade available. Isotonic buffer solution used was citric acid–Na2HPO4 (pH 3.0).

Animals

Male golden hamsters (100–120 g) were used under urethane anesthesia (1.5 g/kg, i.p.).

Histological Assessment of Oral Mucosae

Six regions of hamster oral mucosa were surgically removed. They were the sublingual mucosa from the floor of the mouth adjacent to the lingual frenum (sublingual mucosa), the posterior part of the buccal mucosa adjacent to the molar teeth (buccal mucosa), the mucosa of the dorsal surface of corpus linguae (dorsum of tongue), the mucosa of the ventral surface of corpus linguae (ventral surface of tongue), the labial mucosa from the inside of the lower lip (labial mucosa), and the mucosa of the middle part of a cheek pouch (cheek pouch mucosa). Small blocks of each region were fixed in formalin and embedded in paraffin wax, and the sections, 6 μm thick, were stained with hematoxylin and eosin and examined with a light microscope. Two nonserial sections showing the narrow elongate connective tissue papillae were used for histological assessment. The thicknesses of both the stratum corneum layer and the epithelial layer (except the stratum corneum layer) of tops and bottoms of five papillae were determined in every section. In selecting the sites for determination, care was taken not to slant the cross sections of their basal cells. The thickness of papillae was also determined in three mucosae; ventral surface of tongue, dorsum of tongue, and buccal mucosa, where the papillae were well developed.

Preparation of Film-Dosage Form Containing Salicylic Acid

Film-dosage forms were prepared with HPC according to our previous paper (3). A mixture of 2.0 g of HPC-L and 280 mg of salicylic acid was dissolved in 25 ml of ethanol, and 0.75 ml of isotonic buffer solution (pH 3.0) and 0.2 g of polyethylene glycol 300 were added to the ethanolic solution. The pH of the resulting viscous solution was 2.9–3.1. This viscous solution of HPC containing salicylic acid was molded into a Teflon tray and dried at 60°C for 24 hr. The film-dosage form thus prepared was nearly transparent and approximately 0.3 mm thick. The apparent content of salicylic acid was 43.3 μmol/cm².

Absorption Experiments of Salicylic Acid in Vivo

Solution

A plastic cell system (4-mm i.d.), shown in Fig. 1, was newly designed. Salicylic acid dissolved in the isotonic buffer solution (pH 3.0) was applied (15 μmol/0.5 ml/kg) to the cell system, which was fixed on the surface of an oral mucosa of hamster with cyanoacrylate tissue cement (Aron Alpha, Toa Chemicals Co., Tokyo). Because of the limitation of mucosal area, the mucosae capable of investigation
were restricted to four mucosae: sublingual mucosa, dorsum of tongue, ventral surface of tongue, and cheek pouch mucosa. Blood samples were then collected periodically from the carotid artery and plasma concentrations of salicylic acid were determined by high-performance liquid chromatography (HPLC) equipped with a fluorescence detector at 300 and 430 nm for excitation and emission, respectively, as described previously (4,8).

**Film-Dosage Form**

Aluminum foil was used as a backing of the film-dosage form containing salicylic acid, not to contact the back surface of the preparation with other mucosae in application. The preparation was cut with a circular steel punch (5-mm i.d.), and the resulting disk preparation containing salicylic acid (8.5 μmol/piece) was administered onto an oral mucosa. The preparation adhered easily to the mucosa and swelled gradually (3). The plasma concentrations of salicylic acid were periodically determined by HPLC in a similar manner to that described above.

**Evaluation of Absorption Characteristics**

The area under the plasma concentration–time curve