J. Pharmacy. 1989, 41: 712–713
Communicated January 9, 1989

The influence of changes in buccal potential difference on the buccal absorption of propranolol

A. HITOGLOU-MAKEDOU, A. HEDGES, P. TURNER, *Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE, UK*

Abstract—A buccal potential difference (b.p.d.) exists across the mucous membrane of the mouth, which can be made less negative by contact with aspirin. The influence of changing the b.p.d. with aspirin on the buccal absorption of propranolol from a series of buffers of pH5-10 has been studied in eight volunteers. The study confirmed that the buccal absorption of propranolol was markedly pH dependent, but pretreatment of the buccal membrane with aspirin had no influence on the absorption of propranolol.

Several models have been proposed to describe the kinetics of buccal absorption of drugs. Beckett & Hossie (1971) suggested that a three compartment model was adequate, but Dearden & Tomlinson (1971) added a fourth, suggesting that inclusion of protein binding into the model could best explain the observed rapid initial loss of drug from the buccal cavity.

Schurmann & Turner (1978) made two assumptions in their modifications of the original three compartment model. The first was that the third compartment, the systemic circulation, acts as a sink of infinite volume of distribution in comparison with the amount of drug dissolved, so that absorption is unidirectional and back diffusion does not occur. This has been shown to be untrue, however, in several studies (Davis et al 1979; Henry et al 1980). The other assumption made by Schurmann & Turner (1978) was that there is an aqueous pH buffering surface close to the buccal mucosa in the first compartment. It is known that there is a buccal potential gradient (b.p.d.) across the buccal membrane which can be influenced by a variety of drugs, including aspirin and other non-steroidal anti-inflammatory drugs (Huston 1978; Shah et al 1986). The purpose of this study was to examine the possibility that this b.p.d. is the same as the hypothetical aqueous pH buffering surface postulated by Schurmann & Turner (1978), by determining if changing the b.p.d. with aspirin influences the buccal absorption of a test drug, propranolol.

Materials and methods

Eight healthy volunteers gave their informed consent to participate in the study which had been approved by the local ethics committee. None had a history of sensitivity to non-steroidal anti-inflammatory drugs, or any contraindication to receiving propranolol. They were instructed to refrain from hot or caffeine containing food or drinks, alcohol and smoking for at least one hour before the start of each experimental session until its completion. They were also asked to avoid taking aspirin for at least one week before and during the complete course of the study.

Buffers. Sorensens's phosphate buffer was used to prepare solutions of pH 5·0–8·0, and Sorensen's glycine buffer for solutions of pH 9·0 and 10·0 (Documenta Geigy, 1975).

Method. In principle, the study involved estimating the buccal absorption of propranolol from a series of buffers after pretreatment of the buccal mucosa with aspirin or with placebo. The volunteers were randomised into two groups of four. One group received aspirin in the first period and placebo in the second, and the other group vice versa. Each period consisted of six days, on each of which the subject held in the mouth aspirin 600 mg or placebo (maize starch) in suspension in 20 mL citric acid buffer (pH 4·5) for 3 min, following which the b.p.d. was immediately measured. The buccal absorption of propranolol 200 ng mL^{-1} from buffers of pH 5 to 10 was then estimated. Three free days elapsed between each period of treatments.

Buccal p.d. was measured by the method of Huston (1978) using a probe electrode constructed from a Perspex (lucite) tube containing a silver–silver chloride junction in contact with a short column of saline agar. The skin electrode was also constructed of Perspex and contained a silver–silver chloride junction. The potential difference was measured with an Orion 701 millivolt meter. The skin electrode was strapped over an intradermal bleb raised on the forearm by an injection of 0·1 mL normal saline. The probe electrode was applied to the middle of the lower lip between lip margin, and gum, the head resting on a restraining device to maintain constant contact pressure. The subject first rinsed the mouth with deionised water (20 mL) and expelled the contents, after which the b.p.d. was measured at 30 s intervals for 3 min (control values). Either aspirin or placebo was then swilled around the buccal cavity for 3 min without swallowing. After the contents were expelled, the mouth was again rinsed with deionised water and the b.p.d. (test values) measured again over 3 min as before. The mean control and test values were calculated from individual data over the 3 min periods.

Buccal absorption was measured by the method of Beckett & Triggs (1967). Propranolol 200 ng mL^{-1} was prepared in a series of buffers of pH5–10. Drug free buffer, 10 mL, was used to rinse the subject's mouth for 30 s and discarded before each absorption.Then 20 mL of the same buffer solution containing propranolol 200 ng mL^{-1} was taken into the mouth and circulated using tongue and cheek movements at approximately one circuit per second for 5 min. The buffer was expelled into a measuring cylinder. A further 20 mL of buffer was then used to rinse the mouth for 10 s to remove any propranolol from the small amount of buffer solution still remaining in the mouth. This rinse was expelled and added to the solution in the cylinder. The total volume was made up to 50 mL with distilled water, and a sample was stored at −20°C until analysis. The order in which each subject received the various buffers was randomized, and 24 h elapsed between each buffer.

Propranolol was estimated by the fluorometric method of Shand et al (1970).

Data were analysed using multiple linear regression with percent buccal absorption as the dependent variable, and pH, b.p.d., together with treatments and subjects, as continuous independent variables.

Results

The change in b.p.d. after pretreatment with aspirin (18·1 ± s.d. 9·7 mV) was significantly greater ($P < 0.0001$) than after control (0·2 ± 5·5 mV).

The mean percentage buccal absorption of propranolol over

Correspondence to: A. Hedges, Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE, UK.

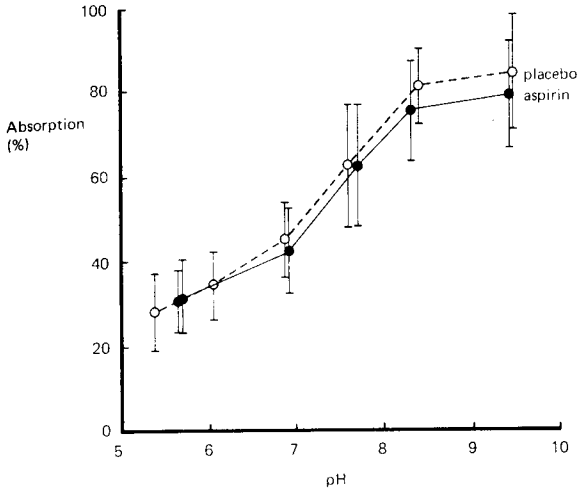

FIG. 1. Effect of changes in buccal potential difference produced by aspirin and placebo on the buccal absorption of propranolol.

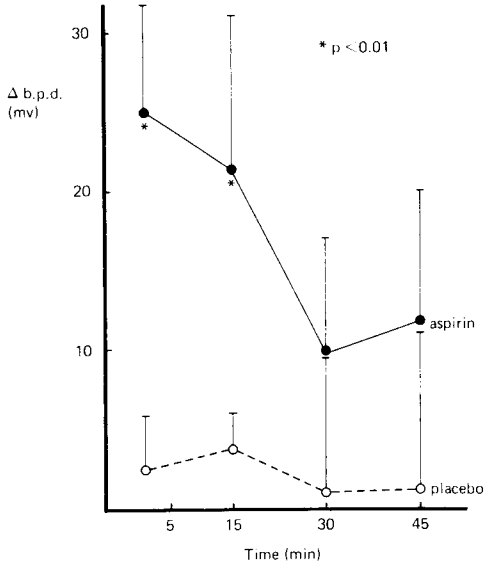

FIG. 2. Time course of changes (mean ± s.d.) in buccal potential differences (mV) produced by aspirin compared with placebo in six subjects. * $P < 0.01$ compared with placebo.

the pH range studied after treatment of the buccal mucosa with aspirin or placebo is shown in Fig. 1. Multiple linear regression analysis confirmed that buccal absorption was significantly influenced by pH ($P < 0.0001$), but that there was no difference between the buccal absorption curves after the two pretreatments.

Discussion

These results suggest that the changes in b.p.d. of about 18 mV induced by aspirin did not significantly influence the buccal absorption of propranolol measured within the next 15 min. Aspirin-induced changes on b.p.d. persist for 15 min or more (Hedges & Jain, unpublished observations, Fig. 2) which is longer than the duration of estimation of the buccal absorption, and it is unlikely, therefore, that this lack of influence is due to a return to control b.p.d. before the end of the experiment. Nor is it likely that propranolol reversed the effect of aspirin on b.p.d., because preliminary studies (Makedou et al 1989) have shown that propranolol in concentrations up to 200 $\mu g\ mL^{-1}$ has no effect on b.p.d.

It may be concluded, therefore, that the hypothesis put forward by Schurmann & Turner (1978), that there is an aqueous pH buffering surface close to the buccal mucosa which influences the ionization of drug in the buccal fluid, is not supported by these experimental data. On the other hand, it might be argued that the b.p.d. measured here is not identical with this hypothetical aqueous pH buffering surface, or that the changes in propranolol absorption produced by the changes in b.p.d. following exposure to aspirin were too small to be detected in this study. Further evidence might be obtained by studying the influence of larger changes in b.p.d. on the buccal absorption of other weakly basic and acidic drugs. The question is of more than academic importance because of increasing interest in the use of the buccal membrane as a site of drug delivery in man.

We thank the Lawson Tait Medical and Scientific Research Trust for support.

References

Beckett, A. H., Hossie, R. D. (1971) Buccal absorption of drugs. In: Handbook of experimental pharmacology. Ed. Brodie, B. B., Gillette, J. R., Berlin, Springer-Verlag. pp. 25–46

Beckett, A. H., Triggs, E. J. (1967) Buccal absorption of basic drugs and its application as an in vivo model of passive drug transfer through lipid membranes. J. Pharm Pharmacol. 19 (Suppl.): 31S

Davis, B. J., Johnston, A., Turner, P. (1979) Buccal absorption of verapamil-evidence for membrane storage. Br. J. Clin. Pharmacol. 7: 434P

Dearden, J. C., Tomlinson, E. (1971) A new buccal absorption model. J. Pharm. Pharmacol. 23: 68S–72S

Documenta Geigy (1975) Scientific Tables, 7th Edition, pp. 280–282

Henry, J. A., Ohashi, K., Wadsworth, J., Turner, P. (1980) Drug recovery following buccal absorption of propranolol. Br. J. Clin. Pharmacol. 10: 61–65

Huston, G. J. (1978) The effects of aspirin, ethanol, indomethacin and 9-alpha fludrocortisone on buccal mucosal potential difference. Br. J. Clin. Pharmacol. 5: 153–160

Makedou, A., Hedges, A., Turner, P. (1989) The effect of propranolol on buccal potential difference. Ibid. 27:676 P

Schurmann, W., Turner, P. (1978) A membrane model of the human oral mucosa as derived from buccal absorption performance and physicochemical properties of the beta-blocking drugs atenolol and propranolol. J. Pharm. Pharmacol. 30: 137–147

Shah, K., Jackson, S.H.D., Hedges, A., Turner, P. (1986) Comparison of effects of lysine aspirin, soluble aspirin and conventional aspirin on buccal potential difference in healthy volunteer subjects. Human Toxicol. 5: 329 331

Shand, D. G., Nuckolls, E. M., Oates, J. A. (1970) Plasma propranolol levels in adults with observations in four children. Clin. Pharmacol. Ther. 11: 112–120