Barltrop, D. (1963) Lancet i: 276–278

Evans, W. S., Borges, L. C., Kaiser, D. L., Vance, M. L., Sellers, R. P., Macleod, R. M., Vale, W., Rivier, J., Thorner, M. O. (1983) J. Clin. Endocrinol. Metab. 57: 1081–1083

Hoover, R. T. (1971) Am. J. Obstet. Gynec. 110: 788–794

Itabashi, A., Katayama, S., Yamaji, T. (1982) Lancet i: 108

Morimoto, K., Morisaka, K., Kamada, A. (1985) J. Pharm. Pharmacol. 37: 134–136

Ohwaki, T., Ando, H., Watanabe, S., Miyake, Y. (1985) J. Pharm. Sci. 74: 550–552

Richardson, D. W., Robinson, A. G. (1985) Ann. Int. Med. 103: 228–239

J. Pharm. Pharmacol. 1987, 39: 934–935
Communicated June 12, 1987

Influence of pH on the buccal absorption of morphine sulphate and its major metabolite, morphine-3-glucuronide

O. AL-SAYED-OMAR, A. JOHNSTON, P. TURNER*, *Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE, UK*

Buccal absorption of morphine sulphate and morphine-3-glucuronide at various buffer pH values (4 to 10) over 5 min has been investigated in seven and four normal healthy volunteers, respectively. Increasing pH caused an increase in buccal absorption of both. The maximum mean absorption was 37% at pH 10 for morphine and 19% at pH 8 for morphine-3-glucuronide.

The method of buccal absorption was established by Beckett & Triggs (1967) as an example of an in-vivo model of passive drug transfer through a lipid membrane, and although later work has shown that absorption occurs into, rather than across, the buccal membrane (Davis & Johnston 1979), the technique has proved useful in predicting the influence of urinary pH on drug excretion (Muhiddin & Johnston 1981; Muhiddin et al 1984). We investigated the extent of buccal absorption of morphine sulphate and its major metabolite morphine-3-glucuronide in normal volunteers and the influence of pH upon it.

Materials and methods

Eleven volunteers gave their informed consent to participate in the study which had been approved by the local ethics committee.

Buffers. Three different buffer types were used, McIlvaine (citric acid/phosphate) for the pH values of 4, 5, 6, 7, Sørensen (phosphate) for pH 8 and Sörensen (glycine/NaOH) for pH values of 9 and 10 (Documenta Geigy 1975).

Method. Standard samples were prepared from a stock solution of 1000 μg mL^{-1} morphine sulphate and of morphine-3-glucuronides separately in distilled water, and were then diluted to 25 mL in the appropriate buffer to reach a final concentration of 20 μg mL^{-1}, 5 mL of which was kept refrigerated as standard (A). Drug free buffer, 10 mL, was used to rinse the subject's mouth for 10 s before each absorption and then 20 mL buffer containing drug was taken into the subject's mouth and agitated by movement of the cheeks and tongue for 5 min. The solution was then expelled into a plastic container, after which the subject rinsed his mouth for 30 s and these solutions were combined. The end volume was measured and an aliquot stored at −20 °C until analysis. The order in which each subject received the buffer was randomized and a minimum of 24 h elapsed between each buffer. The subjects fasted and refrained from smoking for at least 2 h before each test.

Buccal absorption of morphine sulphate was measured in seven subjects, and that of morphine-3-glucuronide in four subjects.

The estimations of morphine sulphate and morphine-3-glucuronide in the buccal fluids were carried out by centrifuging 2 mL of the buccal samples in plastic tubes for 10 min, and injecting 100 μL aliquots into the chromatograph.

Chromatographic conditions. The chromatographic system consisted of a Rheodyne model syringe loading sample injector with a 50 μL loop (model 7125 Rheodyne, Berkeley CA, USA). The column was 10 μm micro bond pack C18 30 × 3·9 mm, the solvent delivery system was a Spectroflow 400 pump (Kratos Analytical Instruments) and the solvent flow rate was 1·5 mL min^{-1}. A spectroflow monitor SF 770 UV-detector at wavelength 210 nm. (Schoeffel Instrument-Corp) was used to measure morphine, and a FS 970 fluorometer at an excitation wavelength of 210 nm (Kratos) was used for morphine-3-glucuronide. A computing integrator (Pye Unicam CD4) was used to derive the chromatographic data.

* Correspondence.

Determination of percentage amount absorbed. The percentages of morphine sulphate and morphine-3-glucuronide absorbed at pH 4 to 10 were determined by measuring the total volume expelled, and peak heights of the sample and the standard (A). The initial concentration and volumes were fixed. The percentages absorbed were calculated as follows:

Amount remaining
= (Volume expelled × peak height sample × initial concn)/(peak height standard (A)).
% Amount absorbed
= (1 − (Amount remaining × 100)/(Initial volume × initial concn)).

Results

The linear plot of peak height ratios against concentrations over the range measured of 500 ng–20 μg mL^{-1} and 10 ng–3 μg mL^{-1} for morphine sulphate and morphine-3-glucuronide, respectively, gave correlation coefficients of >0·99. The coefficient of variation of the method was less than 3·0%. The mean percentage buccal absorption over the pH range studied in seven volunteers for morphine sulphate and four volunteers for morphine-3-glucuronide is shown in Fig. 1. Maximum absorption was 37% at pH 10 for morphine and 19% for the morphine-3-glucuronide. Absorption of morphine sulphate appeared to be more dependent on pH than that of morphine-3-glucuronide.

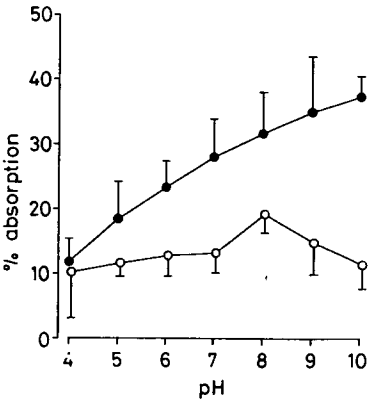

FIG. 1. Mean buccal absorption of morphine sulphate (●) and morphine-3-glucuronide (○) (±s.d.) in seven and four volunteers, respectively.

Discussion

The oral mucosa behaves in a manner similar to other biological lipoidal membranes (Beckett & Hossie 1971). Beckett & Triggs (1967) suggested that the amount of drug absorbed depended on several factors, including the pK_a, rate of partitioning of the un-ionized form of the drug, the lipid-water partition coefficient and molecular weight of the drug, passive diffusion, and the pH of the solution in the mouth. Other factors include protein binding on the surface of the buccal mucosa (Dearden & Tomlinson 1971) and membrane surface pH (Schurmann & Turner 1978).

This study has shown that morphine is moderately well absorbed into the buccal membrane, about 40% being absorbed over 5 min, at pH 10. Uptake was less at lower pH values, which is consistent with morphine's basic nature. A water soluble metabolite would be expected to be less well taken up by the buccal membrane than the parent drug, and this is confirmed with morphine-3-glucuronide which showed a markedly lower buccal absorption over the pH range studied. This is consistent with the observation of Shimomura et al (1971) that morphine-3-glucuronide is highly water-soluble and readily excreted in urine. The dependence of buccal absorption of morphine upon pH implies that its urinary excretion is pH dependent but this awaits confirmation.

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

REFERENCES

Beckett, A., Hossie, R. (1971) Handbook of experimental pharmacology vol. XX VIII/1 Concepts in Biochem. Pharmacol. Part 1. Brodie, B. B., Gillette, J. R. (eds.). Springer, N.Y. Chapter 3, pp 25–46

Beckett, A. H., Triggs, E. J. (1967) J. Pharm. Pharmacol. 19: supp. 31S

Davis, B. J., Johnston, A. (1979) Br. J. Clin. Pharmacol. 7: 434P

Dearden, J. C., Tomlinson, E. (1971) J. Pharm. Pharmacol. 23: 68S–72S

Documenta Geigy (1975) Scientific Tables, seventh edition, pp 280–282

Muhiddin, K. A., Johnston, A. (1981) Br. J. Clin. Pharmacol. 12: 283P

Muhiddin, K. A., Johnston, A., Turner, P. (1984) Ibid. 17: 447–451

Schurmann, W., Turner, P. (1978) J. Pharm. Pharmacol. 30: 137–147

Shimomura, K., Kamata, O., Ueki, S., et al (1971) Tohoku J. Exp. Med. 105: 45–52