quently increase the yield of eicosanoids (Capasso et al 1984; Capasso unpublished observation), thereby increasing the laxative effect.

REFERENCES

Al-Awqati, Q., Greenough, W. B. (1972) Nature 238: 26–27

Autore, G., Capasso, F., Mascolo, N. (1984) Br. J. Pharmacol. 81: 347–349

Bennett, A. (1984) Scand. J. Gastroenterol. 19: 59–64

Bertaccini, G. (1982) in: Bertaccini G. (ed.) Mediators and Drugs in Gastrointestinal Motility, Vol. II. Berlin, Springer Verlag, pp 1–10

Beubler, E., Juan, H. (1978) Naunyn-Schmiedeberg's Arch. Pharmacol. 305: 241–246

Beubler, E., Juan, H. (1979) J. Pharm. Pharmacol. 31: 681–685

Capasso, F., Mascolo, N., Autore, G., Duraccio, M. R. (1983) Prostaglandins 26: 557–562

Capasso, F., Tavares, I. A., Bennett, A. (1984) Eur. J. Pharmacol. 106: 419–422

Capasso, F., Tavares, I. A., Tsang, R., Bennett, A. (1985) Prostaglandins 30: 119–124

Cohen, H. H. (1982) Prostaglandins Leukotrienes and Med. 8: 389–397

Collier, H. O. J. (1974) in: Robinson, H. J., Vane J. E. (eds) Prostaglandin Synthetase Inhibitors. New York, Raven Press, pp 121–133

Derksen, A., Cohen, P. (1975) J. Biol. Chem. 250: 9342–9347

Donowitz, M., Charney, A. N., Heffermam, J. M. (1977) Am. J. Physiol. 232: E85

Donowitz, M., Wicks, J., Battisti, L., Pika, G., De Lellis, R. (1984) Gastroenterology 87: 503–512

Flower, R. J., Blackwell, G. J. (1976) Biochem. Pharmacol. 25: 285–291

Karim, M. M. (1974) Ann. Acad. Med. 3: 201–206

Koskowski, W. (1926) J. Pharm. Exp. Ther. 26: 413–416

Lee, J. S., Silverberg, J. W. (1976) Am. J. Physiol. 231: 793–799

Pierce, N. F., Carpenter, C. C. J., Elliott, H. L. (1971) Gastroenterology 60: 22–32

Powell, D. W., Field, M. (1980) in: Field M., Fordtran, J. S., Schultzs, G. (eds) Pharmacological approaches to treatment of secretory diarrhoea, Bethesda, pp 187–214

Rask-Madsen, J., Bukhave, K. (1981) Clinical Research Reviews (Suppl. 1) 1: 33–48

Rask-Madsen, J., Bukhave, K. (1983) in: Turnberg, L. A. (ed.) Intestinal Secretion. Knapp Drewett and Sons Ltd, Great Britain, pp 76–83

Thompson, J. H. (1966) Irish J. Med. Sci. 490: 411–416

Thompson, J. H., Angulo, M. (1968) Eur. J. Pharmacol. 4: 224–227

Williams, E. D., Karim, S. M. M., Sandler, M. (1968) Lancet i: 22–23

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Spectrofluorimetric analysis and buccal absorption of medifoxamine

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Medifoxamine is a new investigational antidepressant drug. Its buccal absorption at pH 5–9, which can be considered as an in-vivo model of passive drug transfer through a lipid membrane, was studied in six normal, healthy volunteers to predict its pharmacokinetic profile in man. Maximum absorption of medifoxamine occurred at pH 8, which is close to its pK_a (8·5).

A study of buccal absorption of drugs at various pH levels (particularly pH 5–9) can be considered as an in-vivo model of passive drug transfer through lipid membranes (Beckett & Triggs 1967) and may help to predict the extent of binding to plasma proteins (Henry et al 1981), the concentration in various body fluids and renal excretion at different urinary pH values (Meyer et al 1974; Ankier & Kaye 1976; Kaye & Long 1976).

Changes in pH relative to the pK_a of a drug alter the extent of its buccal absorption. For a basic drug, maximum absorption occurs at or above its pK_a, with the converse for an acidic drug. However, the controlling factor influencing the extent of absorption of a drug is its innate lipophilicity (Beckett & Triggs 1967).

Medifoxamine is a new investigational antidepressant drug (Bonnet et al 1984). Its buccal absorption at pH 5–9 was studied in normal, healthy volunteers using a method similar to that of Beckett & Triggs (1967).

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Materials and methods

Buccal absorption of medifoxamine. The study was carried out, with informed consent, in 6 normal, healthy, medically qualified volunteers (4 males, 2 females) aged between 25–35 years. They were requested not to eat or drink for at least 1 h before the study. After rinsing the mouth with 20 ml of buffer, 20 ml of medifoxamine solution (50 $\mu g\ ml^{-1}$, in the same buffer) was agitated in the mouth for 5 min, and expelled into a beaker. Immediately after that the mouth was rinsed with 20 ml of the buffer for 30 s and expelled into the same beaker. The volume of the fluid in the beaker was measured and the medifoxamine concentration estimated spectrofluorimetrically, indicating the amount

not absorbed. The % of medifoxamine absorbed at the pH of the buffer was then calculated. The buccal absorption of the drug at different pH levels was studied in the same subject with a wash out period of at least 24 h.

Buffers used: pH 5–8, McIlvaine's citric acid phosphate (citric acid 0·1 M and disodiumhydrogenphosphate 0·2 M); pH 9, Sörensen's glycine (glycine 0·1 M, NaCl 0·1 M and NaOH 0·1 M).

Estimation of medifoxamine in the buccal solution. To 1·0 ml of the sample in a glass tube, 0·5 ml of 4 M NaOH and 6 ml of n-heptane with 1·5% amyl alcohol was added. After mixing (10 min) and centrifugation at 3000 rev min^{-1} (10 min), the heptane layer was transferred into another glass tube containing 3 ml of 0·01 M HCl and the tube was shaken and centrifuged as before. The aqueous layer was removed and medifoxamine read at pH 2·0 in a spectrofluorimeter at excitation and emission wavelengths of 265 and 336 nm, respectively.

Results

Medifoxamine gave a linear plot of fluorescence intensity against concentration over the range measured (1–50 μg ml^{-1}). The limit of sensitivity of the method was 1·0 μg ml^{-1} with a coefficient of variation of 5·3% at 10 μg ml^{-1}. Changes in pH did not markedly affect its fluorescence even after the extraction process (unpublished observation).

There was negligible absorption from the buccal cavity at pH 5 (4·5%) rising to a maximum of 23·05% at pH 8 (Fig. 1). The buccal absorption at pH 5 and 6 was significantly different from that at pH 8 ($P < 0·01$ and 0·05, respectively).

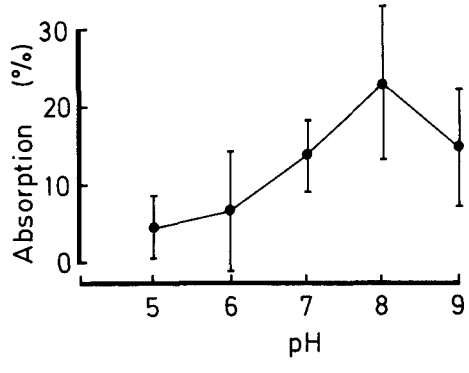

FIG. 1. Buccal absorption of medifoxamine at pH 5–9 (mean ± s.d.).

Maximum absorption of medifoxamine occurred at pH 8, which is close to its pK_a of 8·5 (unpublished observation).

Discussion

Beckett & Triggs (1967) studied the buccal absorption of a number of basic drugs and classified them into four main groups according to the shape of the curve of drug absorption against pH (Class 1, drugs with negligible uptake at pH 4 to 6·5 but a steep rise as pH becomes more alkaline; Class 2, drugs with little uptake at pH 4 to 6·5 and only a slight rise as pH becomes more alkaline; Class 3, drugs with substantial uptake at pH 4 to 6·5 and a steep rise as pH becomes more alkaline; and Class 4, drugs with characteristics between those of Classes 2 and 3).

The shape of the medifoxamine buccal absorption pH curve falls between Classes 1 and 2 of the Beckett & Triggs (1967) classification. We may anticipate, therefore, that its rate of excretion will vary to some extent with normal changes in urinary pH, acidification of urine resulting in some increase in excretion while excretion will be decreased when the urine is made alkaline. Its biological half life will be less when the pH of the urine is kept acidic and more when it is alkaline. We may also predict that it will cross the blood brain barrier slowly and be eliminated gradually from the CSF, and therefore its central effects will probably last longer than anticipated from the plasma half life.

Confirmation of these possibilities and the influence of biotransformation of medifoxamine in the liver on its elimination await further investigation.

The large variation observed between subjects is probably due to biological variation which has been observed in other buccal absorption studies. The decrease in buccal absorption at pH 9 has also been observed in a few other studies but is difficult to explain. There was no significant change in the fluorescence of medifoxamine at pH 9, and so this is unlikely to provide an explanation.

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REFERENCES

Ankier, S. I., Kaye, C. M. (1976) Br. J. Clin. Pharmacol. 3: 672

Beckett, A. H., Triggs, E. J. (1967) J. Pharm. Pharmacol. 19: Suppl. 31S–41S

Bonnet, J., Del Frari, J., Loiseau, A. M., Desgroux, L., Labaune, J. P., Bessin, P. (1984) IUPHAR 9th International Congress of Pharmacology. Abstract No. 1977P. Macmillan, London

Henry, J. A., Dunlop, A. W., Mitchell, S. N., Turner, P., Adams, P. (1981) J. Pharm. Pharmacol. 33: 179–182

Kaye, C. M., Long, A. D. (1976) Br. J. Clin. Pharmacol. 3: 196–197

Meyer, W., Kaye, C. M., Turner, P. (1974) Eur. J. Clin. Pharmacol. 7: 287–289