synergism between the actions of diethylcarbamazine and isoprenaline similar to that between methylxanthines and isoprenaline, indicating that an elevation of cyclic(c) AMP might be the mechanism of the inhibition of mediator release. Engineer et al (1978) with guinea-pig isolated perfused lung showed inhibition of both SRS-A and histamine release by $2{\cdot}6 \times 10^{-3}$ mol litre^{-1}. Our results show a greater sensitivity of guinea-pig chopped lung to diethylcarbamazine, since significant inhibition of SRS-A release is seen at concentrations of diethylcarbamazine of $2{\cdot}5 \times 10^{-4}$ and $7{\cdot}5 \times 10^{-4}$ mol litre^{-1}. Engineer et al (1978) also found a dose-dependent increase in PGE release by 5×10^{-4} and $2{\cdot}5 \times 10^{-3}$ mol litre^{-1} of diethylcarbamazine, and proposed that prostaglandins and related compounds released in anaphylaxis may influence the release of SRS-A, perhaps by way of an interaction with cyclic nucleotide. $PGF_{2\alpha}$ release from guinea-pig chopped lung (2 experiments here) was unchanged by the lower concentrations ($2{\cdot}5$ and $7{\cdot}5 \times 10^{-4}$ mol litre^{-1}) of diethylcarbamazine, and reduced by the higher concentrations ($1{\cdot}3$, $2{\cdot}6$ and $5{\cdot}1 \times 10^{-3}$ mol litre^{-1}). Diethylcarbamazine ($1{\cdot}3 \times 10^{-3}$ mol litre) in the absence of antigen increased $PGF_{2\alpha}$ release by 26%. $PGF_{2\alpha}$ release appears here to be related to SRS-A release, supporting the evidence of Engineer et al (1977) that SRS-A released in anaphylaxis may cause the release of prostaglandin-like substances.

Whereas the inhibition of immunological release of SRS-A and $PGF_{2\alpha}$ by BW755C and CLI can be explained by their inhibition of lipoxygenase and cyclooxygenase, the inhibitor action of diethylcarbamazine appears to involve a different mechanism that may depend on cAMP.

REFERENCES

Adcock, J. J., Garland, L. G., Moncada, S., Salmon, J. A. (1978) Prostaglandins 16: 179–187

Augstein, J., Farmer, J. B., Lee, T. B., Sheard, P., Tattersall, M. L. (1973) Nature New Biol. 245: 215–217

Blackwell, G. J., Flower, R. J. (1978) Br. J. Pharmacol. 63: 360P

Burka, J. F., Paterson, N. A. M. (1980) Prostaglandins 19: 499–515

Engineer, D. M., Piper, P. J., Sirois, P. (1977) Br. J. Pharmacol. 59: 444P

Engineer, D. M., Neiderhauser, U., Piper, P. J., Sirois, I. (1978) Br. J. Pharmacol. 62: 61–66

Higgs, G. A., Flower, R. J., Vane, J. R. (1979) Biochem. Pharmacol. 28: 1959–1961

Ishizaka, T., Ishizaka, K., Orange, R. P., Austen, K. F. (1971) J. Immunol. 106: 1267–1273

Morris, H. R., Piper, P. J., Taylor, G. W., Tippins, J. R. (1980) Prostaglandins 19: 371–383

Nijkamp, F. P., Ramakers, A. G. M. (1980) Eur. J. Pharmacol. 62: 121–122

Orange, R. P., Austen, W. G., Austen, K. F. (1971) J. Exp. Med. 134: 136–148

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Preliminary observations on the excretion of acebutolol and its acetyl metabolite in the urine and faeces of man

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Less than half an oral dose of acebutolol hydrochloride is recovered in human urine (Kaye et al 1976; Meffin et al 1976). It has been suggested that the remainder is unabsorbed and appears in faeces. However, acebutolol and its major metabolite, diacetolol—an acetyl analogue are excreted in human bile (Kaye & Oh 1976) and acebutolol can cross the gut wall from the systemic circulation (Collins & George 1976; George & Gruchy 1979).

We have assessed urinary and faecal excretion of the drug and its metabolites in a healthy male volunteer. Urine and faeces were collected after the administration of one tablet containing 400 mg of acebutolol. Several weeks later urine and faeces were collected after a single intravenous dose of 100 mg of acebutolol. Collections were made on each occasion for the 24 h preceding the dose and daily for 4 days after the dose.

Urine collected after the oral administration of acebutolol contains acebutolol and diacetolol, and small amounts of a second metabolite, M & B 17, 127—the free amine derivative of acebutolol (Andresen & Davis 1979). The assay used is specifically capable of quantitating acebutolol and both metabolites. The procedure for faeces was as follows: 1 g of homogenized faeces was weighed in a centrifuge tube to which was added 2 ml of water and a suitable amount of an internal standard M & B 17, 764—the propionamido analogue of acebutolol; after mixing, the compounds of interest were extracted into ethyl acetate under alkaline conditions, back extracted into acid, and then extracted into chloroform after the addition of excess alkali. For urine, the initial extraction and back extraction were omitted. Each chloroform extract of faeces and urine was evaporated to dryness and the residue taken up in 100 μl of the mobile phase (see below). The compounds of interest were separated and quantitated by reversed-phase high performance liquid chromatography using an analytical column of Spherisorb S5 ODS, protected by a small guard column of Whatman Co:Pell ODS, a mobile phase of water–methanol–triethylamine

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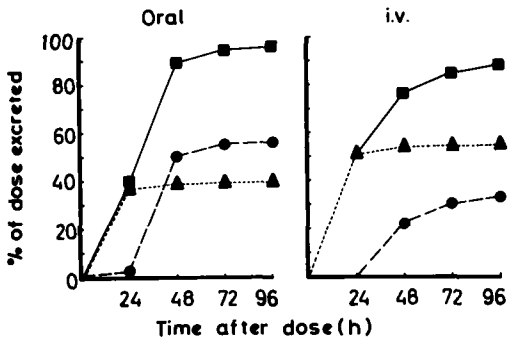

FIG. 1. Cumulative excretion—expressed as molar percentage of dose—of acebutolol, diacetolol and M & B 17, 127 in urine and faeces. ■ urine plus faeces, ● faeces, ▲ urine.

(50:50:0·5, v/v) (French, Gulaid & Lewellen—personal communication), and u.v. detection at 232 nm. The procedure for faeces and urine was validated by adding known amounts of acebutolol, diacetolol and M & B 17, 127 to aliquots of the pre-dose samples of faeces and urine.

The cumulative excretion (expressed as molar % of dose) of acebutolol, diacetolol and M & B 17, 127 in the urine and faeces collected for 96 h after the single oral and intravenous doses is shown in Fig. 1. After the 400 mg oral dose of acebutolol virtually all the drug could be recovered in urine and faeces as acebutolol, diacetolol and M & B 17, 127. The 40% of the dose recovered in urine comprised 29% acebutolol, 62% diacetolol and 8·5% M & B 17, 127, whilst the figures for the 56% recovered in faeces were 49%, 51% and 0% respectively. After the 100 mg intravenous dose about 90% of the dose could be accounted for. The 54% of the dose recovered in urine comprised 58% acebutolol, 36% diacetolol and 5·5% M & B 17, 127, whilst the corresponding figures for the 33% recovered in faeces were 49%, 50·5% and 0·8%. The values obtained for the urinary excretion of acebutolol and diacetolol after oral and intravenous administration of acebutolol are similar to those previously reported (Meffin et al 1976, 1977; Winkle et al 1977; Roux et al 1980).

A number of conclusions can be drawn from these results. Since, in both studies, virtually all of the dose was recovered in urine and faeces as acebutolol and diacetolol accompanied by small amounts of M & B 17, 127, metabolic conversion of acebutolol to other products occurs to a very limited extent in healthy man, and there is little or no formation of conjugates of these compounds. The presence in faeces of 56% of the oral dose and 33% of the intravenous dose confirms the importance of gut excretion. After the oral dose, 27·5% was recovered in faeces as acebutolol; after the intravenous dose the figure was 16%. This suggests that at most only 11·5% of the oral dose of acebutolol was unabsorbed. This was expected because β-adrenoceptor antagonists are generally well absorbed in man (Kiechel & Meier 1978).

The appearance of diacetolol in urine and stool was greater after oral (53% of the dose) than after intravenous (36% of the dose) administration of acebutolol. This is in keeping with 'first-pass' metabolism of acebutolol in man as previously reported (Meffin et al 1976, 1977; Winkle et al 1977). In this study about half of the dose-derived material excreted in faeces was present as the major metabolite diacetolol, and it is unlikely that this conversion occurred within the gut lumen. Munn et al (1980) assumed that diacetolol has a minimal non-renal component of its elimination in man. This preliminary study demonstrates that like acebutolol, substantial amounts of diacetolol can be eliminated in urine and faeces.

REFERENCES

Andresen, B. D., Davis, F. T. (1979) Drug Metab. Dispos. 79: 360–365

Collins, R. F., George, C. F. (1976) Br. J. Clin. Pharmacol. 3: 346P

George, C. F., Gruchy, B. S. (1979) J. Pharm. Pharmacol. 31: 643–644

Kaye, C. M., Kumana, C. R., Leighton, M., Hamer, J., Turner, P. (1976) Clin. Pharmacol. Ther. 19: 416–420

Kaye, C. M., Oh, V. M. S. (1976) J. Pharm. Pharmacol. 28: 449–450

Kiechel, J-R., Meier, J. (1978) Nouv. Presse Med. 7: 2685–2687

Meffin, P. J., Harapat, S. R., Harrison, D. C. (1976) Res. Commun. Chem. Pathol. Pharmacol. 15: 31–52

Meffin, P. J., Winkle, R. A., Peters, F. A., Harrison, D. C. (1977) Clin. Pharmacol. Ther. 22: 557–567

Munn, S., Bailey, R. R., Begg, E., Ebert, R., Ferry, D. G. (1980) N.Z. Med. J. i: 289–291

Roux, A., Flouvat, B., Chau, N. P., Letac, B., Lucsko, M. (1980) Br. J. Clin. Pharmacol. 9: 215–217

Winkle, R. A., Meffin, P. J., Ricks, W. B., Harrison, D. C. (1977) Ibid. 4: 519–522