of the protein. Polyacrylamide gel filtration has further demonstrated the presence of a tightly coupled aldolase–chlorpromazine complex.

REFERENCE

CHOWDHURY, A. K., ROGERS, H., SKINNER, A., SPECTOR, R. G. & WATTS, D. C. (1969). The influence of psychotropic drugs on aldolase, mitochondrial malic dehydrogenase and $Mg^{++}Na^{+}K^{+}$ adenosine triphosphatase. *Br. J. Pharmac.*, **37**, 459–467.

Human pharmacology of taloximine

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Taloximine is a phthalazine derivative [1-hydroxyimino-4-(2-dimethylamino-ethoxy-1-2-dihydrophthalazine monochloride monohydrate)] with respiratory stimulant and bronchodilator properties in animals (Daly, Lightowler & Pickering, 1969). Its respiratory stimulant action is mediated through chemoreceptors in the carotid and aortic bodies (Pearson & Griffin, 1969). This demonstration presents results of studies of taloximine in man.

Human tissue studies

The activity of taloximine was compared with that of aminophylline on human smooth muscle prepared by the method described by Coupar & Turner (1969). The compounds were approximately equipotent in causing direct relaxation of stomach, ileum, colon, rectum and bronchus. Taloximine did not affect the rate of spontaneous contractions of stomach, colon (longitudinal muscle), rectum or uterus, but caused a marked increase in rate of contraction of circular muscle of the colon. It was approximately equipotent with aminophylline in reducing the height of spontaneous contractions of ileum, colon (longitudinal muscle) and rectum, but was less effective than aminophylline on the stomach and failed to reduce amplitude in circular muscle of colon in concentrations of up to 1 mg/ml.

Metabolic fate

Oral route. Fall in plasma concentration of taloximine with time was biphasic after oral administration of 2·0 g. The half times of the two exponentials were 4·8 and 17·1 h respectively.

The following were found in the urine in 24 h after 2·0 g of taloximine; unchanged taloximine, a phthalazinone, demethylated taloximine and a ring hydroxylated form. Taloximine and its metabolites were present in free, glucuronated and sulphated forms, each of which was measured quantitatively. The total phthalazines recovered from the urine accounted for 23·2% of the total dose.

Intravenous route. After intravenous administration of 200 mg taloximine to one subject there was a biphasic fall in plasma taloximine concentration, the half times being 0·6 h and 2·7 h respectively.

Bile was collected from an indwelling T-tube inserted during operation into the common bile-duct of a patient undergoing cholecystectomy in whom common

bile-duct exploration was necessary. Taloximine, 150 mg, was given as a resuscitant procedure and samples of bile were collected over the following 48 h. 31·4% of the taloximine injected was recovered over this period, mainly as glucuronated derivatives.

Respiratory effects

Peak plasma levels of taloximine after 2·0 g orally coincided with hyperventilation accompanied by a respiratory alkalosis, a fall in mixed venous pCO_2 and a rise in plasma and urinary pH (Prime, Griffin, Turner, Ben-Dyke & Pickering, 1970).

We gratefully acknowledge the help of our colleagues in these studies.

REFERENCES

COUPAR, I. M. & TURNER, P. (1969). Relative potencies of sympathetic amines in human smooth muscle. *Br. J. Pharmac.*, **36**, 213–214*P*.

DALY, M., LIGHTOWLER, J. E. & PICKERING, R. W. (1969). Taloximine, a new respiratory stimulant with bronchodilator properties. *Br. J. Pharmac.*, **35**, 283–294.

PEARSON, J. A. & GRIFFIN, J. P. (1969). Investigations into the site of action of taloximine: a new respiratory stimulant molecule. *Experientia*, **25**, 716–717.

PRIME, F., GRIFFIN, J. P., TURNER, P., BEN-DYKE, R. & PICKERING, R. W. (1970). Metabolic studies of taloximine and its effects on the respiratory response to carbon dioxide. *Pharmacologia Clinica*, in the Press.

Isotope dilution in drug analysis

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There is a constant need for sensitive and specific methods for determination of drug concentrations in biological fluids. An additional problem, especially prominent in the field of clinical pharmacology, is the frequent need for a general technique that can be applied at short notice to the analysis of a new compound. Isotope dilution techniques may be useful in overcoming some of these problems.

Isotope dilution techniques are widely used in chemistry, and in pharmacological investigations of endogenous materials, but they are rarely used for the measurement of concentrations of foreign compounds in the body. In an isotope dilution method, a known quantity of radioactively labelled compound is added to a sample containing an unknown quantity of unlabelled compound, and labelled and unlabelled compound are then extracted into an organic solvent. A distribution property of combined labelled and unlabelled material in the concentrated extract is used to display a ratio of radioactivity. This ratio changes with total concentration, so that by reference to standards it indicates the concentration of total material present. The original concentration of unlabelled compound is then calculated.

There are three ways in which a usable ratio for drug analysis might occur. First, for a number of drugs in plasma, the fraction bound to protein varies with overall concentration; in using this property, the extraction step could possibly be omitted. Second, in place of protein, an insoluble binding agent such as charcoal might be used. Third, a complexing agent could be used under substoichiometric conditions.

Complex formation under substoichiometric conditions has been used in preliminary experiments with fluphenazine and morphine. Both of these compounds readily