Clofibrate: antisecretory-antiulcer activity in the rat

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Clofibrate (ethyl *p*-chlorophenoxyisobutyrate, Atromid-S) is an effective agent in reducing cholesterol and lipids in the liver and/or serum of various species, e.g. rat (Thorp & Waring, 1962), monkey (Thorp, 1962) and man (Oliver, 1971). The ester is rapidly hydrolysed to the corresponding free acid, i.e. clofibric acid, after oral administration. Clofibric acid is present in the serum and is considered to be the active moiety (Thorp, 1962). In the present studies clofibrate and the free acid have been found to inhibit gastric acid secretion and ulcer formation in the rat.

Basal gastric acid secretion was measured essentially according to the method of Shay, Sun & Gruenstein (1954) as described by Lippmann (1970). The animals (8–12 per group) were killed 4 h after pylorus ligation. The determination of the effects of the drugs on ulcer formation induced by pylorus ligation was carried out according to Shay, Komarov & others (1945) as described by Lippmann & Seethaler (1973). There were 8–15 animals per group. Clofibrate (Atromid-S) was from Ayerst Research Laboratories and the free acid was prepared by Dr. G. Myers (Ayerst Research Laboratories). In the evaluation of the data through the analysis of variance, the validity of parallel line biological assay was established (Finney, 1964). The values for the relative potencies are given with the 95% confidence limits.

Clofibrate administered orally 1 h before the pylorus ligation inhibited the basal gastric acid secretion (ED50: 325 mg kg^{-1}; Fig. 1). Clofibric acid also exhibited the activity being similar in potency (ED50: 270 mg kg^{-1}; 1·20 (0·85 to 1·82); Fig. 1A). Both drugs also decreased the volume of gastric juice produced in a highly significant ($P < 0{\cdot}01$) dose-response manner (1·19 (0·87–1·90); Fig. 1B). Similar effectiveness by clofibrate was observed when the drug was given 0·5 h rather than 1 h before the ligation (ED50: 300 *vs* 225 mg kg^{-1}, respectively; 1·33 (0·92 to 2·08)).

Clofibrate, given 1 h before ligation, exhibited similar antisecretory activity when given orally as intraperitoneally (ED50: 170 *vs* 180 mg kg^{-1}). The drug thus appears to be well-absorbed. In contrast to being effective when given orally before the ligation, clofibrate was ineffective when administered immediately after the ligation (ED50: 150 mg kg^{-1} *vs* no significant decrease at 500 mg kg^{-1}). In this regard it is possible that the drug acts systemically rather than locally.

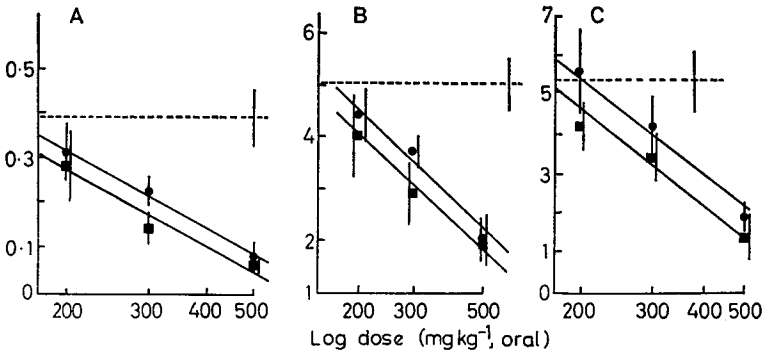

FIG. 1A, B. Inhibition of basal gastric acid secretion by clofibrate and clofibric acid. Ordinate A—Gastric acid output (mequiv 4 h^{-1} ± s.e.). Ordinate B—Volume of gastric juice (ml 4 h^{-1} ± s.e.).

C. Inhibition of pylorus ligation-induced ulcer formation by clofibrate and clofibric acid. Ordinate—Ulcer formation (score ± s.e.).

● Clofibrate. ■ Clofibric acid. – – – Control.

Clofibrate administered orally 1 h before pylorus ligation antagonized the induced ulcer formation with the ED50 being 430 mg kg^{-1} (Fig. 1C). Clofibric acid also exhibited the activity being similar in potency (ED50: 340 mg kg^{-1}; 1·28 (0·95 to 1·87)).

The present findings demonstrate that clofibrate is an effective inhibitor of gastric acid secretion and ulcer formation in the rat. In comparison, clofibric acid administered orally exhibited essentially the same activities thus indicating the activities are due to the free acid form of the drug. Such a suggestion would be consistent with the observation that the free acid is rapidly formed from the ester (Thorp, 1962). Clofibrate, and the free acid, appears to be a potentially useful therapeutic agent for the treatment of hypergastric acid secretion and peptic ulcers.

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REFERENCES

FINNEY, D. J. (1964). *Statistical Method in Biological Assay*, New York: Hafner Co.

LIPPMANN, W. (1970). *J. Pharm. Pharmac.*, **22**, 568–573.

LIPPMANN, W. & SEETHALER, K. (1973). *Experientia*, **29**, 993–995.

OLIVER, M. F. (1971). *Br. med. J.*, **4**, 767–775.

SHAY, H., SUN, D. C. H. & GRUENSTEIN, M. (1954). *Gastroenterology*, **26**, 906–913.

SHAY, H., KOMAROV, S. A., FELS, S. S., MERANZE, D., GRUENSTEIN, M. & SIPLET, H. (1945). *Ibid.*, **5**, 43–61.

THORP, J. M. (1962). *Lancet*, **1**, 1323–1326.

THORP, J. M. & WARING, W. S. (1962). *Nature (Lond.)*, **194**, 948–949.

Evaluation of the binding of some substituted anthraquinones and naphthacenequinones to DNA

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We have previously reported the interactions of a series of substituted anthraquinones with DNA (Double & Brown, 1975). These anthraquinone derivatives were designed to incorporate features known to be essential for binding to DNA and were found to have affinity constants for the interaction with DNA within the range of these constants for drugs known to intercalate into DNA. All intercalating agents contain, as an essential requirement, a planar electron-rich chromophore, and binding to DNA is enhanced when there is a substituent bearing an amino group which can bind electrostatically to the phosphate groups of the DNA. The area of the planar chromophore has been calculated as 38–49 $Å^2$ for acridines and benzacridines which intercalate (Albert, 1973) and this compares favourably with a value of about 50 $Å^2$ for the area of a hydrogen-bonded base pair in the B form of DNA (Arnott, 1970). This means that it is possible for planar tricyclic and tetracyclic ring systems to be accommodated between successive base pairs. The compounds tested previously (Double & Brown, 1975) were tricyclic, and the overall effect of increasing the system to four rings cannot be predicted as two opposing forces would be expected. The increase in electron density should increase the stability of the complex and consequently the association constant, whereas the increase in size could give an inhibitory steric effect. Hence four further compounds (Ia–d), containing an equivalent tetracyclic chromophore, have been prepared to examine the effect of increasing the size of the planar ring system on the binding to DNA.