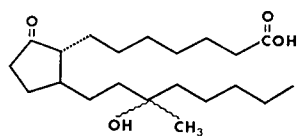
Inhibition of gastric acid secretion in the rat by orally-administered synthetic prostaglandin analogues: enantiomorphs of 15-hydroxy-15-methyl-9-oxoprostanoic acid

As with certain natural prostaglandins, synthetic prostaglandin analogues, e.g. 11-deoxyprostaglandins, may inhibit gastric acid secretion. Various of these synthetic PGE-type analogues inhibit basal and pentagastrin-induced gastric acid secretion in the rat when given subcutaneously (Lippmann, 1969, 1970, 1971), and 15-hydroxy-15-methyl-9-oxoprostanoic acid (AY-22469) inhibits secretion when administered orally (Lippmann, 1973).

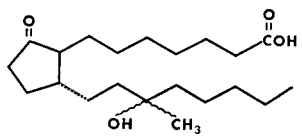
In the present study the effects of orally-administered enantiomorphs of AY-22469 have been determined on basal gastric acid secretion and also on the incidence of diarrhoea. Natural prostaglandins increase the incidence of diarrhoea thus limiting their potential usefulness (Horton, Main & others, 1968; Misiewicz, Waller & others, 1969).

Basal gastric acid secretory activity was measured according to the method of Shay, Sun & Gruenstein (1954) as described by Lippmann (1973) in female albino rats. Appearance of diarrhoea was noted in groups of 8–10 rats (24 h-starved) or mice (non-starved) 60 min after the oral administration of the analogue. The percent of animals exhibiting diarrhoea was determined; the data were evaluated by probit analysis (Finney, 1947).



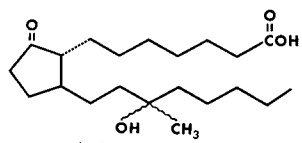
(±), rac-AY-22469

I



(+), ent-AY-22469

II



(−), nat-AY-22469

III

The synthetic prostaglandin racemate AY-22469 (I), administered orally, inhibited the basal gastric acid secretion with an ED50 of 4·3 mg kg^{-1} (Fig. 1A). The *ent*-isomer (II) was similarly active with a parallel log dose-response curve which could coincide with that for the racemate [ED50 of 5·2 mg kg^{-1}, relative potency 1·24 (0·82 to 1·91)]. The *nat*-isomer III was 2·8 times less effective than the *ent*-isomer (1·31 to 4·78) with a parallel log dose-response curve not coinciding with that for the *ent*-isomer (Fig. 1B). The compounds did not, in general, alter the volume of gastric juice produced (Fig. 1A, B).

In mice receiving AY-22469 orally up to 240 mg kg^{-1}, diarrhoea was caused only to an extent of 13%, and at this dose the *ent*- and *nat*-isomers each caused a 25% incidence. PGE_2 caused diarrhoea with an ED50 of 43 mg kg^{-1}. In rats AY-22469 caused diarrhoea with an ED50 of 120 mg kg^{-1}.

Thus, in rats both enantiomorphs of the synthetic prostaglandin analogue AY-22469 inhibit basal gastric acid secretion when administered orally but cause diarrhoea only at relatively high doses in mice. There is also no appreciable tendency of AY-22469 to cause diarrhoea in rats.

The more potent *ent*-isomer has the opposite optical configuration to that of the natural prostaglandins; *ent*-11,15-epi-PGE_2 is more active than the *nat*-isomer in rat uterus and gerbil colon preparations (Corey, Terashima & others, 1972).

The antisecretory activity of AY-22469 and the enantiomorphs appears to be due to their action on the acid concentration since the volume of gastric juice is generally unchanged. Cyclic adenosine-3′,5′-monophosphate (cyclic AMP) may be involved.

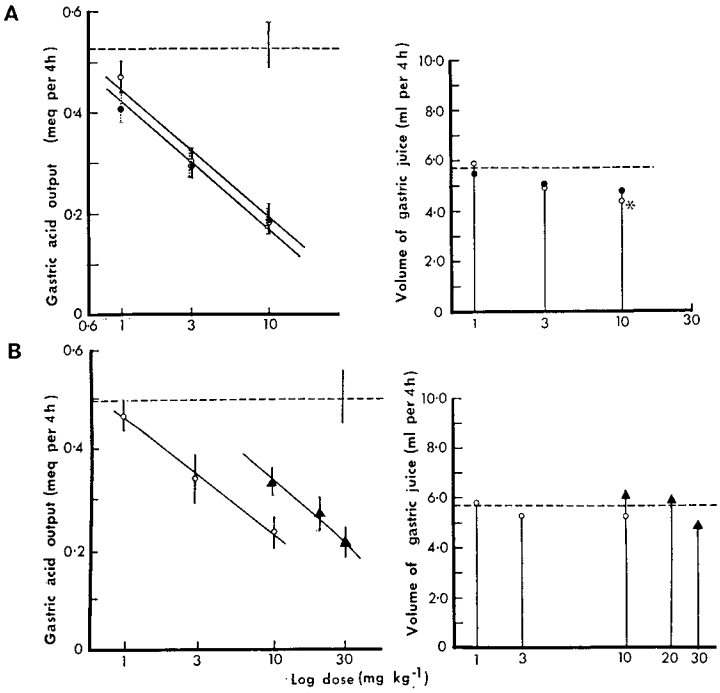


FIG. 1. The inhibition of gastric acid secretion by A. AY-22469 (●), *ent*-isomer (○); B. *ent*-isomer (○), *nat*-isomer (▲); control (– – –). The prostaglandin analogues were administered (0·2 ml) w/v in 0·2% carboxymethyl cellulose (sodium form) immediately after pyloric ligation and the animals were killed 4 h later. There were 8–18 animals per group and values are the mean ± s.e. Analysis of variance and regression study were used in the evaluation of the data (Bliss, 1952). The equations for the best parallel fitted lines were calculated (95% confidence level).
*$P<0{\cdot}02$. The values for the relative potencies are given with the 95% confidence limits.

It inhibits gastric secretion in the rat (Taft & Sessions, 1972), man and dog (Levine & Wilson, 1971); similar activities are exhibited by prostaglandins, e.g. PGE_1 (Wilson & Levine, 1969) and PGA_1 (Wilson, Phillips & Levine, 1971). Synthetic prostaglandin analogues of the type employed in the present studies also alter cyclic AMP formation as shown by studies in other tissues (Lippmann, W., in preparation).

Alteration of blood flow is also a possible basis for the antisecretory effects of prostaglandins and cyclic AMP. After administration of natural prostaglandins or cyclic AMP, secretion and aminopyrine clearance are reduced (Wilson & Levine, 1969; Levine, 1971), but other findings in dogs and rats indicate that prostaglandin-induced blood flow changes are secondary to inhibition of gastric acid secretion (Jacobson, 1970; Main & Whittle, 1972). It is therefore possible that AY-22469 exerts its antisecretory activity by a local action; in this regard AY-22469 does not appreciably lower blood pressure when given orally in the rat (Vavra, I., in preparation) and does when given intravenously in the cat (Beaulieu, G, in preparation).

In addition to reducing gastric acid secretion when given orally in the rat, AY-22469 is also a potent inhibitor of ulcer formation (Lippmann & Seethaler, 1973). The low incidence of diarrhoea suggests that an enantiomorph of AY-22469, like AY-22469, is a potentially useful therapeutic agent for the treatment of gastric hypersecretion and peptic ulcers.

The author acknowledges the technical assistance of Mr. J. Lacasse and Miss A. Tom. The synthetic prostaglandin analogues were prepared by Dr. J. F. Bagli of Ayerst Research Laboratories.

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February 20, 1974

REFERENCES

BLISS, C. I. (1952). *The Statistics of Bioassay.* New York: Academic Press.
COREY, E. J., TERASHIMA, S., RAMWELL, P. W., JESSUP, R., WEINSHENKEN, N. M., FLOYD, D. M. & CROSBY, G. A. (1972). *J. org. Chem.*, **37**, 3043–3044.
FINNEY, D. J. (1947). *Probit Analysis*, 2nd edn. London: Cambridge Press.
HORTON, E. W., MAIN, I. H. M., THOMPSON, C. J. & WRIGHT, P. M. (1968). *Gut*, **9**, 655.
JACOBSON, E. D. (1970). *Proc. Soc. exp. Biol. Med.*, **133**, 516–519.
LEVINE, R. (1971). *Ann. N.Y. Acad. Sci.*, **180**, 336–337.
LEVINE, R. A. & WILSON, D. E. (1971). *Ibid.*, **185**, 363–375.
LIPPMANN, W. (1969). *J. Pharm. Pharmac.*, **21**, 335–336.
LIPPMANN, W. (1970). *Ibid.*, **22**, 65–67.
LIPPMANN, W. (1971). *Ann. N.Y. Acad. Sci.*, **180**, 332–335.
LIPPMANN, W. (1973). *Experientia*, **29**, 990–991.
LIPPMANN, W. & SEETHALER, K. (1973). *Ibid.*, **29**, 993–995.
MAIN, I. H. M. & WHITTLE, B. J. R. (1972). *Br. J. Pharmac.*, **44**, 331P–332P.
MISIEWICZ, J. J., WALLER, S. L., KILEY, N. & HORTON, E. W. (1969). *Lancet*, **1**, 648–651.
SHAY, H., SUN, D. C. H. & GRUENSTEIN, M. (1954). *Gastroenterol.*, **26**, 906.
TAFT, R. C. & SESSIONS, J. T. Jr., (1972). *Ibid.*, **62**, 820.
WILSON, D. E. & LEVINE, R. A. (1969). *Ibid.*, **56**, 1268.
WILSON, D. E., PHILLIPS, C. & LEVINE, R. A. (1971). *Ibid.*, **61**, 201–206.

Antispasmodic action of quaternary compounds administered orally

Hyoscine *N*-butylbromide, a spasmolytic quaternary ammonium compound, has been reported to be less effective after oral than parenteral administration (Guignard, Herxheimer & Greenwood, 1968; Herxheimer & Haefeli, 1966). But when it was administered enterally to anaesthetized animals, an appreciable spasmolytic effect was found by Pennefather, McCulloch & Rand (1968) and Pomeroy & Rand (1969). These differences may be related to differences in species, in drug administration routes, and to such factors as anaesthesia and surgical intervention. We have examined the quaternary antispasmodics, hyoscine *N*-butylbromide and *N*-(2,2-diphenyl-1,3-dioxolanyl-4-methyl)piperidinium methylbromide, in unanaesthetized rabbits to determine whether they are effective after oral administration.

Male rabbits (2·5 to 3·5 kg) were laparotomized under sodium pentobarbitone (35 mg kg^{-1}, i.v.) anaesthesia. A rubber microballoon was implanted into the muscle layer of the pyloric antrum (Fig. 1). At least three days after the implantation, and after being fasted for 24 h, rabbits were used without anaesthesia. The internal pressure of the balloon was adjusted to 5 cm H_2O during muscle relaxation.

The antispasmodics used were hyoscine *N*-butylbromide, atropine sulphate, papaverine hydrochloride, *N*-(2,2-diphenyl-1,3-dioxolanyl-4-methyl)piperidinium methylbromide (Anacoline, Toyamakagaku, Toyama, Japan) and *N*-(2,2-diphenyl-1,3-dioxolanyl-4-methyl)piperidine hydrochloride (tertiary analogue of Anacoline). These drugs were administered into the auricular vein or into the stomach by a feeding tube. Normal saline solution was used as vehicle and all doses of the drugs were given in 1 ml kg^{-1} intravenously or 10 ml kg^{-1} orally. Changes in the internal pressure of the balloon were recorded by a low pressure transducer before and after drug