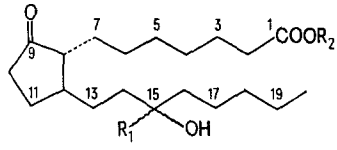
Oral Antigastric Acid Secretory Activity of Synthetic Prostaglandin Analogues (9-Oxoprostanoic Acids)

Prostaglandins appear to play a physiological role in regulation of gastric acid secretion. In the anesthetized rat, prostaglandin E_1 (PGE_1), infused i.v., decreases the spontaneous release of acid in the gastric effluent and also the acid secretion induced by various agents such as pentagastrin and histamine[1]. PGE_1 inhibits gastric acid secretion in the unanesthetized rat when administered s.c. either by injection or by constant infusion[2]. In the dog PGE_1 and PGE_2, infused i.v., reduce histamine- or food-induced gastric acid secretion; PGA_1 decreases the food-induced gastric acid secretion[3]. Perfusion of the rat stomach with PGE_1 results in decreases both in the basal and in the induced gastric acid secretion caused by such agents as pentagastrin and histamine[1]. Various synthetic PGE type analogues inhibit the basal and the pentagastrin-induced gastric acid secretion in the rat when administered s.c.[4–6]. The present studies demonstrate the effects of oral and different modes of s.c. administration of the synthetic PGE analogues (9-oxoprostanoic acids) on the basal gastric acid secretion in the rat.

Materials and methods. The determination of basal gastric acid secretion was carried out as described by LIPPMANN[4]. In the studies in which the analogues were administered perorally before the pyloric ligation, 1 ml of an aqueous suspension of the analogue (containing 2 drops of Tween 80 per 14 ml) was given; these animals were killed 3 h after pyloric ligation. There were 6–10 animals in each group of a determination and the results represent at least 2 determinations. When the analogues were administered perorally after the pyloric ligation, 0.2 ml of the aqueous suspension was given and the animals were killed 4 h later; there were 7–10 animals in each group. The synthetic prostaglandin analogues used [15-hydroxy-9-oxoprostanoic acid (AY-22,093), 15-hydroxy-15-methyl-9-oxoprostanoic acid (AY-22,469) and 15-hydroxy-15-methyl-9-oxoprostanoic methyl ester (AY-22,443)] (Figure 1) were prepared by Drs. J. F. BAGLI and T. BOGRI of Ayerst Laboratories.



	R_1	R_2
AY-22,093	H	H
AY-22,469	CH_3	H
AY-22,443	CH_3	CH_3

Fig. 1. Structures of analogues.

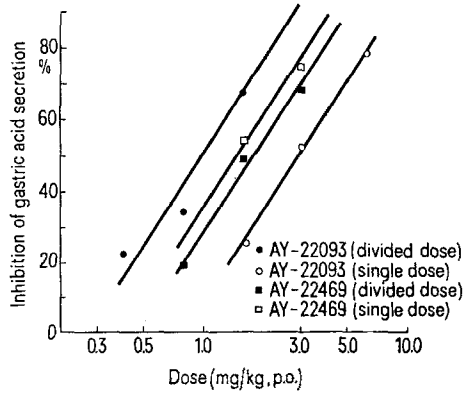


Fig. 2. Effects of modes of s.c. administration of synthetic prostaglandin analogues on basal gastric acid secretion.

Results and discussion. When the compounds were administered s.c., one-half the dose being given immediately after pyloric ligation and the other half 2 h later, with the animals being killed 4 h after the pyloric ligation, AY-22,469 was similar to AY-22,093 (ED_{50}: 1.8 vs 1.0) in causing inhibition of basal gastric acid secretion (Figure 2).

When given s.c. in a single administration, AY-22,469 exhibited activity in a similar range to AY-22,093 (ED_{50}: 1.5 vs 3.0). AY-22,093 was 3 times less active when given by a single rather than a divided administration (ED_{50}: 3 vs 1) whereas AY-22,469 exhibited comparable activities under these two conditions (ED_{50}: 1.5 vs 1.8). It is possible that the difference could be due to a more rapid metabolism of AY-22,093.

AY-22,469 given perorally 1 h before the pyloric ligation caused an inhibition of gastric acid secretion with the ED_{50} value being 44 (Figure 3A). In contrast, AY-22,093 did not exhibit appreciable inhibition. When the analogues were administered perorally immediately after the pyloric ligation, AY-22,469 was again effective, as the ED_{50} under these conditions was 3, while inhibitory activity was not observed after AY-22,093 (Figure 3B). Similar results were obtained with AY-22,469 when the vehicle employed was 0.2% carboxymethyl cellulose. AY-22,443, the methyl ester, also exhibited inhibitory activity under these conditions and was similar in activity to AY-22,469 (ED_{50}: 6.3 vs 5.0) (Figure 3C). It appears that the possible difference in rate of metabolism is of importance in regard to the activities observed (AY-22,469 and AY-22,443 vs AY-22,093).

The results obtained after peroral administrations, as well as those showing AY-22,093 to be less active when given as a single, rather than a divided, s.c. administration, indicate that the nature of the substituents on C-15 is of significance, as the hydrogen atom in AY-22,093 is replaced by a methyl group in AY-22,469. The presence of such a group could lead to a higher activity through interference in the metabolism of this analogue. In this regard it is of interest that, in the lungs of guinea-pig, rat, sheep and human, in the metabolism of PGEs the hydroxyl group is oxidized to form a carbonyl at C-15[7]. Also, the derivative of PGE_1 containing a carbonyl at C-15 exhibits greatly reduced activities (on smooth muscle preparation and blood pressure in rabbit and guinea-pig[8]) in comparison to PGE_1. This derivative is also ineffective in inhibiting platelet aggregation in contrast to PGE_1[9]. In the human the major urinary metabolites of the PGEs appear to have been formed by dehydrogenation of the alcohol group at C-15, reduction

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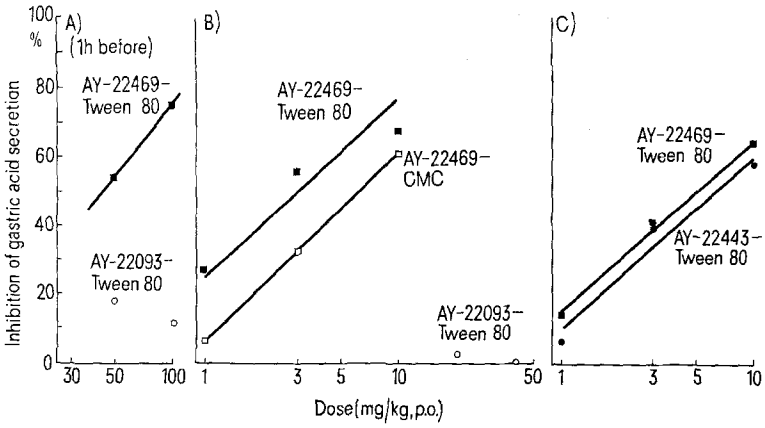

Fig. 3. Effects of peroral administration of synthetic prostaglandin analogues on basal gastric acid secretion.

at the $\Delta 13$ double bond, two steps of β oxidation and ω oxidation[10,11]. As AY-22,469 is a racemate with 4 possible optical isomers, the activities of the isomers are of interest.

The findings of oral activity with the synthetic PGE analogues is also of interest in regard to studies on the oral activity of PGE_1 in the human. PGE_1 increases the propulsive activity of the gut and it was suggested that metabolites of PGE_1 might be of importance with respect to the effects observed[12]. PGE_1 is ineffective in inhibiting gastric acid secretion induced by pentagastrin in doses exhibiting effects on gastrointestinal motility[13]. Use of a higher level of PGE_1 or a different prostaglandin might have resulted in a demonstration of antisecretory activity, the latter in view of the findings[14] that human gastric mucosa contains PGE_2. In this connection PGA_1, infused intravenously, decreases gastric acid secretion induced by histamine[15].

Résumé. L'analogue synthétique de la prostaglandine, AY-22,093, exerce moins d'inhibition sur la sécrétion basale de l'acide gastrique chez le rat lorsque administré en dose unique plutôt qu'en dose divisée, par voie sous-cutanée. Par contre, l'analogue AY-22,469 contenant un groupe méthylé en C-15, montre des effets semblables. AY-22,469 et son ester méthylique AY-22,443 sont efficaces lorsque administrés par voie orale, tandis que le composé AY-22,093 ne l'est pas.

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The Effect of Small Doses of Mecamylamine on Shuttlebox Behavior in the Guinea-Pig[1]

Although mecamylamine has found wide application in recent years as an anti-nicotinic agent in various studies with different species, its influence on animal behavior has not been extensively studied, especially in the lower dose ranges. Preliminary experiments with rats at this laboratory have indicated that mecamylamine in small doses (up to 0.3 mg/kg) facilitates both swimming endurance and shuttlebox performance in that species[2]. On the other hand, an impairment of active avoidance learning in mice has been demonstrated with higher doses of this substance. Whereas Oliverio[3] obtained this effect with doses ranging between 1.2 and 5.0 mg/kg, however, Goldberg et al.[4] reported that doses of mecamylamine in excess of 6.25 mg/kg were necessary to impair active avoidance learning. These and other differences in results between and within species and various tests, in addition to the increasing importance of mecamylamine in nicotine and tobacco smoke studies, prompted this initial investigation into the effects of mecamylamine on guinea-pig behavior. Since the earliest reports concerned with the pharmacological properties of mecamylamine[5], there has been no mention in the literature of its use in any behavioral testing situations with guinea-pigs.

The guinea-pig has, however, found increasing use in shuttlebox-avoidance experiments in recent years, having been so tested in relation to the effects of various brain lesions[6,7], and of different drugs, such as amphetamine[8],

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