it would appear that the differences between the maximum inhibitions observed after these two routes of administration would support the contention that the mechanism(s) of action by these routes may not be identical.

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The effect of combination of aspirin and sodium salicylate on the rat stomach

P.N.C. ELLIOTT

Pharmacology Department, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF

The finding that sodium salicylate could inhibit the ulcerogenic action of other non-steroidal anti-inflammatory drugs (NSAIDs) (Ezer, Palosi, Hajos & Szporny, 1976; Hayden, Thomas & West, 1978) is of considerable interest since it raises the possibility that the use of certain combinations of NSAIDs may be better tolerated in man than any of the drugs used alone. It has also been shown, however, that whilst there is a positive correlation between dose and gastrotoxicity for the NSAIDs, there is an optimal lesion-inducing dose above which the number of gastric lesions declines (Hummett, Jennewein & Waldeck, 1976). Thus it is possible that the inhibition of aspirin-induced lesions caused by sodium salicylate may be due, not so much to an antagonism, but rather to a complementary effect, where the combined dose of the two NSAIDs exceeds the optimal lesion-inducing dose.

Table 1 Effect of aspirin and sodium salicylate on the rat gastric mucosa

Dose of drug given (mg/kg)				
Aspirin	*Sodium salicylate*	*Dose expressed as mg salicylate/kg*	*Number of animals*	*Number of lesion mean ± s.e. mean*
		0	10	0.6 ± 0.2
115		87.5	10	25.2 ± 3.2
	102	87.5	10	12.4 ± 2.6
115	102	175	10	35.6 ± 3.6*
230		175	10	37.7 ± 4.1*
	205	175	10	35.0 ± 3.2*
230	205	350	10	7.2 ± 2.4
460		350	10	11.8 ± 3.6
	409	350	10	7.2 ± 2.1

* The number of lesions produced in each group receiving a total of 175 mg salicylate/kg was significantly greater ($P > 0.05$) than in each other treatment group (Student's *t*-test).

To investigate this possibility, aspirin, sodium salicylate or combinations of the two drugs were given orally in a range of concentrations in 1 ml of water to male Wistar rats previously starved for 24 hours. The animals were killed two hours later, their stomachs removed, cut open and everted for examination.

The results show that whether given as aspirin or sodium salicylate or as a mixture of the two, a dose of 175 mg salicylate/kg produced significantly more lesions than a dose of 87.5 mg salicylate/kg and a dose of 350 mg salicylate/kg produced significantly fewer lesions than a dose of 175 mg salicylate/kg. Thus the ulcerogenic effects of aspirin and sodium salicylate are clearly additive. The sodium salicylate induced inhibition of ulcerogenecity previously reported appears, from these results, to be due only to the use of a high total dose of drugs exceeding the optimal lesion-inducing dose.

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Effects of diltiazem and verapamil on the mechanical performance of the rabbit myocardium perfused with an oxygenated and an hypoxic medium

J.P. BOUDOT &. I. CAVERO

Department of Biology SYNTHELABO (L.E.R.S.), Cardiovascular Group, 58, rue de la Glacière, 75013 Paris, France

Heart muscles from several animal species undergo an increase in resting tension accompanied by a decrease in developed contractile force when perfused with an hypoxic medium (Winbury, 1956; Bing, Brooks & Messer, 1973; Nayler, Yepez & Poole-Wilson, 1978). These effects which are accompanied by marked biochemical and structural modifications of myocardial tissue (Nayler, Grau & Slade, 1976), have been shown to be influenced by several experimental conditions such as, glucose concentration (Winbury, 1956) and pH (Bing, *et al.*, 1973) of the perfusing fluid or addition of various drugs to the perfusate (Nayler, *et al.*, 1978; Durrett & Adams, 1979).

The present communication describes the effects of diltiazem and verapamil, two compounds presently classified as calcium antagonists, on the diastolic and systolic tension of rabbit hearts perfused with an oxygenated and an hypoxic medium. In this preparation verapamil has been reported to exert a protective action against both the mechanical and biochemical deterioration produced by hypoxia (Nayler, *et al.*, 1976).

Rabbits (Fauve de Bourgogne, 2–3 kg body weight) were sacrificed by cervical dislocation and their hearts perfused using the Langerdoff technique at constant flow (20 ml/min) with glucose-free (replaced with mannitol) Krebs–Henseleit buffer (pH 7.4) solution gassed with 95% O_2 + 5% CO_2. Following an initial 30 min stabilisation period, the oxygenated solution was replaced for certain preparations with an hypoxic perfusate (gassed with 95% N_2 + 5% CO_2) for 30 minutes. Thereafter, perfusion was continued for further 30 min with an oxygenated medium. Isometric myocardial force of contraction was measured with a transducer (Grass FT03C) attached via a thread to the ventricular apex. The heart (deprived of both atria) was always paced (6–8 V, 1 ms, 137 beats/min) with the exception of a group of preparations in which the electrical driving was suspended during the period of hypoxia. Experiments were carried out in hearts perfused over 30 min with either oxygenated or hypoxic solutions containing no drug, diltiazem (1.0–10.0 μM) or verapamil (0.03–3.0 μM).

Both resting and peak systolic tension in the paced rabbit heart perfused with oxygenated Krebs–Henseleit solution remained constant over the 90 min control period. In this preparation diltiazem (1.0–10.0 μM) and verapamil (0.03–3.0 μM) produced concentration-related decreases in developed tension and their EC_{50}'s (concentration decreasing tension by 50%) were 3.36 ± 0.25 and 0.12 ± 0.01 μM, respectively. Thus, verapamil was about 28 times more cardiodepressant than diltiazem. The systolic contractile force was decreased by approximately 90% at the end of 30 min perfusion with an hypoxic medium. In contrast, the myocardial resting tension (control value: 2.9 ± 0.3 g, n = 10) increased by 13.8 ± 1.0 g for the same time period. Addition of diltiazem (10.0 μM) or verapamil (3.0 μM) to the hypoxic perfusate acceler-