cats (2.4–2.9 kg) anaesthetized with chloralose (90 mg/kg i.v.) AH 6696 (10–30 mg/kg i.v.) produced transient depressor responses of 40–80 mmHg (1 mmHg ≈ 133 Pa) but did not affect the vasodepressor responses to either acetylcholine or histamine. Clearly, AH 6696 has no anticholinergic, H_2-blocking and little or no H_1-blocking activity.

In conscious dogs with Heidenhain pouches AH 6696 (15–25 mg/kg orally) caused a dose-dependent inhibition (39–100%) of submaximal gastric acid secretion induced by pentagastrin, bethanechol or histamine. This effect was accompanied by an increase in the ratio of gastric mucosal blood flow to gastric acid secretion (Curwain & Holton, 1973) indicating that inhibition of secretion was not due to a primary decrease in blood flow.

Inhibition of metabolic processes in the parietal cell could reduce gastic secretion. AH 6696 (2.5 mM) had no significant effect on the rate of oxygen uptake by rabbit parietal cells (McDougal & De Cosse, 1970). Furthermore, AH 6696 (10 mM) neither inhibited nor uncoupled oxidation from phosphorylation using rat liver mitochondria with succinate or β-hydroxybutyrate as substrate. Rat stomach carbonic anhydrase (Roughton & Booth, 1946; Waygood, 1955) was not inhibited by AH 6696, 2.5 mM, whereas acetazolamide (2.5 mM) completely inhibited the enzyme. However, AH 6696 (6.5 mM) did inhibit HCO_3^--stimulated ATPase from rabbit gastric mucosa (Kaskebar & Durbin, 1965; Blum, Shah, St. Pierre, Helander, Sung, Wiebelhaus & Sachs, 1971). This action could account for the observed anti-secretory activity of AH 6696.

In a sub-acute toxicity test in beagles AH 6696 (15 mg/kg orally twice daily for 8 weeks) caused lesions in the pancreas and fibrotic changes in the liver (D. Poynter, personal communication). Thus, AH 6696 has an interesting mechanism of action for inhibiting gastric acid secretion but is too toxic for use in man.

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A comparison between sulphinpyrazone and other drugs on the thrombocytopenia occurring in the Arthus reaction in the guinea-pig

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As has been shown previously in the rabbit (Butler & White, 1975) the complement-dependent thrombocytopenia of the Arthus reaction (Margaretten, Howes & McKay, 1974) may be useful for the investigation of drugs *in vivo* which are capable of having an effect on the reactivity of platelets. A range of such drugs has now been compared in guinea-pigs.

The animals were immunized with 2 mg alum-precipitated ovalbumin given subcutaneously into each of four sites on the back. Two weeks later a boosting dose of antigen (1 mg) was injected and one week after this the animals were challenged intradermally in the shaved abdomen with different doses of antigen dissolved in 0.1 ml of physiological saline.

During the first 15 min after the injection of 100 μg, 500 μg or 1 mg of ovalbumin to groups of five animals there was a mean dose-related fall in the platelet count to 74% (not significant), 53% ($P < 0.05$) and 33% ($P < 0.02$) of control, respectively. There was no statistically significant change in the platelet count during the next 15 min in either of the two groups receiving the higher dose of antigen. Blood samples were taken by cardiac puncture and anti-coagulated with sodium citrate (3.8%). Platelet-rich plasma (PRP) was separated by centrifugation of the blood at 200 *g*

for 15 min at 4°C. Platelet counts in PRP were determined with the Coulter counter model D using a correction for the haematocrit.

The i.v. administration of aspirin (10 mg/kg), phenylbutazone (10 mg/kg), sulphinpyrazone (50 mg/kg) and indomethacin (1 mg/kg) 1 h before challenge with the antigen (1 mg) resulted in 47% ($P < 0.05$), 56% ($P < 0.05$), 79% ($P < 0.05$) and 86% ($P < 0.02$) inhibition of the thrombocytopenia, respectively.

Dipyridamole (100 mg/kg) given orally was not effective, but oral administration of indomethacin (10 mg/kg) resulted in a 70% ($P < 0.05$) inhibition of the thrombocytopenia.

In view of the known properties of aspirin, phenylbutazone, sulphinpyrazone and indomethacin *in vitro* (Mustard & Packham, 1975; Flower & Vane, 1974) it would appear that the ability of these drugs to inhibit thrombocytopenia in the Arthus reaction is probably a reflection of their inhibitory activity towards the release reaction or prostaglandin synthesis, both of which would be stimulated by the interaction between platelets and antigen/antibody complexes.

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Pharmacokinetics of frusemide related to diuretic response

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Frusemide is a potent short-acting diuretic which inhibits ionic reabsorption from the ascending limb of the loop of Henle. Pharmacokinetic studies suggest that bioavailability of the drug after oral administration is approximately 50% of that after intravenous administration (Calesnich, Christensen & Richter, 1966; Kelly, Cutler, Forrey & Kempel, 1974; Beerman, Dalen, Lindstrom & Rosen, 1975). Despite the relationship between the plasma concentration of frusemide and urine and sodium flow rates (Rupp, 1974), the total diuretic response has been observed to be the same after oral or intravenous administration of equal doses of frusemide to normal subjects (Kelly *et al.*, 1973). This study has attempted to elucidate factors which might account for this observation.

Six healthy males were studied on three separate occasions after administration of frusemide (80 mg intravenously, procedure I), orally unstressed (procedure II) and orally 36 h after frusemide (80 mg orally) followed by a 20 mmol sodium and 160 mmol potassium diet (procedure III). Urine and blood samples were collected at frequent intervals for 5 h together with all urine passed over the subsequent 31 hours. Plasma and urinary frusemide was measured by the methods of Hajdu and Haussler (1964). Urine sodium and potassium were measured by flame photometry.

Following procedure I the plasma concentration of frusemide declined in a biexponential manner. The onset of diuresis was rapid and the half-life of the exponential decline in rate of sodium excretion was similar to that of the late phase of the plasma frusemide concentration curve. Thus there was a plasma concentration-response relationship for this phase. Urine clearance of frusemide was 60% of total clearance. In procedure II the mean peak plasma concentration occurred at 90 min and then declined exponentially. The rise and fall in the rate of sodium excretion paralleled that of plasma frusemide. The plasma concentration-response curve had a parallel shift to the right when the decay phase was compared to the absorption phase. The area under the plasma frusemide concentration-time curve after procedure I was twice that after procedure II. A similar ratio was found when comparing the total recovery of frusemide in the urine. After procedure III the mean peak plasma concentration occurred at 45 minutes. The rate of sodium excretion paralleled plasma concentration of frusemide but the plasma concentration-response curve was significantly shifted to the right in

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