The effect of gold salts in kaolin-induced paw oedema and adjuvant-induced arthritis in the rat

D.H. BROWN, J. BRUIN, A.J. LEWIS, A. McNEILLIE & W.E. SMITH

Scientific Development Group, Organon Laboratories Limited, Newhouse and Department of Pure and Applied Chemistry, Strathclyde University, Glasgow

The detection of anti-rheumatic drugs not considered to be 'aspirin-like' in animal models of inflammation has proved problematical. Gold salts, such as aurothiomalate, have been the subject of numerous studies and it has been reported that this compound does not exhibit significant acute anti-inflammatory activity although it is able to effectively suppress adjuvant induced arthritis in the rat (Walz, Di Martino & Sutton, 1974).

We have, in our attempts to clarify the mechanisms of action of gold salts, re-evaluated the effects of aurothiomalate in the kaolin paw oedema and adjuvant arthritis in the rat and also included aurothioglucose and triethylphosphine gold chloride (SK & F 36914), an orally effective form of gold (Walz, Di Martino, Sutton & Misher, 1972) for comparative purposes. Male Wistar rats (CE/CFHB) were used at 80–100 g ($n = 5$) for the kaolin oedema and at 140–160 g ($n = 8$) for adjuvant arthritis. Kaolin oedema was produced by injecting 0.1 ml 10% w/v kaolin into both hindpaws and adjuvant arthritis was induced by injection of 0.05 ml Mycobacterium butyricum in liquid paraffin (10 mg/ml) into the left hind paw only.

The results are summarised in Table 1. Only triethylphosphine gold chloride effectively suppresses the kaolin oedema. This effect is independent of serum gold levels since both aurothiomalate and aurothioglucose produced much greater gold levels after s.c. administration yet were inactive. None of the drugs produced gastric irritation 5 h after administration although gastric swelling was evident after triethylphosphine gold chloride treatment. The same drugs administered at a dose of 5 mg gold kg^{-1} day^{-1} from the day of adjuvant injection until day 20 did not affect either primary (injected) or secondary (uninjected) hind paw swelling as assessed on day 21. Indomethacin was extremely effective using this dose regimen. Triethylphosphine gold chloride again produced lower gold serum levels. Of the other parameters assessed aurothiomalate reduced the number of nodules that appeared on the tails and triethylphosphine gold chloride significantly reduced the elevated serum copper levels produced in the arthritic animals.

The results suggest that gold salts can exhibit potent anti-inflammatory effects although their reported activity in adjuvant arthritis (Walz *et al.*, 1972; Sofia & Douglas, 1973; Walz, Di Martino & Sutton, 1974) is not readily apparent from our studies. It is also evident that parenteral and oral forms of gold may produce differing responses both in terms of their anti-inflammatory effects and their pharmacokinetics.

Table 1 Effect of various gold salts on kaolin oedema and adjuvant arthritis in the rat

			Kaolin oedema		*Adjuvant arthritis*		
Compound	*Dose* (mg/kg or mg kg^{-1} d^{-1})*	*Route*	*% Inhibition (4 h)*	*serum gold‡ (μg/ml at 5 h)*	*% Inhibition (21 d) Injected paw*	*Uninjected paw*	*serum gold (μg/ml)*
Aurothiomalate	5	s.c.	12	41.1 ± 2.1	+3	+10	7.3 ± 0.7
	5	oral	1	1.1 ± 0.2	NT	NT	NT
Aurothioglucose	5	s.c.	10	28 ± 2.1	0	+20	7.0 ± 0.6
	5	oral	−13	0.3 ± 0.03	NT	NT	NT
Triethylphosphine gold chloride	5	oral	114†	4.0 ± 0.3	2	+15	3.0 ± 0.1
Indomethacin	3	oral	40	NT	73†	100†	NT

* Compounds administered in 5% mulgofen dose expressed as mg gold/kg for kaolin oedema and mg gold kg^{-1} d^{-1} for adjuvant arthritis.

‡ Gold analysis performed using atomic absorption spectrometry (Kamel, Brown, Ottaway & Smith, 1976). Values represent the mean (± s.e. mean) of 4–5 animals.

† Significantly different ($P < 0.05$) from control (Student's t-test).

NT, not tested.

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Cerebral perfusion in the dog

J. SEMPIK & J. WILSON

Fisons Research and Development Laboratories, Bakewell Road, Loughborough, Leics.

Cross circulation experiments have proved useful in studying drugs which produce cardiovascular changes by an action on the CNS. The method of Taylor & Page (1951) involves the perfusion of the cerebral vasculature of one dog by the circulation of another and in the method of Barrett, Ingenito & Procita (1969) the cerebral vasculature of the cat is perfused by oxygenated, mechanically pumped blood. A modification of the method of Barrett *et al.* (1969) for cerebral perfusion in the dog is described here.

Anaesthesia was induced in beagle dogs (10–16 kg) using thiopentone sodium (25 mg/kg i.v.) and maintained with chloralose (100 mg/kg i.v.). Blood pressure was recorded from a femoral artery and the heart rate obtained from the blood pressure pulse. The carotid and vertebral arteries and the external jugular veins were located. The thyroid and internal jugular veins and all branches of the external jugular veins caudal to the point of cannulation were ligated. 200 units/kg heparin was administered intravenously.

A Bentley 'Temptrol' infant-sized blood oxygenator (Q-130) and a 'Sarns' pump (Model 3500), primed with 500 ml of heparinised (100 units/ml) dog blood, were used to perfuse the head of the animal. Blood was pumped to the head via both common carotid arteries and venous drainage was taken from the external jugular veins. The vertebral arteries were then ligated. Perfusion was carried out at a flow rate of approx. 100 ml/min at a mean perfusion pressure of 100 mmHg. Injections were made via a carotid artery into the cerebral circulation and the effects on systemic blood pressure, heart rate and central perfusion pressure were observed.

Although the vertebral venous sinuses were not ligated, leakage into the systemic circulation was found to be low. This corresponded to approximately 5%/min of a centrally injected dose of Evans Blue dye (assayed spectrophotometrically at 600 nm using a 'Cecil' CE 272 spectrophotometer). Thus cardiovascular responses to catecholamines injected into the cerebral circulation could be obtained which were not subject to interference by effects on the systemic circulation. Similarly, intravenous injection of catecholamines produced only reflex changes in cerebral perfusion pressure.

If the responses to drugs with a longer duration of action are to be investigated, the vertebral venous sinuses may be ligated using the method of Taylor & Page (1951). However, this procedure involves extensive surgery and reduces the life of the preparation to 2–3 h compared with 3–5 h if the sinuses are left intact.

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