Table 1 The effect of anti-rheumatic agents on three parameters of tuberculin pleurisy in the guinea-pig

Drug	Dose (mg/kg)	Route	Time* Schedule	% Changes Exudate Volume	% Changes Total Cell Count	% Changes β-glucuronidase Release
Prednisolone	40	Oral	A	−44.9†	−32.4†	−24.5
Myocrisin	2.5 (Au)	i.m.	B	−34.5	−25.4	−5.8
	5 (Au)	i.m.	B	−79.7†	−43.2†	−33.1
	10 (Au)	i.m.	B	−96.8†	−79.0†	−65.0†
Indomethacin	20	Oral	A	+4.7	+7.3	+43.9
Penicillamine	50	i.p.	B	−34.3	+4.7	−36.2†
	12.5	i.p.	C	−31.8	+7.3	−47.4
	25	i.p.	C	−53.3†	−11.3	−63.4†
	50	i.p.	C	−52.1†	−7.6	−67.5†
	100	i.p.	C	+14.6	+5.7	−29.6
Chloroquine	50	Oral	B	−5.5	−20.1	+40.0
	100	Oral	B	−19.9	−19.5	+4.2
Levamisole	5	Oral	B	−10.8	−30.9	−1.0
	15	Oral	B	−1.4	−17.8	−6.5
	45	Oral	B	−16.6	−2.1	−25.2
	50	Oral	B	+43.6	+14.4	+68.9

* Time Schedules: A = 1 h before and 24 h after challenge. B = 48, 24 and 1 h before and 24 h after challenge. C = Dosed 5/7 days per week for 5 weeks starting 6 days before sensitization.
† Significantly different from controls ($P < 0.05$) by Student's '*t*' test.

enzyme release without affecting the population of cells. This effect is best seen in animals which have been dosed over a long period. Chloroquine and levamisole produced inconsistent effects using the dosing regimens tried so far.

References

ALLEN, J.C., & APICELLA, M.A. (1968). Experimental pleural effusion as a manifestation of delayed hypersensitivity to tuberculin PPD. *J. Immunol.*, **101**, 481–487.

LEIBOWITZ, S., KENNEDY, L., & LESSOF, M.H. (1973). The tuberculin reaction in the pleural cavity and its suppression by anti-lymphocyte serum. *Br. J. exp. Path.*, **54**, 152–162.

YAMAMOTO, S., DUNN, C.J., CAPASSO, F., DEPORTER, D.A., & WILLOUGHBY, D.A. (1975). Quantitative studies on cell-mediated immunity in the pleural cavity of guinea-pigs. *J. Path.*, **117**, 65–73.

YAMAMOTO, S., DUNN, C.J., & WILLOUGHBY, D.A. (1976). Studies on delayed hypersensitivity pleural exudates in guinea pigs. I. Demonstration of substances in cell-free exudate which cause inhibition of mononuclear cell migration *in vitro*. *Immunology*, **30**, 505–511.

Modulation of spontaneous and acetylcholine-induced contractions of rat ileum by betamethasone

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Anti-inflammatory steroids inhibit the contraction of smooth muscle produced by various stimulating drugs (Bass & Setliff, 1960). Dexamethasone (10^{-5} g/ml and above) inhibits both the electrically-induced and acetylcholine-induced contractions of the guinea-pig ileum (Cheng & Araki, 1978). In this study the effects of betamethasone disodium phosphate (10^{-10} to 10^{-3} g/ml) on the contractions of the rat ileum are reported.

Male Sprague-Dawley rats (200 g) were killed and 2 cm pieces of ileum were dissected out into Krebs' solution. Contractions were recorded with a Statham isometric transducer and a Grass Polygraph.

Spontaneous contractions occurred when a piece of tissue was suspended in Krebs' solution at 37°C. The tissue was allowed to contract for a 10 min control period. The drug was added, left in contact for 10 min and washed out. After a 10 min recovery

period the next control period was started. The doses were administered in a Latin Square order. The response to a dose of drug was calculated as follows: (Mean amplitude of contraction × frequency in drug contact period) ÷ (Mean amplitude × frequency in control period) × 100%.

The mean response of eleven preparations to 1×10^{-10} g/ml was 100 ± 9 (s.d.)%. 1×10^{-9} g/ml produced a significantly different ($p < 0.05$) response to this of 122 ± 8%. Doses greater than this produced progressively smaller responses, those above 1×10^{-6} g/ml being lower than 100%. The mean response to 5×10^{-3} g/ml was 18 ± 21%.

Cumulative dose response curves to acetylcholine were obtained on tissues maintained at 30°C. Five doses between 5×10^{-8} and 8×10^{-7} g/ml acetylcholine chloride were given at 30 s intervals. Maximal responses to ACh were obtained both at the start and the finish of the experiment.

Responses were expressed as a percentage of a mean of these two. Betamethasone was added to the bath 5 min before the first dose of ACh. Betamethasone in concentrations below 1×10^{-7} g/ml did not affect the response to ACh significantly. Concentrations above 1×10^{-7} g/ml inhibited the response significantly; the dose response curve being shifted downward but not parallely. The response to ACh was completely abolished by 1×10^{-4} g/ml of betamethasone but was recovered after washing.

Cheng & Araki (1978) postulated that anti-inflammatory steroids can inhibit the movement of Ca ions in the muscle of the guinea-pig ileum. Henry, Jackson & Knifton (1973) suggested a similar mechanism in the uterus with betamethasone and cortisol, but also showed that low doses could potentiate the movement of Ca ions. These results suggest that betamethasone may behave in the same way on the rat ileum. However, it would appear that the potentiation of Ca ion movements at low doses is only significant in the spontaneously active and not the ACh-stimulated preparation.

References

BASS, A.D. & SETLIFF, J.A. (1960). The *in vitro* actions of steroids on smooth muscle. *J. Pharmac. exp. Ther.* **130**, 469–473.

CHENG, J.T. & ARAKI, H. (1978). Inhibitory mechanism of dexamethasone on contractions induced by drugs and by transmural stimulations in isolated guinea-pig ileum. *Japan. J. Pharmac.* **28**, 755–762.

HENRY, ANNE M., JACKSON, J. & KNIFTON, A. (1973). Effects of adrenal corticosteroids on the motility of the uterus *in vitro*. *Res. Vet. Sci.* **14**, 263–265.

Chlorimipramine-induced phospholipidosis: biochemical and pharmacokinetic observations

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A large variety of amphiphilic cationic drugs which are in widespread clinical use produce a generalized phospholipidosis when administered for prolonged periods in animals. Chlorimipramine (CI) has been reported to induce an accumulation of myeloid bodies, typical of the lipidosis-like drug-induced alterations, in lung and liver cells of chronically treated rats (Lüllmann-Rauch & Scheid, 1975). We have investigated the possibility that these modifications were sustained by an alteration of phospholipid metabolism. Furthermore, as the tricyclic antidepressant drugs are known to accumulate in certain organs, we wanted to verify whether the effects on lipid metabolism could be related to the tissue levels of CI or its demethylated metabolite (DMCI).

Male Sprague-Dawley rats (200–250 g body wt) were treated orally with CI·HCl (Ciba-Geigy, Milano, Italy) in a daily dose of 150 mg (Group A) and 90 mg/kg body wt (Group B) and killed after one week under diethylether anaesthesia. Total phospholipids (TPL) were measured as described by Ruggieri, Fallani & Tombaccini (1976). Tissue levels of CI and DMCI were measured by g.l.c. using a nitrogen detector (Broadhurst, James, Della Corte & Heeley, 1977). The histological examination revealed that CI treatment induced in lung the presence of huge 'foam cells' filled up by myeloid bodies, in a dose related fashion. As shown in Table 1, TPL content measured in Group A animals was markedly enhanced in the lung, while it was slightly modified in the other organs. CI and DMCI tissue levels were measured in Group B animals. The amount of the demethylated metabolite was always higher than that of the parent drug and the DMCI/CI ratio ranged from 16 in the liver to 40 in the lung. As in control animals the TPL content was lower in lung than in liver or kidney, it is suggested that the ability of rat tissues to store DMCI is independent of their basal TPL content.