Action of Some Drugs on the "One-Footed Position Test" in the Pigeon

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The potencies of various anti-inflammatory drugs are evaluated in the pigeon by means of a simple functional test. Indomethacin is more active than dexamethasone, contrary to the results obtained by other anti-inflammatory tests. The activity of the drugs seems unrelated to the antinociceptive properties. Histamine, but not serotonin, seems to be involved in the production of the local injury.

It is common knowledge that in the series of events occurring in inflammation there are dilatation and increase in blood vessel permeability, leucocytic emigration, fluid accumulation, cellular proliferation, etc., with functional changes of the injured tissues. A simultaneous evaluation of all the above mentioned modifications is not possible by using the routine methods of testing for anti-inflammatory activity.

Various techniques have been devised to study the effects of drugs upon (*a*) increased vascular permeability: hind-paw edema (1), thermal injury to the skin (2), leakage of dyes into the skin (3), vascular changes from intradermal injection of antibodies (4), and ultraviolet erythema (5); (*b*) leucocytic emigration: true chemotaxis (6), adhesion of leucocytes to vessels (7), and mast-cell disruption and changes in fibroblast (8); (*c*) tissue proliferation: granuloma pouch (9) and cotton-pellet granuloma (10). None of these methods estimates the functional impairment resulting from tissue damage. On the other hand, the function impairment is particularly important considering that anti-inflammatory agents are employed chiefly in diseases such as rheumatoid arthritis.

For this purpose the experimental arthritis in the pigeon, as described by Floersheim *et al.* (11), seems particularly suitable. According to these authors the intra-articular injection of talc produces an acute synovitis with local hyperthermia, cellular infiltration, changes in permeability, and fluid accumulation. As a consequence of these conditions, the pigeon lifts the injured leg. The beginning of these phenomena can be delayed by pretreatment with anti-inflammatory drugs.

METHOD

Two hundred and five pigeons (Columba livia), weighing 0.320 ± 0.03 Kg., were employed; 0.1 ml. of a 4% talc suspension in 25% gum arabic suspension was injected into the right intratarsal joint. The mode of standing was observed every 5 min. during 3 hr. after talc injection. In the control animal (n = 20), the duration of the two-footed position was 75.25 ± 2.75 min.; the one-footed standing lasted continuously during the remainder of the period of observation. Drug activity was evaluated as ability to delay the beginning of the one-leg standing. The drugs were injected subcutaneously 30 min. before talc injection.

The following drugs were employed.

Anti-Inflammatory Agents.—1-Phenyl-2,3-dimethyl - 5 - pyrazolone - 4 - methylaminomethanesulfonate sodium (dipyrone); sodium salicylate; 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone); 11β,17α,21-trihydroxy-4-pregnene-3,20-dione (hydrocortisone); 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione (prednisone); 9α-fluoro-11β,17α,21 - trihydroxy - 16α - methyl - 1,4 - pregnadiene-3,20-dione (dexamethasone); and 1-(*p*-chlorobenzoyl) - 5 - methoxy - 2 - methyl - indole - 3 - acetic acid (indomethacin).

Antihistaminic or Antiserotonin Agents.—2-[*p*-Chloro-α-(2-dimethyl-aminoethyl)benzyl]pyridine (chlorpheniramine); 2-[(2-dimethyl-aminoethyl) (*p*-methoxybenzyl)amino]pyridine (pyrilamine); 1-methyl - 4 - (5 - dibenzo[*a*,*e*]cycloheptatrienylidene) piperidine (cyproheptadine); and *N*,*N*-diethyl-D-lysergamide (LSD-25).

Analgesic Drug.—Morphine sulfate.

Muscle-Relaxant Drug.—2-Methyl-2-propyl-1,3-propanediol dicarbamate (meprobamate).

RESULTS

Figure 1 reports the dose-response curves of anti-inflammatory drugs. The estimated relative potencies, with 95% confidence limits, are the following: dipyrone, 0.22 (0.17–0.27); Na salicylate, 0.44 (0.35–0.54); phenylbutazone, 1.0; hydrocortisone, 3.22 (2.77–3.86); prednisone, 21.2 (17.8–25.2); dexamethasone, 86.5 (81.3–97.0); indomethacin, 206.4 (172.4–524.8).

Figure 2 reports the dose-response curves of the antihistaminic and antiserotonin drugs. The evaluation of the relative potencies could not be determined owing to the very different slopes of the curves. Morphine, at dose levels of 0.5, 1.0, 2.0 mg./Kg. s.c., was ineffective, while meprobamate (100–200 mg./Kg. s.c.) was active, as it is reported in Fig. 2.

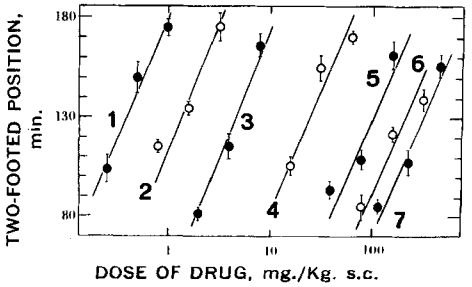

Fig. 1.—Log dose/response curves for anti-inflammatory drugs: indomethacin (*1*), dexamethasone (*2*), prednisone (*3*), hydrocortisone (*4*), phenylbutazone (*5*), Na salicylate (*6*), and dipyrone (*7*). The doses of drugs are plotted on the abscissae: note logarithmic scale. The ordinate shows the duration of two-footed position. Each point represents the mean ± standard error.

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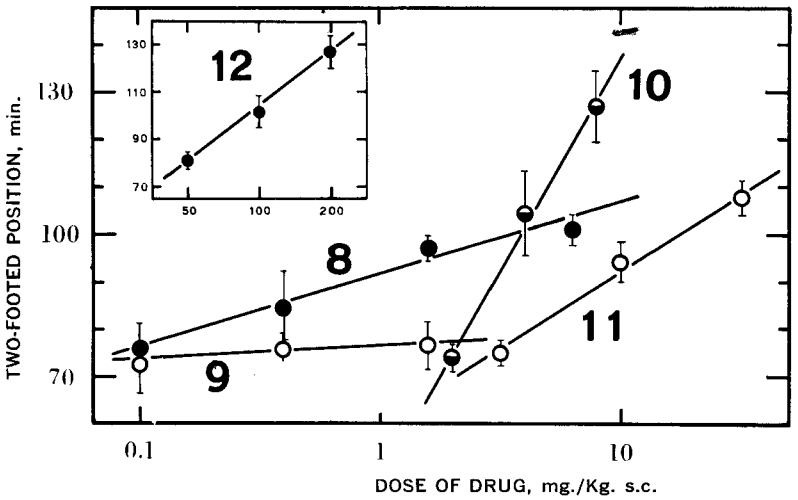

Fig. 2.—Log dose/response curves for antihistaminic or antiserotonin agents: cyproheptadine (*8*), LSD-25 (*9*), chlorpheniramine (*10*), and pyrilamine (*11*). Insert shows the log dose/response curve for meprobamate (*12*). The dose of drugs are plotted on the abscissae: note logarithmic scale. The ordinate shows the duration of two-footed position. Each point represents the mean ± standard error.

DISCUSSION

In the present test indomethacin is more active than dexamethasone, while in the carrageenin edema test and in the cotton-pellet granuloma test dexamethasone was more active than indomethacin (12, 13). Therefore, the activity of anti-inflammatory drugs observed by using the pigeon test seems to be different from that evaluated either by the granulation test or by nonproliferative methods previously employed. The activity of meprobamate and zoxazolamine (11) and the inactivity of morphine leads to the supposition that in the pigeon test there exists a nervous component, but at the spinal level. Therefore, the high activity of indomethacin is not dependent upon its antinociceptive property.

In the pigeon test the local injury seems to be unrelated to a release of serotonin as shown by the inactivity of LSD-25. On the contrary, in agreement with Floersheim *et al.* (11), the activity of chlorpheniramine and pyrilamine indicates that histamine may play a role. The activity of cyproheptadine, which is an inhibitor of histamine and 5HT (14), is probably due to the antihistaminic component.

SUMMARY

Anti-inflammatory drug activity was evaluated as ability to delay the beginning of the one-leg standing after intratarsal injection of talc suspension. The potencies were in the sequence: indomethacin > dexamethasone > prednisone > hydrocortisone > phenylbutazone > Na salicylate > dipyrone. The greater activity of indomethacin in comparison with dexamethasone indicates that the evaluation of anti-inflammatory drugs by the pigeon test seems to be different from that observed by proliferative or by other nonproliferative methods. In the pigeon test, the local injury seems to be unrelated to a release of serotonin; on the other hand, histamine may play a role.

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