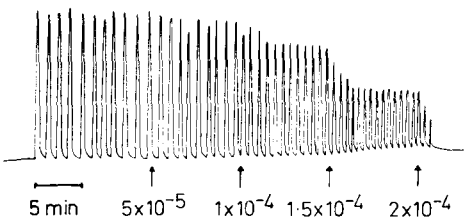

FIG. 1. The effect of ketamine g ml^{-1} on the contractions of the pregnant rat uterus. Note that the rate of contractions increases with the lower concentrations of this agent.

desipramine and diazepam all decreased the force without affecting the rate of contraction. However, the potent anti-inflammatory agents indomethacin, phenylbutazone, acetylsalicylic acid and flufenamic acid reduced both rate and force of contraction of the isolated uterus preparation. Contractions of the uterus were completely inhibited by higher doses of all of the above compounds.

Our studies suggest that although the isolated pregnant rat uterus is a simple technique for detecting compounds that inhibit prostaglandin synthetase activity, the results must be interpreted with caution due to the lack of specificity of the preparation. The use of the preparation as a quantitative technique is also limited as some inhibitors of prostaglandin synthetase such as indomethacin have, in addition, inhibitory effects on smooth muscle by mechanisms independent of any effect involving prostaglandin synthesis (Northover, 1971; Flores & Sharp, 1972).

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Anti-inflammatory action of azapropazone

D. A. LEWIS*, R. BEST, J. BIRD, *Pharmacological Laboratories, Department of Pharmacy, University of Aston in Birmingham, Birmingham B4 7ET, U.K.*

Azapropazone (Rheumox, A. H. Robins Ltd.) is recommended in the treatment of rheumatoid disease at a dose of 1200 mg day^{-1}. In previous publications (Lewis, Capstick & Ancill, 1971; 1972), we have shown that the drug possesses some biochemical properties in common with some other non-steroidal antirheumatic agents which, theoretically at least, could form a basis for their anti-inflammatory action.

The anti-inflammatory action of azapropazone has been demonstrated on acute inflammatory animal models, such as bradykinin-induced inflammation, ultraviolet erythema and the rat paw oedema tests (Jahn & Wagner-Jauregg, 1974).

We now report on the action of azapropazone on the development of granulation tissue in cotton wool pellets implanted in the rat and on the polyarthritis in the adjuvant arthritic rat. We have also re-examined the action of azapropazone on membranes.

* Correspondence.

Our previous model involving rat liver lysosomes is subject to the disadvantages pointed out by Ignarro (1971) in that different experimental conditions can lead to different results. In this work we have examined the action of azapropazone on polymorphonuclear leucocytes (polymorphs) since these cells are considered to make a sizeable contribution to the release of lysosomal degradative enzymes in the joints of patients with rheumatoid disease (Smith & Hamerman, 1962). Adjuvant arthritis was induced in Wistar strain male rats (0·2 kg) as previously described (Lowe, 1964). Treated rats were dosed daily by intraperitoneal injection with either 20 or 40 mg kg^{-1} of azapropazone dispersed in saline by compound tragacanth powder B.P. The azapropazone was omitted from the controls. Primary and secondary inflammation was assessed by measuring foot volume by means of a mercury bath connected with a pressure transducer linked to a Devices recorder. The volumes of both hind feet were measured.

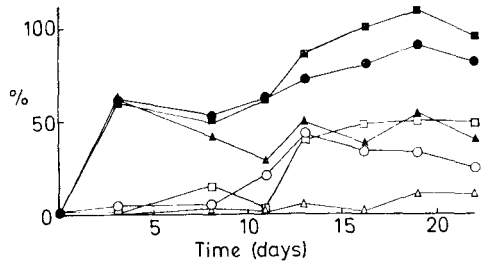

FIG. 1. The effect of azapropazone on the adjuvant arthritic rat. ■ injected foot, □ non-injected foot (no drug treatment) ● injected foot, ○ non-injected foot (20 mg azapropazone daily) ▲ injected foot, △ non-injected foot. (40 mg azapropazone daily). y axis—% increase in foot volume.

The cotton wool granulation test was a modification of the method of D'Arcy, Howard & others (1960). Weighed and matched pellets were implanted subcutaneously in the axillary and pubic region of male Wistar rats (0·3–0·4 kg) and some rats were dosed daily with azapropazone as described. Azapropazone was omitted from the controls. After six days the rats were killed and the pellets dissected out and dried. The protein present in each pellet was determined by the buiret method (Gornall, Bardawill & David, 1949).

In the polymorph experiments guinea-pigs were injected intraperitoneally with 100 ml of saline and 12 h later the dose was repeated. The peritoneal cavity was then drained and the polymorphs isolated from the exudate by centrifugation. The polymorphs were washed in cold saline (4°) and finally suspended at a protein concentration of 7 mg ml^{-1} in phosphate buffered saline (pH 7·4). Portions (0·1 ml) of azapropazone dissolved in dimethylsulphoxide were added to 2 ml portions of the polymorph suspension. Azapropazone was omitted from the controls. After incubation for 90 min at 37° in a shaking reactor incubator the suspensions were centrifuged and portions of the supernatants assayed for acid phosphatase (Symons, Lewis, & Ancill, 1969).

The effect of azapropazone on the adjuvant arthritic rat is shown in Fig. 1. Clearly azapropazone was anti-inflammatory against this model at both dose levels. In the cotton wool granulation test with 20 experiments in each group the mean values of protein in each pellet was 8·97 mg (controls), 7·62 mg (rats dosed with 20 mg azapropazone daily) and 6·84 mg (rat dosed with 40 mg azapropazone daily). The significance range between the control and experimental groups was $P<0·1$ at the 20 mg dose and $P<0·0025$ at the 40 mg dose. Collectively the two experimental models demonstrate that azapropazone is an effective anti-inflammatory agent against these two chronic inflammatory conditions.

The drug also stabilized polymorphs. At 10^{-3}M azapropazone inhibited the release of acid phosphatase by 61%. The effect declined with decreasing drug concentration but was still 30% at a drug concentration of 10^{-6}M. This result is consistent with its action on rat liver lysosomes (Lewis & others, 1971).

It is generally agreed that existing methods for screening compounds for anti-inflammatory activity have limitations but within the limits of our present knowledge, azapropazone exhibits pharmacological and biochemical properties similar to several other non-steroidal anti-rheumatic drugs.

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