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Use of the adjuvant-induced arthritic rat model to evaluate non-steroidal anti-inflammatory analgesics

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Although chronic pain is often more difficult to control clinically than acute pain, most analgesic testing in animals employ models of acute pain. Such tests typically use thermal, mechanical or chemical stimuli to elicit an acute motor reaction such as tail-flick, paw-lick, biting, etc. (Romer 1980). Moreover, most of these tests are better evaluators of narcotic analgesics, e.g. morphine, than they are of non-steroidal anti-inflammatory analgesics (NSAIDs), such as aspirin.

Thus, the need exists for an analgesiometric procedure which would evaluate NSAIDs in a chronic pain model. Costa et al (1981) recently reported on a model of chronic pain in the rat. They noted that adjuvant-induced arthritic rats exhibited a scratching behaviour that persisted beyond the apparent inflammatory stage. Since the scratching was antagonized by subsequent morphine administration they suggested it was an indicator of chronic pain.

The research detailed in this report was designed to determine if scratching in 'arthritic' rats may be used to evaluate the analgesic activity of NSAIDs.

Male Wistar rats (175–225 g) were inoculated intradermally at the base of the tail with 0·05 ml of a mineral oil suspension of heat-killed *Mycobacterium butyricum* (4·0 mg ml^{-1}). The rats were housed 5 per cage and received food and water as desired. The animals were visually monitored for scratching behaviour 30 days post-inoculation as described by Costa et al (1981).

Each animal was placed in a clear plastic bin (29 cm × 17·5 cm × 12 cm) and for the subsequent 10 min period the number of distinct times at which each rat initiated scratching behaviour was recorded; animals were observed in groups of 3. Following this control test period, the animals were administered either drug or vehicle. Thirty minutes after drug or vehicle administration, the animals were again subjected to the identical 10 min behavioural observation described above. Thus the animals served as their own controls and the change in number of scratches initiated was determined. Studies were conducted with 100, 250 and 400 mg kg^{-1} doses of aspirin, flurbiprofen, indomethacin and zomepirac. All of these drugs were prepared as 10 mg ml^{-1} suspended in 0.25% methylcellulose, and were administered orally. In addition, morphine was dissolved in 0·9% NaCl vehicle and administered 10 mg kg^{-1} subcutaneously. Data were analysed for significance using the Student's t-test at $P < 0{\cdot}05$.

The scratching behaviour reported by Costa et al (1981) in adjuvant-induced arthritic rats was readily observed. However, none of the NSAIDs tested produced a dose-dependent reduction in scratching behaviour. The greatest reduction in scratching produced by a NSAID occurred with zomepirac, yet it only reduced scratching 28% less than vehicle. The only drug tested which significantly reduced scratching was morphine. None of the 6 rats given morphine scratched during the post-drug observation period.

These results do not necessarily conflict with Pircio et al (1975) who reported that adjuvant-induced arthritic rats can be used to evaluate analgesics. They used the vocalization produced by grouping rats 16 to 18 days post-inoculation as their nociceptive end point. The only NSAID tested in that study was aspirin which was administered subcutaneously.

There are several possibilities why NSAIDs do not significantly reduce scratching behaviour. (1) Doses other than those employed may be required for a antinociceptive effect. (2) The pain produced may be such that an opioid is required for an antinociceptive effect. (3) There may not be a significant inflammatory component in the pain occurring 30 days after inoculation such that anti-inflammatory analgesics do not have a marked effect. (4) The scratching behaviour elicited is not a nociceptive response.

Whatever the case, these results indicate that, with the methodology employed herein, the scratching observed in adjuvant-induced arthritic rats is not a good evaluator of the analgesic activity of NSAIDs.

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