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INDOMETHACIN: A NEW NON-STEROID ANTI-INFLAMMATORY AGENT

(By F. Dudley Hart, M.D., F.R.C.P., and P. L. Boardman, M.B., M.R.C.P.)

The measurement of joint-swelling in the human subject is not easy, but in the assessment of drugs purporting to have an anti-inflammatory effect in conditions characterized by the presence of chronic inflammatory swelling, such as rheumatoid arthritis, some clinical measure is essential. We have found that the only practical and reliable measurement which can be done repeatedly and reasonably quickly in the wards is finger-swelling measured by jewellers' rings (Hart and Clark, 1951). All patients with active rheumatoid arthritis entering our wards have finger-swelling measured in this way twice weekly by the same clinician at approximately the same time of day as a routine measure. Also, the patient's own assessment of pain, stiffness, the number of analgesic tablets taken daily, the time taken to limber-up in the morning, and the clinician's assessment of grip strength, joint tenderness, and sedimentation rate are done routinely on all patients as measures of progress irrespective of the treatment given throughout their stay in hospital.

Measurable reduction of joint-swelling occurs regularly and demonstrably with steroid therapy, but not with salicylates, phenacetin, paracetamol, or the pyrazoles (phenylbutazone or oxyphenbutazone) as measured by this method; and since the early use of the corticosteroids and corticotrophin no other therapeutic substances of the many we have tried have produced a measurable reduction in swelling of the interphalangeal joints. It was therefore a pleasant surprise when we found that in indomethacin (MK 615) we had the first non-corticosteroid agent which produced a predictable and measurable reduction in joint-swelling in most cases of active rheumatoid arthritis.

CHEMISTRY

Indomethacin is a non-steroid anti-inflammatory and antipyretic agent. Its activity does not depend upon pituitary-adrenal stimulation and it is fully active in adrenalectomized animals. Chemically it is 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid, having the empirical formula of $C_{19}H_{16}NO_4Cl$ and a molecular weight of 357.8. It is relatively insoluble in water but soluble in the common organic solvents. It is rapidly cleared from the plasma, having a half-life of 0.3–4 hours in various species. From 46 to 63% of an intravenous dose of indomethacin-2-C^{14} is rapidly exreted in bile of dogs, guinea-pigs, and monkeys (Hucker, Zacchei, and Cox, 1963). Its anti-inflammatory activity can be demonstrated in rats by the cotton-pellet granuloma-inhibition test and by inhibiting oedema on subplantar injection of irritant agents. Granuloma inhibition can be observed by oral administration or by local application to the cotton pellet in the same animal. After oral administration to rats the drug appears to be well absorbed and gives an estimated plasma half-life of about 21 hours; about 90% of the drug in plasma is bound to the non-diffusable constituents. Excretion in rats is largely through the kidney, little being found in the faeces. That rat and the dog apparently tolerate the drug less well than does man or monkey.

Antipyretic activity has been demonstrated by inhibiting the fever produced by injection of *Escherichia coli* endotoxin in both rats and rabbits. Analgesic effects could not be demonstrated in mouse or rat by current methods. Toxic effects in rat, dog, and monkey consist largely of gastrointestinal irritation, monkeys tolerating larger doses of the drug than rat or dog. Judged by the work on animals, gastro-intestinal toxicity seemed to be the only effect likely to occur in man, but early clinical trials in the United States of America indicated that it was usually well tolerated by the human digestive tract (R. Hodgkinson, personal communication, 1963).

MATERIAL AND METHOD

Indomethacin has been used in the treatment of a group of patients in whom a clinical response might be anticipated from administration of a compound with anti-inflammatory, antipyretic, and possible analgesic properties (see Table I).