[Chem. Pharm. Bull. 19(7)1506—1508(1971)]

UDC 615.276.076.9

A Simple Method for Evaluating Analgesic Efficacy of Non-Steroidal Anti-Inflammatory Drugs

Acute arthritis resembling gout can be induced in dogs by injection of micro-crystalline sodium urate suspension in the knee joint of hind legs.[1] It was reported by some workers that the gross manifestations of this experimental arthritis were suppressed by intra-articular injection of insoluble glucocorticoids together with the urate suspension,[2] or by oral, pre-administration of phenylbutazone and indomethacin.[3] As for evaluating efficacy of these compounds, the previous authors have adopted a scoring system in respect to general behavior, such as restlessness, whimpering, limping and 3-legged gait, of which limping walk, due to rapid onset of pain, is the most striking.

In the present communication, the degree and change of the urate-induced pain are quantitatively measured by weighing the body weight of dogs which is supported with the urate-injected hind leg, and analgesic effect of non-steroidal anti-inflammatory drugs are tested.

A micro-crystalline urate suspension (10 mg in 0.2 ml of saline) was prepared according to the method of McCarty, Jr., *et al.*,[2] and injected exactly in the knee joint of a hind leg of well-trained Beagle dogs weighing about 12 kg, under a X-ray fluoroscope. They were placed

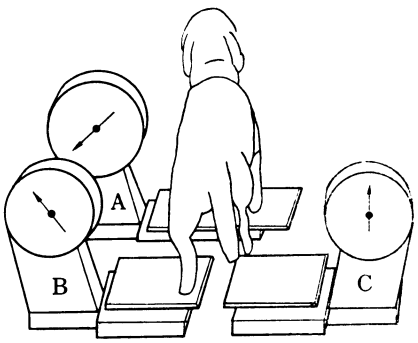

Fig. 1. Diagram of Apparatus used to Record Weight Changes in the Fore and Hind Legs of a Dog after Intra-Articular Injection of Urate Suspension.

A: 10 kg-gauge B and C: 5 kg-gauge

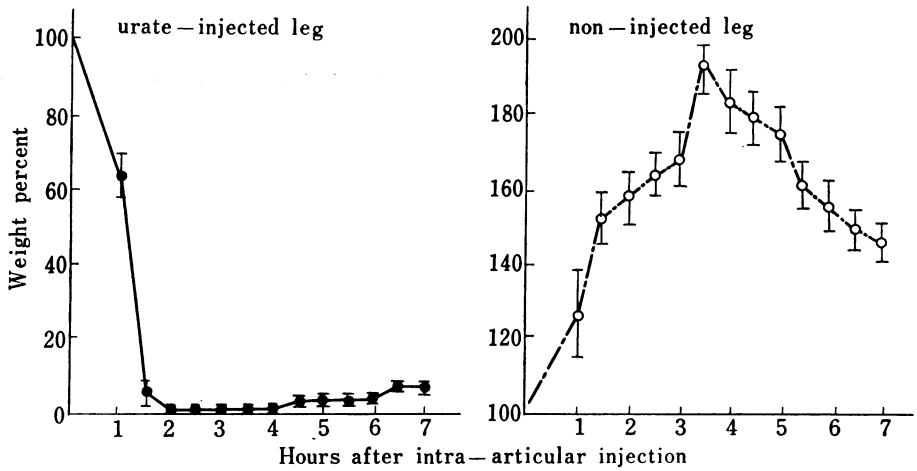

Fig. 2. Relative Change of Wieght in Each Hind Leg after Intra-Articular Injection of Urate Suspension

Each point represents the mean of twenty-five determinations (± standard error).

1) J. Faires and D. McCarty Jr., *Lancet*, **2**, 682 (1962).
2) D. McCarty, Jr. and J. Faires, *Curr. Ther. Res.*, **5**, 284 (1963).
3) M. Rosenthale, J. Kassarich, and F. Schneider, Jr., *Proc. Soc. Exp. Biol. Med.*, **122**, 693 (1966).

on three weighing-machines as shown in Fig. 1, and the weight on each balance was recorded. Soon after the urate-injection, the weight being supported with the affected leg began to decrease, while the weights with the other legs increased concomitantly. This relation is shown in Fig. 2. The maximum response was observed invariably within 2 hr after the injection of urate suspension.

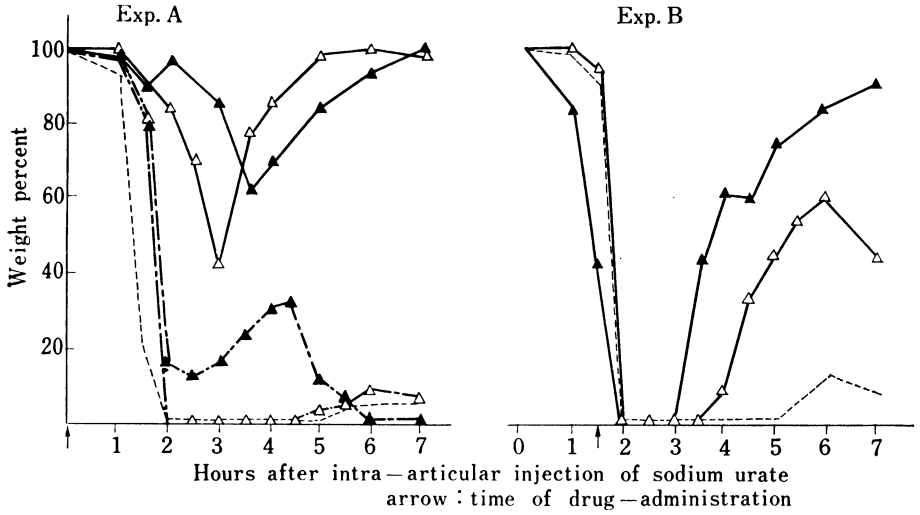

Fig. 3. The Effect of Acetylsalicylic Acid and Aminopyrine on Holding of the Leg Intra-articularly Injected Microcrystalline Sodium Urate

Experiment A: simultaneous administration of acetylsalicylic acid (△) and aminopyrine (▲) in the oral dose of 50 (————) or 25 (—·—·—) mg/kg, Experiment B: post-administration of each drug in the oral dose of 50 mg/kg. Each group including control (----------) consists of four dogs.

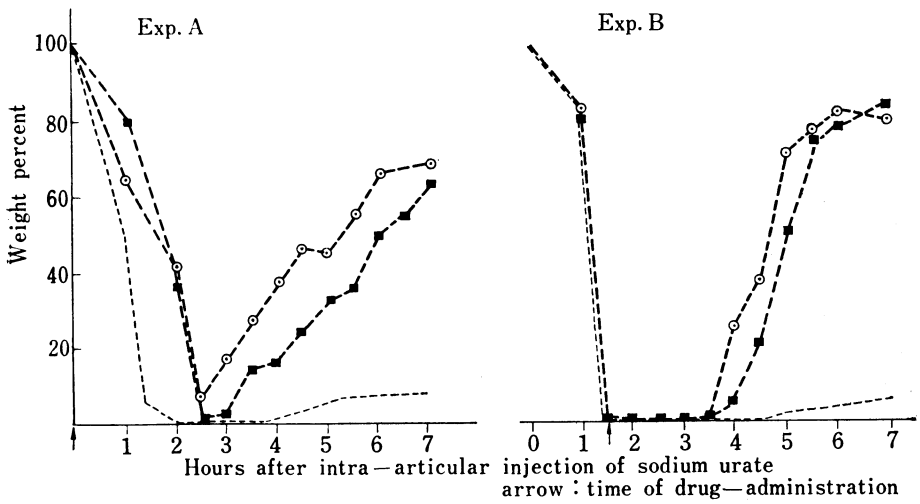

Fig. 4. The Effect of Phenylbutazone (○) and Aluminium Flufenamate (■) on Holding of the Leg Intra-Articularly Injected Microcrystalline Sodium Urate

Each drug was orally given to dogs simultaneously with the injection of urate suspension (Experiment A), or at the time of the maximum response to irritant (Experiment B), in the dose of 12.5 mg/kg. Each group including control (----------) consists of four dogs.

The test-drugs in capsule were orally given to dogs simultaneously with the urate-injection, or at the time of the maximum response. The results are summarized in Fig. 3 and 4. A dosage of 50 mg/kg of acetylsalicylic acid inhibited greatly the onset of pain when simultaneously given, while an initial promotion of pain-relief followed by rapid loss of the effect was observed when administered at the time of the maximum response. Aminopyrine in a dose of 25 mg/kg demonstrated an inhibition, similarly to acetylsalicylic acid, against the established pain. Phenylbutazone and aluminium salt of flufenamic acid,[4] together in a dose of 12.5 mg/kg, prevented and reversed effectively the urate-induced pain. The dosage levels of all the drugs tested here are in the range of clinical use.

The previous authors[3] described that acetylsalicylic acid, even in an oral dose of 150 mg/kg, was ineffective in this gouty arthritis when the overall inflammatory symptoms were apparently evaluated by the scoring method. The present study showed that the compound was sufficiently effective in such small doses as clinically used, probably because of limiting the point of evaluation to the analgesic efficacy. The method used here is simple, sensitive and reproducible for the objective evaluation of analgesic efficacy of non-steroidal anti-inflammatory drugs in dog urate synovitis.

Research Laboratory,
Taisho Pharmaceutical Co., Ltd.,
Takata-3-chome, Toshimaku,
Tokyo

Eiichi Fujihira
Tomizo Mori
Masao Nakazawa

Pharmaceutical Institute,
Tohoku University

Hikaru Ozawa

Received December 21, 1970

4) T. Seki and Y. Watanabe, U.S. Pat., 3409 655 (1968).

[Chem. Pharm. Bull. 19(7)1508—1509(1971)]

UDC 547.551.42.04

C-C Bond Fission in Carboxamide. Intermediacy of Phenylcarbamate Ion in the Alkaline Hydrolysis of Trichloroacetanilide

In the alkaline hydrolysis of anilides no one has considered the possibility of C-C bond fission; this is probably because C-N bond fission is widely accepted, and one of the final products in both C-N and C-C bond fission is an aniline. Eriksson and Holst, therefore, did not describe about C-C bond fission at all in their paper reporting the alkaline hydrolysis of trichloroacetanilide, though they noticed a distinct odour of phenylisocyanide.[1] Previously we reported a novel reaction pathway for alkaline hydrolysis of α-nitroisobutyramide, that is, C-C bond fission besides the usual C-N bond fission,[2] but it was considered rather special case for the compound. If hydrolysis of trichloroacetanilide involves C-C bond fission just as that of α-nitroisobutyramide, phenylcarbamate ion and chloroform will be produced in the first step, and then the former will decompose to aniline, as shown in the schemes. As chloroform reacts with aniline in alkaline solution to give phenylisocyanide and chloride ion, the formation of these compounds may be explained on the basis of the following schemes.

1) S.O. Eriksson and C. Holst, *Acta Chem. Scand.*, **20**, 1892 (1966).
2) M. Masui, H. Sayo, H. Ohmori and T. Minami, *Chem. Commun.*, **1969**, 404.