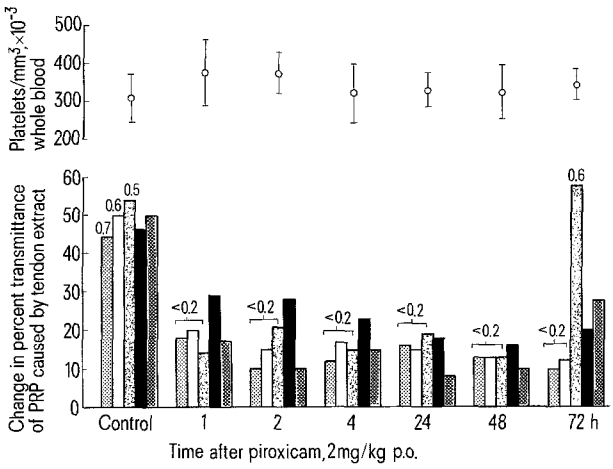

Effect of piroxicam, 2 mg/kg, on collagen (TE)-induced platelet aggregation and platelet count at intervals after oral administration to 5 dogs. Each bar shows the response of platelets from an individual dog. Platelet release of ADP ($\mu M/10^{11}$ platelets) is shown above the platelet response to TE (3 dogs). O represents the mean ±S.D.

Also, inhibition of collagen-induced platelet aggregation following treatment of dogs with piroxicam was comparable to that observed after treatment of animals with higher doses (25–200 mg/kg) of aspirin[11-14]. In a recent study piroxicam was also more potent than aspirin in inhibiting second-phase aggregation of human platelets caused by ADP[15]. Piroxicam is therefore similar in its platelet effects to sudoxicam, a structurally-related NSAI agent[16] which, in addition, inhibits experimental thrombosis in dogs[3] and prolongs platelet survival in baboons[17]. Of the NSAI agents used in humans, aspirin and sulfinpyrazone are equipotent inhibitors of platelet release[1], but sulfinpyrazone[18], unlike aspirin[19], prolongs platelet survival. In a recent study sulfinpyrazone reduced mortality in myocardial infarction patients[20], whereas results of a similar study with aspirin were inconclusive[21]. Platelets have a major role in thrombogenesis and agents which interfere with platelet function may be useful in the treatment of thromboembolic disease[22].

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Percutaneous penetration of indomethacin

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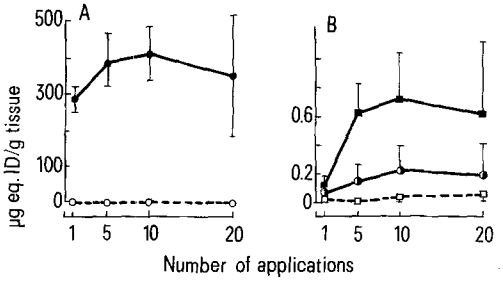
Summary. ^{14}C-Indomethacin (ID) was applied to the skin of guinea-pigs as an ointment. After several applications, the concentration of ID in the skin and muscle under the applied site reached a constant level. The concentration of ID in the muscle as well as the skin may be enough to exert an anti-inflammatory effect.

Indomethacin (ID), a potent nonsteroidal anti-inflammatory agent, is widely used for the treatment of various inflammatory diseases. We are developing a jelly-type ointment of ID for the topical treatment of inflammatory diseases in the soft tissues. The purpose of this study is to investigate the percutaneous penetration of ID into the skin and muscles of guinea-pigs.

Materials and methods. A jelly ointment containing 1% of (2-^{14}C)ID (Sumitomo Chemical Co., Osaka) was prepared by dissolving the labelled compound in a gel base containing water, ethanol, propylene glycol and carboxyvinyl polymer. For each experiment, 5 male Hartley guinea-pigs weighing 285–370 g were used. A 30-mg of the ointment was applied uniformly to an area of 1.25×2 cm (2.5 cm^2) on the dorsal skin of guinea-pigs, once or every 12 h. The unabsorbed ointment was wiped off with a piece of wetted cotton before the following application. The animals were killed 12 h after the final application, and their skins at the applied and nonapplied site were removed. The muscles under the same site were also removed and divided into 2 parts, a shallow (2–4 mm in depth from the skin surface) and a deep (4–6 mm in depth) part. Each sample was lyophilized and then combused by a Sample Oxidizer (Packard, Tri-Carb 305). Its radioactivity was measured by a liquid scintillation spectrometer (Packard, Tri-Carb 3255).

Results. The radioactivities expressed as μg equivalent of ID/g tissue (μg ID/g) in the skin and muscle are shown in



Concentration of (^{14}C)indomethacin (ID) in the skin (A) and muscle (B) of guinea-pigs by the topical application. ●—●, Skin at the applied site; ○----○, non applied skin; ■—■, shallow muscle under the applied site (ca. 3 mm in depth); ◑—◑, deep muscle (ca. 5 mm in depth); □----□, muscle under the non applied skin (ca. 3 mm in depth). Each symbol represents the mean value of 5 experiments. The vertical bars show SD.

the figure. The concentration of ID in the skin of the applied site increased with the repeated applications and reached a constant level of about 400 μg ID/g after 5 applications (figure 1A). The concentration of ID in the shallow part of the muscle under the applied site reached a constant level of about 0.7 μg ID/g after 5 applications, and that in the deep part of the muscle reached a level of 0.04–0.5 μg ID/g (about 0.2 μg ID/g in average) after 10 applications (figure 1B). The concentration of ID in the skin and muscle of nonapplied portion was negligible.

Discussion. It was reported that some drugs diffused into the muscle through the skin[1,2]. However, the p.c. penetration of drugs with repeated applications has not been well studied. The present experiments show that the topically applied ID penetrated through the skin, reached to the muscle as deep as 5 mm from the surface, and the concentration of ID in the muscle increased to a constant level after the several applications. Some drugs including anti-inflammatory agents are known to distribute preferentially in the inflamed tissue[3]. Therefore, the concentration of ID in the inflamed s.c. tissues attained by the topical application of ID may be higher than that in noninflamed tissues. The concentration of ID in the synovial fluid from arthritic patients after the oral administration of 50 mg of ID was reported to be 0.3–0.9 μg/ml[4]. The present study suggests that ID may possess anti-inflammatory activity in some s.c. soft tissues when applied to the skin as an ointment.

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Antihypertensive activity of some novel pyridinylidene arylurea derivatives in spontaneously hypertensive rats

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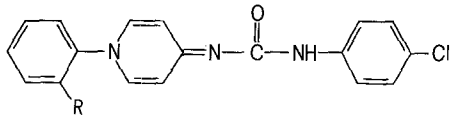
Summary. 3 novel pyridinylidene arylurea derivatives were found to lower arterial pressure in spontaneously hypertensive rats. Their relative oral potency ranged from 6 to 32 times that of guanethidine. The onset of antihypertensive action following their oral administration was less than 1 h and the duration of action ranged from 8 to over 24 h. The antihypertensive activity of the pyridinylidene arylureas was found to be associated with depletion of tissue catecholamines. Compound C depleted cardiac norepinephrine with little or no effect on total brain norepinephrine levels. It is suggested that compound C may have useful antihypertensive properties without CNS depressant activity.

In the search for antihypertensive drugs with novel chemical structures, we evaluated a series of antihypertensive pyridinylidene arylurea derivatives. A detailed structure activity study with this class of compounds will be published elsewhere[2]. The preliminary pharmacological studies with 3 compounds of this series are reported here. The chemical structures of the 3 selected compounds (A,B,C) are shown below:



Compounds	R
A	F
B	Cl
C	OCH_3

Spontaneously hypertensive (SH) rats of the Wistar Okamoto strain were purchased from Charles River/Lakeview Co. (Wilmington, MA). Arterial pressure was recorded in conscious male rats of 300–350 g b. wt by a direct technique involving cannulation of the caudal artery as described by Watson and Ludden[3]. Mean arterial pressure and heart rate values were printed at 0.5-h intervals through a data acquisition system (Data Graphics Corp., San Antonio, TX and Novatronics Co., Montgomeryville, PA) by means of ASR-33 teletype units. All drugs were administered in volumes of 2 ml/kg. Compounds A, B and C were suspended in 1% methylcellulose while guanethidine was dissolved in distilled water. The doses of all drugs were expressed in terms of base weight. Compound A was used as a fluorosulfonate salt, compound B as a free base, compound C as a hydrochloride salt and guanethidine as a sulfate salt. The calculations of the relative potency, its 95% confidence limits and regression lines were based on procedures described by Finney[4].

All 3 compounds were first tested in SH rats at 20 mg/kg i.p.; they lowered mean arterial pressure and reduced heart rate. At this dose, compound A was lethal in ½ and compound B in ¾ rats, while ½ rats which were treated with compound C survived. In further studies the compounds were administered p.o., each at 3 doses with 2–8 rats per dose. Their relative potency was calculated on the basis of maximal fall in arterial pressure over a 24-h period and compared with that of guanethidine which was previously evaluated under similar experimental conditions. The