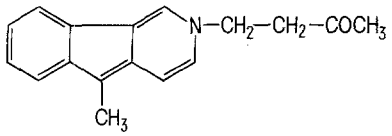

Fig. 1. Structural formula of YG 19-256, 4-(1,3,4,9b-tetrahydro-5-methyl-2H-indeno [1,2-c] pyridine-2-yl)-2-butanone.

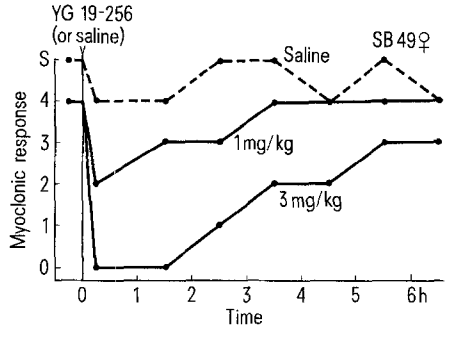

Fig. 2. Graph showing the effect of YG 19-256, 1 or 3 mg/kg i.v., on epileptic responses to intermittent photic stimulation (IPS) in a highly photosensitive baboon (SB 49).
Abscissa: time after the injection of saline or YG 19-256. Ordinate: Response to standardized test with IPS, graded as: 1 = myoclonus of eyelids during IPS; 2 = myoclonus of muscles of face and neck during IPS; 3 = myoclonus involving all the trunk and limbs during IPS; 4 = myoclonus continuing after IPS is terminated; S = tonic clonic seizure.

or 2 mg/kg, reduced the IPS-induced EEG spikes and waves for 2–3 h and abolished the myoclonic responses for 3–6 h. In the most photosensitive baboon (which consistently showed self-sustaining myoclonic, or seizure responses to IPS) YG 19-256, 1 mg/kg, prevented self-sustaining responses to IPS for 2.5 h, and YG 19-256, 3 mg/kg, abolished myoclonic responses for 1.5 h, and prevented self-sustaining responses for 6.5 h (figure 2).

Testing with IPS 5–10 min after YG 19-256, 3 mg/kg, in the 2 baboons pretreated with DL-allylglycine 175 min earlier, instead of the seizures or self-sustaining myoclonic responses expected 3 h after DL-allylglycine, myoclonic responses were found to be absent in 1 baboon and reduced to stimulus-limited responses in the other.

The preliminary studies in rodents and these experiments in baboons indicate that YG 19-256 possesses an unusual spectrum of activity as an anticonvulsant. Other drugs that are effective against maximal electroshock in rodents (e.g. diphenylhydantoin and carbamazepine) are approximately equipotent in rodents and primates and produce marked acute neurological toxicity in the baboon at doses that block self-sustaining myoclonic responses[7], whereas YG 19-256 is more potent as an anticonvulsant in the baboon than in the rodent and has little acute neurological toxicity.

1 We thank the Medical Research Council, The Wellcome Trust and the British Epilepsy Association for financial support, and Drs D.M. Loew and H. Weber (Sandoz Ltd) for the gift of YG 19-256.

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The effect of piroxicam on platelet aggregation

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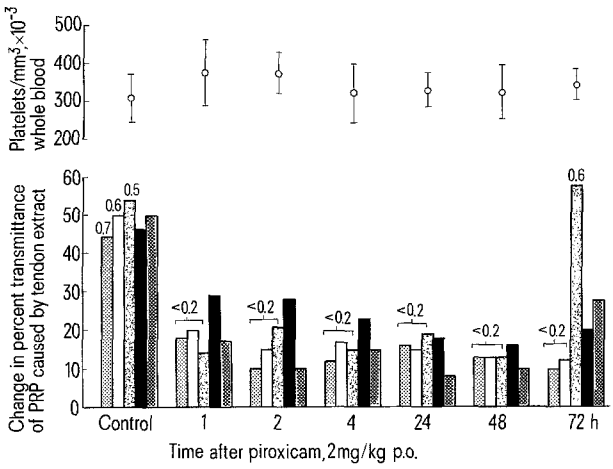
Summary. Piroxicam inhibited aggregation of human and dog platelets caused by collagen, but not by adenosine diphosphate (ADP). Release of platelet ADP was inhibited by piroxicam.

Non-steroidal anti-inflammatory (NSAI) agents inhibit collagen-induced platelet aggregation by interfering with the release of platelet constituents[1]. We report here the effects of piroxicam, a new NSAI agent[2], on aggregation of animal and human platelets.

Methods. Platelet-rich plasma (PRP) was prepared[3] from fasted humans and beagle dogs. Platelets were counted in whole blood[4]. Collagen was prepared as a crude suspension of minced rabbit tendon[5,6], and is referred to as tendon extract (TE). Platelet aggregation was studied at room temperature (20 °C) using a modification[7] of Born's turbidimetric method[8]. For in vitro experiments, piroxicam (0.5–100 μM) or 0.154 M NaCl solutions were added to PRP samples from 5 humans 10 min before addition of adenosine diphosphate (ADP) or TE. Concentrations of drugs are final concentrations in plasma. Minimum (20%) inhibitory concentrations (IC_{20}) were calculated by regression analysis. For in vivo experiments, a single oral dose of piroxicam, 2 mg/kg, was given to 5 dogs; platelet responses to ADP (10 μM) and TE, platelet counts, and release of platelet ADP[3] (3 dogs) were determined 24 h prior to and 1, 2, 4, 24, 48 and 72 h after administration of drug.

Results. Piroxicam, 1–100 μM, inhibited TE-induced aggregation of human platelets (IC_{20} = 3.9 μM); ADP-induced platelet aggregation was not affected by piroxicam 100 μM. In dogs piroxicam had no effect on ADP-induced platelet aggregation or platelet count. TE-induced platelet aggregation and release of platelet ADP were inhibited 1 h after oral administration of piroxicam to dogs and for 48–72 h thereafter (figure).

Discussion. The fact that ADP release from dog platelets in response to TE was diminished after oral administration of piroxicam suggests that, like other NSAI agents[1], piroxicam interferes with the release of platelet constitutents. Piroxicam did not inhibit primary ADP-induced platelet aggregation, which is independent of platelet release[9], but it inhibited TE-induced aggregation of human platelets at a concentration 1/60 that reported for aspirin (IC_{20} = 230 μM)[10].



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