# EXPERIMENTAL STUDY OF INTERACTION BETWEEN NONSTEROIDAL ANTI-INFLAMMATORY DRUGS VOLTAREN AND ACETYLSALICYLIC ACID AND β-ADRENOBLOCKERS

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Information in the literature on the role of adrenergic mechanisms in inflammation and on the effect of β-adrenoblockers (BAB) on the action of nonsteroidal anti-inflammatory drugs (NAID) is contradictory [4-6, 9, 13].

The object of this investigation was to study the effect of two BAB widely used in medical practice, namely propranolol (Anaprillin, Inderal) and pindolol (Visken) on the therapeutic (anti-inflammatory, analgesic, and antipyrexial) and toxic (injury to the gastric mucosa) effects of anti-inflammatory drugs, namely voltaren and acetylsalicylic acid (ASA).

## EXPERIMENTAL METHOD

Experiments were carried out on 560 noninbred male rats weighing 130-160 g in four series. Acute inflammation of the paw was induced by subplanar injection of 0.1 ml of 1% carrageenin [14]. The volume of the paw was measured by a plethysmometer (Ugo Basile, Italy) before and 3 h after the injection of carrageenin. Voltaren (10 mg/kg) and ASA (200 mg/kg) were given internally 1 h before carrageenin, and the BAB were injected subcutaneously 15 min before NAID in doses of 0.3, 1, and 3 mg/kg.

Adjuvant arthritis (chronic immunologic inflammation) was induced by subplantar injection of 0.1 ml of a suspension of Freund's adjuvant in mineral oil [11]. The reaction of primary edema at the site of injection of the adjuvant was estimated plethysmometrically on the 4th day, and the secondary reaction on the opposite limb on the 14th day. Voltaren (3 mg/kg internally) and BAB (propranolol 1 mg/kg, pindolol 0.3 mg/kg, subcutaneously) were given daily for 14 days.

The effect of BAB on the analgesic effect of NAID, estimated from the change in threshold of nociceptive sensation of the inflamed rat limb [12], was studied by means of an analgesimeter (Ugo Basile). Voltaren (10 mg/kg internally) and ASA (200 mg/kg internally) were given 1 h after the injection of carrageenin, whereas the BAB — propranolol and pindolol, 1 and 0.3 mg/kg respectively — were injected subcutaneously 15 min before NAID.

A hyperthermic reaction was induced by injection of the 20% suspension of bakers' yeast (1 ml/100 g body weight, subcutaneously) 18 h before the experiment [10]. Changes in the rectal temperature were recorded by a TPÉM-1 electrothermometer before and 2 h after administration of voltaren (10 mg/kg, internally). Propranolol (3 mg/kg) and pindolol (1 mg/kg) were injected subcutaneously 15 min before voltaren.

The ulcerogenic effect of NAID (voltaren 30 mg/kg, ASA 300 mg/kg, internally) on the gastric mucosa was assessed in rats deprived of food for 20 h before the experiment, on a 4-point scale [7]. Gastrotomy was performed 3 h after administration of NAID. The BAB (10 mg/kg, subcutaneously) were injected 15 min before NAID.

## EXPERIMENTAL RESULTS

Propranolol in doses of 0.3 and 1 mg/kg (subcutaneously) had no effect on the intensity of the inflammatory reaction to carrageenin. An increase in its dose to 3 mg/kg caused an

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TABLE 1. Effect of Propranolol and Pindolol on Anti-Inflammatory Action of Voltaren and ASA in Acute Inflammation Induced by Carrageenin in Rats

| Drugs and mode of administration | Dose, mg/kg | Edema of limb, percent of control |
|---|---|---|
| Voltaren (internally) | 2 | 66±7 |
| | 10 | 46±2 |
| ASA (internally) | 100 | 63±4 |
| | 200 | 39±7 |
| Propranolol (subcutaneously) | 0,3 | 95±4* |
| | 1 | 108±6* |
| | 3 | 130±10 |
| Pindolol (subcutaneously) | 0,3 | 60±15 |
| | 1 | 55±12 |
| | 3 | 40±10 |
| Voltaren (internally) + propranolol (subcutaneously) | 10+0,3 | 96±10* |
| | 1+3 | 89±11* |
| Voltaren (internally) + pindolol (subcutaneously) | 10+3 | 74±12 |
| | 10+0,3 | 47±12 |
| | 10+1 | 54±7 |
| | 10+3 | 52±3 |
| ASA (internally) + propranolol (subcutaneously) | 200+0,3 | 94±4* |
| | 200+1 | 60±6 |
| | 200+3 | 57±8 |
| ASA (internally) + pindolol (subcutaneously) | 200±0,3 | 40±5 |
| | 200+1 | 36±11 |
| | 200+3 | 46±4 |

Legend. *) Difference from control not significant at P = 0.05 level.

TABLE 2. Effect of Propranolol and Pindolol on Anti-Inflammatory Action of Voltaren in Chronic Immunologic Inflammation by Freund's Adjuvant in Rats

| Drugs and mode of administration | Dose, mg/kg | Primary reaction (4th day) | Secondary reaction (14th day) |
|---|---|---|---|
| Propranolol (subcutaneously) | 1 | 110±5[d] | 116±12[d] |
| Pindolol (subcutaneously) | 0,3 | 106±6[d] | 64±10[b] |
| Voltaren (internally) | 3 | 47±6[a] | 60±12[c] |
| Voltaren (internally + propranolol (subcutaneously) | 3+1 | 52±5[a] | 92±3[e] |
| Voltaren (internally) + pindolol (subcutaneously) | 3+0,3 | 51±5[a] | 64±8[c] |

Legend. a) $P < 0.001$, b) $P < 0.01$, c) $P = 0.02$, d) $P > 0.25$, e) $P = 0.5$.

increase of 30% in the edema. In the doses studied propranolol weakened the anti-inflammatory action of voltaren by 18-40% and of ASA by 18-55%. Pindolol in the same doses reduced edema by 40-60% but had no effect on the action of NAID (Table 1).

Neither BAB studied had any effect on the development of the primary reaction of edema at the site of injection of Freund's adjuvant in rats or altered the action of voltaren (Table 2). Additionally, propranolol had no effect on the development of the secondary reaction (polyarthritis), but abolished the action of voltaren virtually completely. Pindolol reduced the intensity of the polyarthritis by 36% but did not change the anti-inflammatory action of voltaren.

Propranolol and pindolol raised the threshold of nociceptive sensation in the inflamed limb 1 and 2 h after injection by 50-67 and 83-84%, respectively (Fig. 1). Propranolol, 1 h after injection, reduced the analgesic effect of both voltaren (by 71%) and ASA (by 66%); however, by the 2nd hour after its injection propranolol no longer modified the effects of NAID. Pindolol did not change the analgesic action of NAID throughout the period of observation.

Voltaren (10 mg/kg internally) lowered the hyperthermia by 1.6 ± 0.1°C. Propranolol, in the dose studied, potentiated the antipyrexial effect of voltaren by 33% (2.0 ± 0.1°C), whereas pindolol did not change it (1.5 ± 0.2°C; $P > 0.05$).

BAB in a dose of 10 mg/kg (subcutaneously) did not change the state of the gastric mucosa of the rats (Fig. 2). Voltaren (30 mg/kg) and ASA (300 mg/kg), i.e., in doses about three times higher than therapeutic (on experimental models of inflammation), caused damage to the gastric mucosa: hyperemia, and in some animals, petechial hemorrhages (0.6 point). Pindolol did not alter the ulcerogenic action of NAID, but propranolol potentiated the ulcerogenic effect of voltaren to 2.6 points (multiple hemorrhages, erosions), and of ASA to 1.4 point (petechial hemorrhages, single erosions).

These results confirm data in the literature on the ability of propranolol to diminish the anti-inflammatory effect of NAID [13]. At the same time significant differences were found between the action of propranolol and that of the other BAB, pindolol, which itself exhibited both anti-inflammatory and analgesic properties. Pindolol differs from propranolol

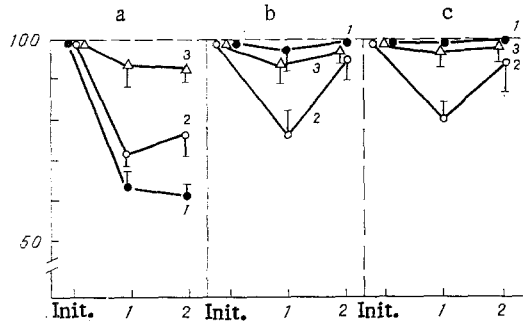


Fig. 1

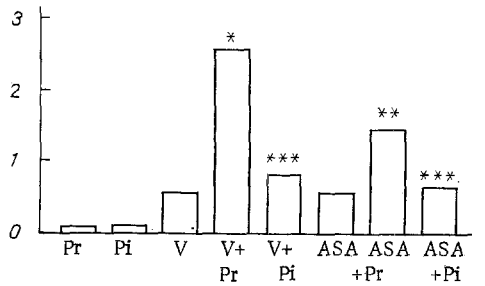


Fig. 2

Fig. 1. Effect of propranolol and pindolol on analgesic action of voltaren and ASA. Abscissa, time after injection of NAID (in h); ordinate, threshold of nociceptive sensation (in percent of initial). a: 1) Control; 2) propranolol (1 mg/kg subcutaneously); b: 1) ASA (200 mg/kg internally); 2) ASA + propranolol; 3) ASA + pindolol; c: 1) voltaren (10 mg/kg internally); 2) voltaren + propranolol; 3) voltaren + pindolol.

Fig. 2. Effect of propranolol and pindolol on ulcerogenic action of voltaren and ASA in rats. Ordinate, ulcerogenic effect (in points). Pr) propranolol (10 mg/kg subcutaneously), Pi) pindolol (10 mg/kg subcutaneously), V) voltaren (30 mg/kg internally), ASA 200 mg/kg (internally). *P < 0.001, **P < 0.05, ***P > 0.25 compared with ulcerogenic effect of NAID.

in its action on the specific and side effects of the NAID voltaren and ASA. The difference in the action of these BAB is probably due to differences in their pharmacological spectrum. Unlike propranolol, pindolol has partial agonistic (isoproterenol-like) activity [8], which may be responsible for weakening of the symptoms of inflammation, that are characteristic of sympathomimetics with direct and indirect types of action [2, 4, 5]. It has also been shown that adrenomimetics and the BAB pindolol have antibradykinin activity [3]. Meanwhile propranolol has marked membrane-stabilizing properties [8] and inhibits the conduction of pain impulses along nerve fibers [1], which evidently accounts for its analgesic effect.

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