STUDY OF SOME CARDIOVASCULAR EFFECTS OF DICLOFENAC SODIUM AND PIRPROFEN

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ABSTRACT

Rabbit's isolated perfused aortic strips and hearts have been used to study the effects of diclofenac and pirprofen, non-steroidal anti-inflammatory drugs (NSAIDs). Although diclofenac and pirprofen in concentrations ranging from 0.5-8 ug/ml and 12.5-100 ug/ml respectively had no effect on the resting tonus of the aortic strip preparations, yet both of them in the same concentrations produced a dose-related statistically significant augmentation of adrenaline and noradrenaline induced contractions of the preparations, which were less evident in preparations isolated from reserpinized rabbits (0.1 mg/kg body weight S.C. reserpine for 10 successive days). These augmenting effects of both drugs were almost absent in denuded aortic strips, in which the intimal endothelial cells were removed.

Diclofenac (1-16 ug/ml perfusion fluid) had no effect on the contractility of isolated perfused rabbit heart, but in a concentration of 50ug/ml perfusion fluid it exerted a positive inotropic effect, which was almost absent in specimens obtained from reserpinized rabbits. Larger doses (200 ug/ml perfusion fluid) exerted a toxic cardio-inhibitory effect. Pirprofen exerted no effect on cardiac contractility in concentrations ranging from 2.5-800 ug/ml perfusion fluid.
INTRODUCTION

Inhibition of enzyme systems, termed collectively prostaglandin synthetase, has gained wide acceptance as the postulated primary mechanism of action of nonsteroidal anti-inflammatory drugs, NSAIDs (Malmsten 1986).

It is well established that the endothelial lining of all blood vessels produces continuously prostaglandins (Mullane and Fornabaio 1988) e.g. the rat mesenteric vasculature releases PGE$_2$-like material at rest (Stanton et al. 1986).

Noradrenaline release and stimulation of adrenergic nerve release a PGE-like substance from various tissues (Farber and Gross 1989).

Prostaglandins I$_2$ and E$_2$ relax smooth muscle cells of different arterial beds e.g. mesenteric arteries of rabbits (Armstrong and Thirsk 1979), of rats (Coupar 1980), of dogs (Desjardins-Glasson et al., 1982), of cats (Fowler et al. 1983), and of men (Hadhazy et al. 1983).

The above mentioned findings prompted us to investigate the effects of two nonsteroidal anti-inflammatory drugs namely: diclofenac (a phenylacetic acid derivative) and pirprofen (a propionic acid derivative) on the isolated aortic strips either intact or denuded and also on the isolated perfused hearts of rabbits.

The selected drugs are rather widely used at present time in treatment of a variety of rheumatic disorders including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis etc. (Kummer and Nekora 1985, Caldwell 1986).
MATERIAL AND METHODS

I- Isolated rabbit aortic strip:
was prepared according to the method described by
Furchgott and Bhadrakon (1953). Krebs' solution
was used containing (g/L distilled water): sodium
chloride 6.8, potassium chloride 0.35, calcium chlo-
ride 0.28, magnesium chloride 0.29, sodium hydrogen
phosphate 0.16, sodium bicarbonate 2.1 and glucose
2.0. The preparation was left for one hour as an
equilibration period. The drugs tested were left in
the bath for one and half minutes.

II- Aortic strips isolated from reserpine treated rabbits:
A group of rabbits were injected with 0.1 mg/kg
body weight reserpine S.C. daily for 10 successive
days before the day of the experiment and then the
aortic strips were prepared as described by the
method of Furchgott and Bhadrakon 1953.

III- Isolated denuded rabbit aortic strips:
Aortic strips were obtained as abovementioned and
then were prepared by gentle rubbing of the luminal
surface with sand paper as described by Cherry et
al. 1982. Lastly aortic strips were fixed in 10%
formalin and histological sections were prepared and
stained with Haematoxylin and Eosin.

IV- Isolated perfused rabbit hearts:
was dissected and prepared according to Langendorff
technique (1895) and as outlined by Burn (1952). Ringer
Locke solution of the following compositions was
used: (g/L distilled water) sodium chloride 9.0,
potassium chloride 0.32, calcium chloride 0.24, sodium
bicarbonate 0.15 and glucose 2.0.

V- Statistical analysis of the results was carried out,
using the one tailed "Student's t test".
Drugs used:
1) Diclofenac sodium (Voltaren) (Ciba-Geigy, Switzerland). Diclofenac powder was dissolved in distilled water.
2) Pirprofen (Rengasit) (Ciba-Geigy, Switzerland). 100mg pirprofen powder were dissolved in 1 ml benzyl alcohol and diluted to 10 ml with distilled water. A similar solution containing the same concentrations of benzyl alcohol and distilled water was used as a control.

The doses of dichlofenac and pirprofen used in the present study was determined by preliminary pilot experiments guided by doses used by other workers.
4) Angiotensin II (Hypertensin) (Ciba-Geigy, Switzerland).
5) Histamine hydrochloride (Aldrich Chemical Co., Ltd).
6) Isoprenaline hydrochloride (Wintrop, England).
7) Noradrenaline hydrochloride (Arterenol) (Hoechst AG, West-Germany).
9) Reserpine (Serpasil) (Ciba-Geigy, Switzerland).

All drug solutions tested were freshly prepared before each experiment.

RESULTS
A- Effects of diclofenac and pirprofen on the isolated Rabbit aortic strips:

1) Effect of diclofenac and pirprofen on adrenaline induced contractile responses:

Diclofenac as well as pirprofen produced a dose related potentiation of the contractile response of rabbit aortic strip induced by submaximal dose of adrenaline (Figs. 1,2).

When either diclofenac or pirprofen was added to the perfusion fluid to make a final concentration of
4 µg/ml or 100 µg/ml respectively, it augmented the contractile responses induced by adrenaline in doses of 0.1, 0.2 and 0.4 µg/ml (Figs. 3,4).

The solvent of pirprofen benz alcohol was completely devoid of any effect (Fig. 2).

The values of percentage increase in the adrenaline induced contractile responses are illustrated in the form of bar charts in Figs. 5, 6 and the aforementioned results were demonstrated in a graphical form in Figs. 7, 8. Both diclofenac and pirprofen caused shift to the left of contraction response curve of adrenaline.

II) Effect of diclofenac and pirprofen on the adrenaline induced contractile responses of aortic strips isolated from reserpinized rabbits:

The enhancing effect of either diclofenac (4µg/ml) of pirprofen (100µg/ml) on adrenaline induced contractile responses were much less in aortic strips isolated from reserpine treated rabbits (Figs. 9, 10).

III) Effect of diclofenac and pirprofen on the adrenaline induced contraction of isolated rabbit aortic strips with denuded intima:

Removal of endothelium have no effect on the contractile responses induced by adrenaline. Neither diclofenac nor pirprofen alter the adrenaline induced contractions in preparations with removed endothelium (Figs. 11, 12).

Figs. 13 & 14 show histological sections of normal and endothelium denuded - aortic strip.

B- Effects of diclofenac and pirprofen on the isolated perfused rabbit hearts:

The action of diclofenac on the response of the isolated perfused heart was dose-dependent. Diclofenac