

PREVENTION OF TACHYCARDIC ACTION OF HYDRALAZINE

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The hypotensive action of hydralazine (0.5-2 mg/kg) was enhanced by pre-treatment of normotensive anesthetized rats with the drugs: haloperidol (0.21 mg/kg), indomethacin (3 mg/kg) and atropine (0.5 mg/kg). The corresponding tachycardia produced by hydralazine was abolished by haloperidol or indomethacin or atropine. The hypotensive potentiation of the drugs with hydralazine is worth studying.

Key words : hydralazine, atropine, haloperidol, indomethacin.

INTRODUCTION

Hydralazine has been used widely to treat hypertension that occurs during pregnancy. Parenteral administration of hydralazine has also been used for the treatment of hypertensive emergencies⁽¹⁾ Hydralazine produces tachycardia which is generally attributed to reflex. **Correspondence : Dr. Prasert Songkittiguna**, Department of Pharmacology, Faculty of Dentistry, Chulalongkorn University, Bangkok 11330, Thailand. stimulation of cardiac sympathetic nerves^(1, 2) The palpitation is one of the side effects frequently complain by patients undergoing antihypertensive treatment. The aim of the study is to select the drugs that could attenuate the tachycardic side effects. Therefore, the effects of haloperidol, indomethacin and atropine on the blood pressure and heart rate of anesthetized and pithed rats were studied

MATERIALS AND METHODS

Anesthetized normotensive rat

Wistar rats of either sex weighing 250-300 g were anesthetized with urethane (10 mg/kg). Urethane (25%) in normal saline solution was injected intraperitoneally. The trachea was cannulated to maintain the animals on positive ventilation in order to avoid any complicating effects of respiration. The rectal temperature was also maintained throughout the course of the experiments by

irradiation with infrared light. The blood pressure was recorded directly from carotid artery on a Grass Polygraph Model 79 (FT03). The heart rate was recorded from tachometer. The freshly-prepared hydralazine including other drugs under investigation in NSS were injected into the femoral vein cannula.

Pithed rat

Normotensive Wistar rats of either sex weighing 250-300 g were anesthetized with diethyl ether and immediately cannulated with tracheal cannula. The brain and spinal cord were then destroyed by passing a steel pithing rod through the orbit and artificial respiration was started immediately by connecting the tracheal cannula to a small animal respiratory pump. The rate of respiration was set at 70 strokes per minute. Both anesthetized and pithed rats blood pressures were measured from the carotid carotid artery through a small bore polyethylene cannula (No 260) and recorded on a Grass recorder (as above). The heart rate was recorded by triggering a Grass tachometer with the pulse wave derived from the blood pressure channel.

Statistical analysis of results

One-way analysis of variance was performed on grouped data followed by the paired or unpaired student's t-test (where appropriate).

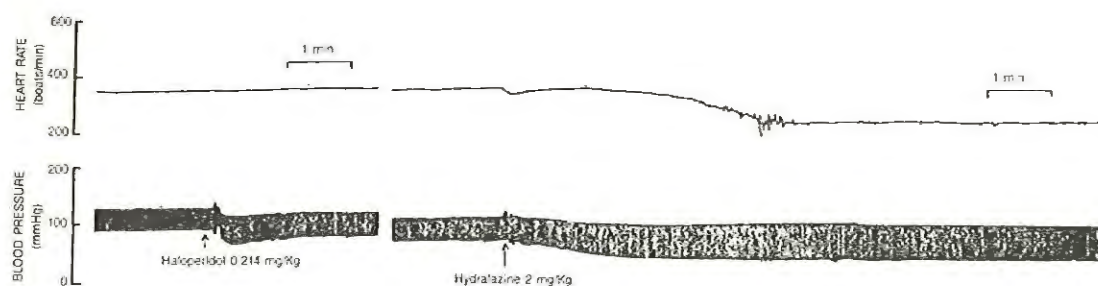


Fig. 1. The effect of haloperidol (0.214 mg/kg) on the cardiovascular effects of hydralazine (2 mg/kg) in anaesthetized rat.

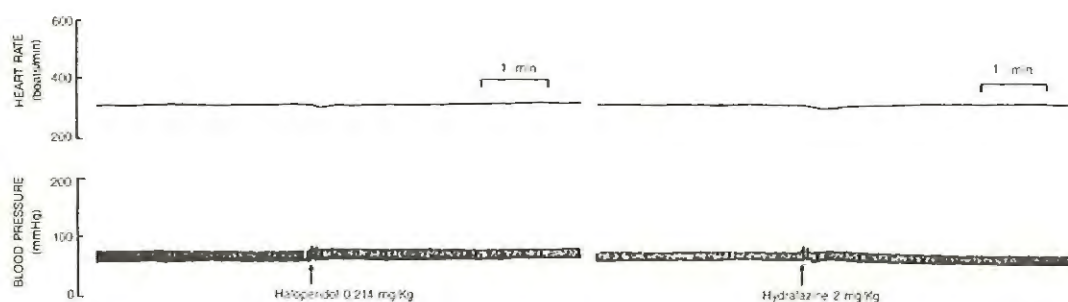


Fig. 2. The effect of haloperidol (0.214 mg/kg) on the cardiovascular effects of hydralazine (2 mg/kg) in pithed rat.

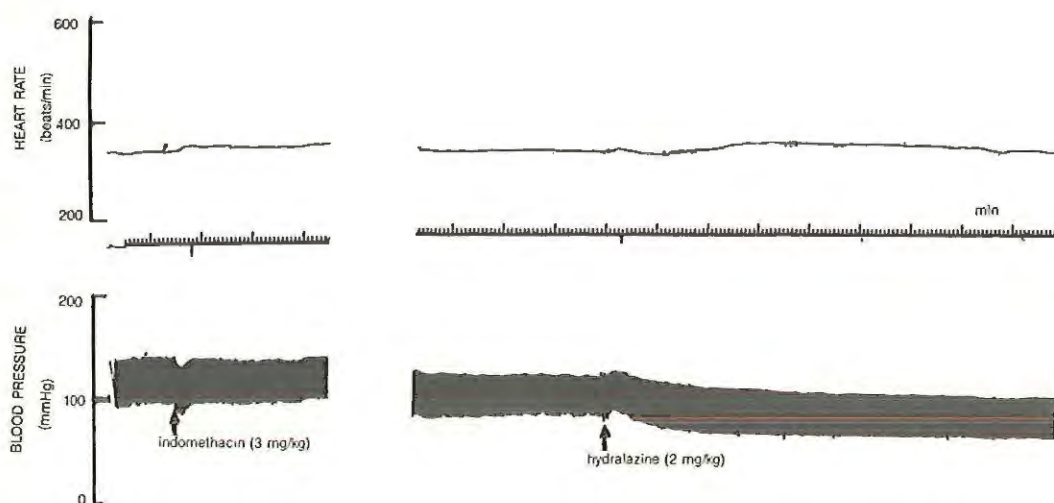
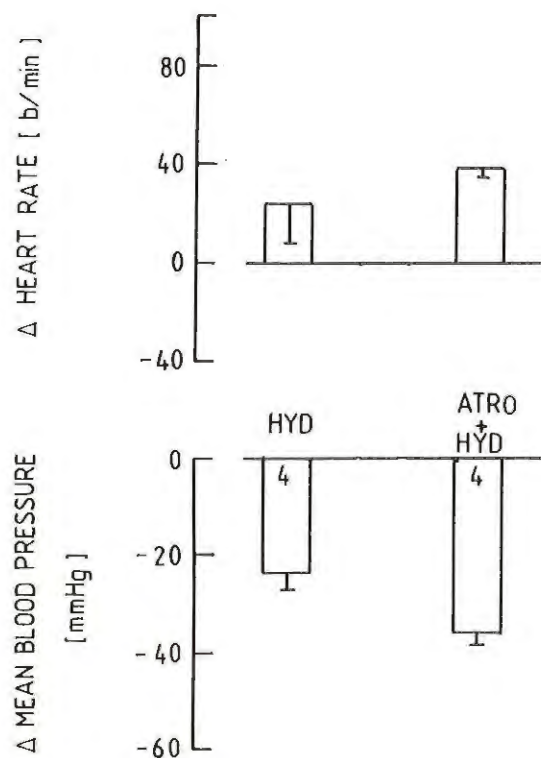


Fig. 3. The effects of indomethacin on the blood pressure and heart rate of anesthetized rat.



HYD HYDRALLAZINE 0.5 mg/kg i.v.

ATRO ATROPINE 0.5 mg/kg i.v.

Fig. 4. The mean blood pressure and heart rate produced by atropine and hydralazine in anesthetized rat.

Drugs

Hydralazine hydrochloride (Ciba-Geigy); haloperidol (Welding & Hamburg); indomethacin (Sigma); atropine (Sigma); urethane (May & Baker).

RESULTS

In five rats pretreated with haloperidol (0.214 mg/kg, IV) for 30 min the blood pressure fell quickly from a mean blood pressure of 85.3 mmHg (s.e.m. = 9.3) to 63.8 mmHg (s.e.m. = 9.2) whereas the heart rate from 370.1 beats/min (s.e.m. = 7.1) to 340.0 beats/min (s.e.m. = 15.4). At the end of thirty minutes after haloperidol administration, hydralazine was injected IV. Hydralazine caused a further reduction in mean blood pressure from 63.8 mmHg (s.e.m. = 9.2)

to 31.6 mmHg (s.e.m. = 2.9). The heart rate was decreased from 340.0 beats/min (s.e.m. = 15.4) to 206.0 beats/min (s.e.m. = 17.7). The typical tracing was shown in Fig. 1.

In five pithed rats, haloperidol (0.214 mg/kg, IV) given prior to hydralazine as above, the calculated values for mean blood pressure before and after haloperidol plus hydralazine were 38.9 mmHg (s.e.m. = 1.2) and 25.3 mmHg (s.e.m. = 2.17) respectively; for the heart rate, it was 268.0 beats/min (s.e.m. = 13.9) and 264.0 beats/min (s.e.m. = 16.0) respectively. The tracing was shown in Fig. 2.

Three rats were pretreated with indomethacin (3 mg/kg IP) one hour before anesthesia. One hour after cannulation hydralazine (2 mg/kg) was administered. Blood pressure fell slowly within 30 min from a mean of 62.70 mmHg (s.e.m. = 4.3) to 39.4 mmHg (s.e.m. = 1.47); the heart rate changed from a mean of 430.0 beats/min (s.e.m. = 21.2) to be 360.0 (s.e.m. = 11.5). The tracing was shown in Fig. 3.

In four rats pretreated for 30 minutes with atropine (0.5 mg/kg). Hydralazine (0.5 mg/kg IV) was then administered. The blood pressure fell from a mean of 78.4 mmHg (s.e.m. = 3.0) to 42.1 mmHg (s.e.m. = 1.6) whereas, the heart rate was changed from 320.0 beats/min (s.e.m. = 10.0) to 290.0 beats/min (s.e.m. = 11.5). Fig. 4 showed the mean blood pressure and heart rate change produced by atropine and hydralazine.

DISCUSSION

Hydralazine caused vasodilation with tachycardia by enhancement of sympathetic tone.^(1,2) However, the molecular mechanism of action of hydralazine is still not precisely defined; unlike diazoxide and minoxidil which are classified as the K⁺ channel openers.⁽³⁾ There is no evidence that hydralazine affects membrane channels or cGMP as has been reported for other vasodilators.⁽⁴⁾ The presence of vasodilatation-induced side effects with hydralazine has led to concurrent use of

adrenergic antagonists and diuretics; the commercial oral preparation of hydralazine with reserpine and thiazide diuretic has been marketed. There is no report on the combination of hydralazine with haloperidol, with indomethacin or with atropine. The results of the present study demonstrated that the equivalent dose of clinically-used haloperidol (0.214 mg/kg) enhanced the hypotensive action of hydralazine (2 mg/kg) in rat. Furthermore, the major cardiac effect (tachycardia) was also abolished. Haloperidol is a butyrophenone derivative antipsychotic drug. Continuous treatment with haloperidol has been reported in some studies to produce a transient increase in HVA levels in the CSF, plasma and urine. After 1-3 weeks, HVA levels decrease to lower than normal level, and this decrease persists. The initial period of dopamine receptor blockade causes a compensatory increase in transmitter turnover, resulting in increased level of dopamine metabolites.⁵ Hydralazine has been reported to block the conversion of dopamine to noradrenaline.⁶ Moreover, hydralazine found to cause an irreversible inhibition of tyrosine hydroxylase and dopamine- β -hydroxylase within the intact medullary cell of bovine.⁷ These may cause abundant increase in available dopamine in the neurons. Dopamine has weak direct action on adrenoceptors and also has indirect sympathomimetic actions. In addition, it acts on specific dopamine receptors of renal and mesenteric vascular smooth muscle to cause vasodilatation. Dopamine, when injected into anesthetized animals with a reasonably high degree of vascular tone, low dose of dopamine produces a fall in blood pressure due to vasodilatation in the splanchnic region and kidneys, although high doses are pressor. The explanation of haloperidol produces a fall in blood pressure and heart rate of rat is that the accumulated dopamine in the nerve cells competes with endogenous noradrenaline for

alpha receptor, and being a weak agonist the resultant effect is a decrease in the vascular tone that is maintained through the action of endogenous noradrenaline on alpha receptors subserving vasoconstriction. Another explanation is that a metabolite having smooth muscle relaxant properties is produced (see 8). Indomethacin is a potent inhibitor of the prostaglandin-forming cyclooxygenase. Thus the biosynthesis of the whole prostaglandins family such as prostaglandin E_1 , prostaglandin $F_{2\alpha}$, prostaglandin E_2 , prostaglandin D_2 , thromboxane A_2 and prostacyclin, could be inhibited. Numerous pharmacological actions of these compounds are reported; some produce vasodilatation whereas the other cause vasoconstriction. M.T. Lin⁽⁹⁾ reported that intravascular or intrahypothalamic injection of prostaglandin E_1 caused vasoconstriction, rather than vasodilatation in the peripheral tissues. Moreover, pretreatment of rat with indomethacin in the present study, the blood pressure and heart rate were both attenuated and even reversed that could be the lackness of central or peripheral prostaglandin actions (Vidrio, H. personal communication). In the present study, atropine seems to reverse the tachycardic effect of hydralazine and to help decrease in blood pressure may explain by the fact that small dose of atropine (0.5-1 mg in man) may temporarily decrease the rate of the heart beat. This has been attributed to a slight central stimulant action of atropine on the vagal centres in the medulla. However, a more likely explanation may be that the initial cardiac slowing is due to stimulation rather than blockade of muscarinic receptors in the heart (see 10).

In conclusion, tachycardic action of hydralazine could be prevented by pretreatment of either haloperidol, or indomethacin or atropine in anesthetized normotensive rat. In addition, the hypotensive action of hydralazine is also potentiated by the drugs.

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