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The Role of The Prostanoid System in Mediating the Haemodynamic Effects of Dihydroergotamine

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ABSTRACT

Dihydroergotamine (DHE) increases tonus in veins, especially in capacitance vessels, thereby reducing blood pooling and increasing venous blood flow velocity and it has been suggested that DHE achieves its effect partially through its influence on prostanoids synthesis and release. Pretreatment with indomethacin did not affect DHE response in central haemodynamic variables or in tissue blood flow in dogs; nor did it affect the reduced venous vessel area, increased venous blood flow velocity (measured ultrasonically), or reduced resting calf volume blood flow (measured by plethysmography), caused by DHE in humans. Although the number of animals and of humans in this study were small, nontheless it seems unlikely that the effect of clinically relevant doses of DHE is appreciably mediated by the prostanoid system.

INTRODUCTION

Dihydroergotamine (DHE) interacts with α-adrenoreceptors, though its effect differs from that of noradrenaline. Some investigators have found that its effect on vessels in vitro is partially mediated by the prostanoid system through the enhancement of endogenous prostanoid synthesis and release (9, 10, 11, 13). This study was made to ascertain wheather inhibition of prostanoid synthesis before administration of DHE would alter the effects of DHE on central and peripheral haemodynamics or tissue blood flow distribution.

MATERIAL AND METHODS

The study was divided in two parts, 1 and 2, as follows:

1.CENTRAL HAEMODYNAMIC AND TISSUE BLOOD FLOW EFFECTS;

Four male dogs weighing between 15-20 kg, anaesthetized with phenobarbital,

were used. The following haemodynamic variables were monitored continuously: systemic arterial and central venous pressure, pressure in the pulmonary trunk, and heart rate. Cardiac output and tissue blood flow were determined with the radioactive microsphere technique. A known amount of radiolabelled microspheres were injected into the left atrium and reference blood was taken from aorta. The activity of blood and tissue samples were measured in a gamma scintillation counter. For methodological details see Lindblad & Bergqvist (2, 3).

Two dogs received 0.01 mg/kg bodyweight DHE (Orstanorm, Sandoz, Sweden) i.v. when baseline values of the different variables had been established. 15 min. later another determination was made. One hour before start of the experiments two dogs received indomethacin (Indomee, LEO, Sweden) in a dose of 2.5 mg/kg bodyweight i.v. to inhibit the cyclooxygenase but not the lipoxygenase pathway of arachidonic acid metabolism. Baseline values were obtained and DHE given (0.01 mg/kg), a second complete evaluation being made 15 min. later. Haemoglobin content, haematocrit and blood gas were analysed immediately before and after experiments.

2.PERIPHERAL HAEMODYNAMIC EFFECTS;

Five healthy human volunteers (age 23-36) were studied. Resting calf volume blood flow was measured plethysmographically, cross-sectional area of the vessels in the groin by ultrasound (Diasonics), and peak blood flow velocity by ultrasound (Dopscan). The experimental design is described in detail elsewhere (5). No pharmacotherapy was allowed during the investigation period or the two previous weeks. Three investigations were made at one week intervals: 1. under control conditions, 2. after administration of DHE and 3. after administration of DHE but with pretreatment with indomethacin. DHE was given sc. in a dose of 0.5mg. Indomethacin pretreatment was given one hour before DHE as a suppository with a dose of 100 mg. Measurements were made before DHE was given and two hours later. In the control group measurements were made to establish baseline values and two hours later.

STATISTICAL ANALYSIS;

The small number of animals investigated permitted no statistical analysis of their data. The results from the study on healthy volunteers were analysed with Student's t-test for paired data. Comparison between the groups were not possible owing to the small number of individuals studied. The level of significance was set at $p<0.05$.

TABLE 1. Central haemodynamic effects of DHE with or without pretreatment with indomethacin in dogs.

	NO PRETREATMENT (n=2)		PRETREATMENT (n=2)	
	Bas. val.	15m.after DHE	Bas. val.	15m. after DHE
Cardiac output l/min·kg	0.18	0.17	0.17	0.16
Heart rate /min	142	126	162	130
Systemic artery press. mmHg	173	185	178	195
Pulmonary artery press.mmHg	15	19	14.5	20.5
Central venous press. mmHg	9	11	5	7

TABLE 2. Tissue blood flow in dogs after DHE with and without pretreatment with indomethacin. ($ml \cdot min^{-1} \cdot 100g^{-1}$ tissue)

TISSUE	NO PRETREATMENT (n=2)		PRETREATMENT (n=2)	
	Bas.val.	15 m. after D H E	Bas.val.	15 m. after D H E
Thyreoid	258	318	274	302
Adrenals	276	328	281	320
Pancreas	84	67	83	63
Liver (hepatic artery flow)	13	26	19	14
Kidney	279	340	278	293
Spleen	123	149	139	197
Stomach	36	32	37	30
Small intestine	64	57	58	55
Large intestine	39	28	30	29
Heart	222	260	175	252
C N S	56	101	42	96

TABLE 3. The effect of DHE given to healthy humans, both with and without pretreatment (indomethacin), on resting calf volume blood flow, cross-sectional area and blood flow velocity (n=5).

	Control conditions		DHE		Indomethacin+ DHE	
	Bas. val.	2 hours after	Bas. val.	2 hours after	Bas. val.	2 hours after
PEAK BLOOD FLOW VELOCITY (cm/sec.)						
Artery	59 -	52	63 -	63	65 -	61
Vein	52 -	48	48 -	71*	48 -	69*
CROSS-SECTIONAL AREA (cm^2)						
Artery	0.71 -	0.66	0.55 -	0.54	0.65 -	0.63
Vein	0.64 -	0.59	0.65 -	0.52*	0.57 -	0.41*
RESTING CALF VOLUME BLOOD FLOW($ml \cdot min.^{-1} \cdot 100g^{-1}$)						
	4.0 -	4.7	4.3 -	3.4*	4.2 -	3.5*

*=$p<0.05$.

RESULTS

The central haemodynamic data are given in table 1. Increased pressures were recorded after DHE, the changes being of the same magnitude in all four animals studied. Tissue blood flow was largely unchanged (Table 2), except in the CNS where it showed a tendency to increase. Baseline values did not differ between animals pretreated with indomethacin and those given only DHE (Table 1 and 2),nor did response to DHE.

Peripheral haemodynamic effects are shown in Table 3. Peak venous blood flow velocity increased, and venous vessel cross-sectional area decreased significantly, after the administration of DHE. Resting calf volume blood flow was significantly reduced in DHE-treated groups. These changes remained unaffected by pretreatment with indomethacin. Haemoatocrit increased after DHE, but blood gases were unaltered.

DISCUSSION

Dihydroergotamine (DHE) increases tonus in veins, especially in capacitance vessels, the increase in tonus being greater in veins than in arteries (5, 8, 15). The vascular effect of DHE can only partly be blocked by phentolamine (1, 11); thus the effect of DHE differs from that of noradrenaline. The tension induced by DHE can be partly blocked *in vitro* by phentolamine, and the resi-

dual tension is blocked by inhibitors of the prostanoid synthesis (9, 10, 11).

When DHE has been added to the fluid in which vein strips from dogs are immersed during measurement of vein tonus, increased activity of a prostanoid E-like substance has been detected; the immersion fluid has been found to bring about partial inhibition of ADP-induced platelet aggregation (10). Increased release of prostacyclin to immersion fluid has also been found (13). Thus there are indications that the vascular effects of DHE may be partially due to increased synthesis or release of prostanoids, though this effect has been said to be species dependent (12).

Our results with dogs showed no differences in haemodynamic response between those dogs pretreated with indomethacin before being given DHE, and those receiving only DHE; neither was there any difference in tissue blood flow between the two categories. The changes observed are in agreement with the findings in larger experimental series on the effect of DHE (2, 3). Nor did we find that indomethacin affected response to DHE in healthy humans, and the increased venous blood flow velocity, decreased venous vessel area, and reduced resting calf volume blood flow were comparable with data reported in another study (5). Although the groups in the present study were small, the data are consistent with our previous studies on the effects of DHE, and it is unlikely that in either dogs or man, a substantial part of the vascular effects of DHE at least when clinically relevant doses of DHE are used is mediated via the prostanoid system. As there was no tendency whatsoever for indomethacin to alter response to DHE, it was considered needless to extend the study to obtain any further data.

Thus, the effect of DHE seems to be mediated mainly by its high affinity for α-receptors, vascular α-receptors being blocked. There have been some reports of an effect of DHE on the haemostatic system (14), but recent studies seem to have ruled out such an effect, at least where clinical doses are concerned (4). That the vascular effect of DHE is more pronounced in veins could be partly due to the higher affinity of DHE to α_2-receptors than to α_1-receptors (7). In addition to the vascular effects of DHE such metabolic effects as a reduction of liver glucose output, inhibition of adrenaline induced hyperglycaemia, stimulation of lipolysis, inhibition of cAMP degradation and increased puruvate/lactate ratio during relative hypoxia, have also been reported (6, 16).

To conclude, it seems unlikely that a substantial part of the vascular effects of DHE is mediated by the prostanoid system in either dogs or man.

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REFERENCES

1. Aellig, W.H.: Venoconstrictor effect of dihydroergotamine in superficial hand veins. Europ. J. clin. Pharmacol. 7:137-9, 1974.
2. Lindblad, B. & Bergqvist, D.: Central haemodynamic effects of dextran 70, dihydroergotamine and their combination. A study in dogs. Acta Chir. Scand. 149:459-65, 1983.
3. Lindblad, B & Bergqvist, D.: Tissue blood flow and blood flow distribution after administration of dextran 70, dihydroergotamine and their combination. A study using the radioactive microsphere technique. Acta Chir. Scand. 149:467-72, 1983.
4. Lindblad, B., Bergqvist, D., Hedner, U.: The effects of dihydroergotamine on platelets, coagulation and fibrinolysis, studied in healthy humans and in dogs. Thromb. Res. 32:35-44, 1983.
5. Lindblad, B., Bergqvist, D., Efsing, H.O., Hallböök, T., Lindell, S-E.: Changes in peripheral haemodynamics induced by dextran 70, dihydroergotamine, and their combination. A study using ultrasonic, serial phlebography, plethysmography and isotope clearance techniques. VASA, in press.
6. Loew, D.M., van Deusen, E.B., Meir-Ruge, W.: Effects on central nervous system. In: Ergot alkaloids and related compunds (eds. B. Berde & H.O. Schild), Springer Verlag, Berlin, Heidelberg, New York. pp421-531, 1978.
7. Nowak, G. & Markwardt, F.: The influence of drugs on disseminated intravascular coagulation (DIC)V. Effects of α-adrenoceptor blocking agents on thrombin -induced DIC in rats. Thromb. Res. 22:417-25, 1981.
8. Mellander, S. & Nordenfelt, I.: Comparative effects of dihydroergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation. Clin. Sci. 39:183-201, 1970.
9. Müller-Schweinitzer, E. & Brundell, J.: Modification of canine vascular smooth muscular responses to dihydroergotamine by endogenous prostaglandin synthesis. Europ. J. Pharmacol. 34:194-206, 1975.
10. Müller-Schweinitzer, E. & Brundell, J.: Enhanced prostaglandin synthesis contributes to the venoconstrictor activity of ergotamine. Blood Vessels 12:193-205, 1975.
11. Müller-Schweinitzer, E. & Stürmer, E.: Investigations on the mode of action of ergotamine in the isolasted femoral vein of the dog. Brit. J. Pharmacol. 51:441-6, 1974.
12. Müller-Schweinitzer, E. & Weidmann, H.: Basic pharmacological properties. In:Ergot alkaloids and related compunds (eds. B. Berde & H.O. Schild) Springer Verlag, Berlin, Heidelberg, New York. pp87-232, 1978.
13. Silberbauer, K., Fitscha, P., Sinzinger, H.: Beeinflussung der Venenwand - Thrombozyten-Interaktion durch Dihydroergotamin. Wien. Klin. Wochenschr. 95:577-61, 1981.
14. Svanberg, L., Bernstein, K., Kullander, S., Åstedt, B.: Effect of dihydroergotamine on coagulation factors and components of the fibrinolytic system. Acta Obstet. Gynecol. Scand. 59:251-5, 1980.
15. Ulrich, J., Jessen, B., Siggaard-Andersen, J.: Comparative effects of dihydroergotamine and Hydergin® on the blood flow, capillary filtration rate and the capacitance vessels in the human calf studied by plethysmography. Angiology 24:657-63, 1973.
16. Wagner, H.:Metabolic effects. In: Ergot alkaloids and related compunds (eds. B. Berde & H.O. Schild) Springer Verlag, Berlin, Heidelberg, New York pp.691-717, 1978.

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