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Title : THE EFFICACY OF NITROPRUSSIDE AND NITROGLYCERIN IN THE PRESENCE OF MINOXIDIL (LONITEN^{R}), A NEW ANTIHYPERTENSIVE DRUG

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Introduction. Minoxidil is a relatively new antihypertensive agent marketed under the trade name of LONITEN^{R}. Its afterload reducing properties, via direct smooth muscle vasodilation, have a long duration of action; 24-48 hrs.[1] With its recent release for clinical use, patients using minoxidil may appear for surgery. Because of minoxidil's long duration, a possibility of interaction with drugs used during anesthesia (particularly other antihypertensive agents) must be entertained. Thus, a study was undertaken to determine efficacy of the antihypertensive agents, nitroglycerin (NTG) and nitroprusside (NP), in the presence of minoxidil.

Methods. Adult male beagle dogs, mechanically ventilated and anesthetized with N_2O (1L), O_2 (2L) and enflurane (1.5-2.0%) were used in these experiments. In initial experiments the hypotensive action of minoxidil over a range of doses from 0.05 to 5.0 mg/kg IV was studied (n=17). Subsequent hemodynamic experiments were carried out using several groups of dogs (n=30). In groups 1 and 2, hemodynamic measurements were made following a 30% reduction of mean BP using nitroprusside (0.1 mg/ml) and nitroglycerin (0.6 mg/ml) infusion. In groups 3 and 4, minoxidil was administered to produce a 10-20% drop in BP followed by nitroprusside or nitroglycerin infusion to lower the mean BP to an end point of 30%↓. Hemodynamic measurements, blood gases and pH were measured at given intervals. Total mgs of NP and NTG administered over the 60 min infusion period were recorded.

Results. Administration of minoxidil over the range of 0.10-3.0 mg/kg produced a dose-related fall in mean BP with a correlation coefficient of 0.969 ($p<.0001$). Major hemodynamic changes that occurred at different minoxidil doses are shown in Table I. Results shown in Table II demonstrate that the μg/kg/min dose of NP used per torr to drop mean BP with minoxidil was not significantly different from the NP dose without minoxidil. In contrast, the administered doses of NTG per torr with minoxidil was found to be significantly less than without minoxidil treatment (Table III).

Discussion. This study has demonstrated intravenous minoxidil to have significant afterload reducing properties in dog over a wide dosage range. Analysis of the hemodynamic changes that occur at various minoxidil doses indicate dose-related effects. At doses of 0.1 mg/kg and below, there is depression in cardiac output and other parameters, while at higher doses when the blood pressure is further reduced cardiac output is increased. From the results, it would appear that the sympatho-adrenal system is involved in causing these differential hemodynamic effects.

The finding that nitroprusside's efficacy is not altered by the presence of minoxidil indicates that these two vasodilators can be used in combination without interactive consequence. On the other hand, the interactive nature of minoxidil and nitroglycerin demonstrated in this study suggests caution with this drug combination until the full extent of the interaction is determined.

TABLE I

MINOXIDIL DOSE RELATED HEMODYNAMIC CHANGES.

	% CHANGE FROM CONTROL						
MINOXIDIL	HR	XBP	SBP	DBP	SV	CI	TVR
0.10	1.5↓	18.4↓	15.0↓	7.8↓	23.3↓	24.3↓	7.5↑
0.50	0	27.5↓	27.4↓	36.0↓	2.3↑	2.3↑	31.9↓
1.00	0	37.5↓	32.0↓	36.9↓	16.4↑	16.3↑	48.7↓
3.00	0	74.0↓	68.0↓	80.0↓	52.8↑	52.8↑	84.8↓

TABLE II

AVERAGE NP DOSES USED TO LOWER BLOOD PRESSURE IN THE PRESENCE OF MINOXIDIL

MINOXIDIL		NITROPRUSSIDE		NITROPRUSSIDE (normalized)
%↓BP	plus	%↓BP	mg/kg	μg/kg/min/torr↓
20		10	0.251	0.45
10		20	0.457	0.33
0		30	0.890	0.74
20		20	0.287	0.25
WITH MINOXIDIL			MEAN	0.44 + 0.20(N=9)*
CONTROL-NO MINOXIDIL		30	MEAN	0.24 + 0.02(N=6)*

*Mean ± standard deviation, non-significant

TABLE III

AVERAGE NTG DOSE USED TO LOWER BLOOD PRESSURE IN THE PRESENCE OF MINOXIDIL

MINOXIDIL		NITROGLYCERIN		NITROGLYCERIN (normalized)
%↓BP	plus	%↓BP	mg/kg	μg/kg/min/torr↓
20		10	0.305	0.57
10		20	0.444	0.43
0		30	0.695	0.41
20		20	0.565	0.67
WITH MINOXIDIL			MEAN	0.52 + 0.22(N=9)*
CONTROL-NO MINOXIDIL		30	MEAN	2.25 + 1.64(N=6)*

*Mean ± standard deviation, $p<.02$

References.
1. Dormois J.E., et al: Minoxidil in severe hypertension: Value when conventional drugs have failed. Am Heart J. 90(3):360-368, Sept. 1975