Title: A COMPARISON OF THE HEMODYNAMIC EFFECTS OF FENTANYL AND MORPHINE IN RIGHT HEART BYPASSED DOGS

Authors: J.L. Robotham, M.D., K.C. Doherty, B.S., and D.G. Lange, M.D., Ph.D.

Affiliation: Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institution, Baltimore, Maryland 21205

Introduction The use of a right heart bypass preparation allows evaluation of a neurally intact cardiovascular system. Using this technique, morphine sulfate (MS) in the dog produced a decreased arterial resistance and increased resistance to splanchnic venous return.[1] We reasoned that if these effects were due solely to histamine release, then fentanyl (F), which is reported not to release histamine, should produce different effects.

Materials and Methods Pentobarbital anesthetized dogs were ventilated at a constant tidal volume and placed on a right heart bypass by cannulating the right atrium (RA) and pulmonary artery (PA). Pressures were measured in the RA (P_{RA}), PA (P_{PA}), left atrium (P_{LA}), aorta (Part), portal vein (P_{PV}) and the airway (Pair). The extracorporeal circuit diverted venous return through a starling resistor which controlled P_{RA} to a calibrated reservoir, variable speed pump, a heat exchanger and flow probe, into the PA. Changes in the reservoir were assumed to reflect the inverse of events in the dog, ($\triangle$ Vol). With constant PA inflow, we determined the pulmonary vascular resistance (PVR), arterial resistance (SVR), and venous compliance (Cv). Acute changes in PA inflow allowed determination of the venous time constant (τ). Excluding the reservoir, the venous return was determined by the P_{RA} allowing determination of venous resistance (Rv), and mean systemic pressure (Pms). Following control (C) measurements in dogs, F 30 mcg/kg was injected into the PA, pressures recorded at 1 and 5 minutes, and the venous bed parameters measured. Naloxone (N) 1.2 mg was then given and the protocol repeated. In 7 dogs following F and N (up to 450 mcg/kg), the acute effects of MS were evaluated. In 3 dogs MS 2 mg/kg was given instead of F. Histamine levels were measured in 4 dogs. Histamine (50 mcg) was given in one dog. Temporal controls confirmed stability of the preparation over the time required for the comparative studies. All pressures are in mmHg, Rv in mmHg/L/min, Cv in ml/mmHg, SVR and PVR in dyne sec/cm^5, $\triangle$ Vol in ml. τ in sec.

Results

	τ	Cv	Rv	Pms
C	11.6	39.1	4.72	7.36
F	14.8*	44.1	4.56	7.41
N	10.3*	33.7*	5.47	8.14

* $P \leq .05$ from the preceding value.

Acute hemodynamic changes at a constant cardiac output with F at 1 and 5 minutes:

	Part	SVR	P_{PV}	$\triangle$ Vol	P_{PA}	P_{LA}	PVR	Pair	HR
C	67.0	2678	10.0		22.0	9.0	435.	9.9	165
F1'	55.6*	2210	9.1	-26.7*	22.0	9.1	434.	9.7	166
F5'	50.7*	1973*	8.8	-110.7*	21.3	9.0	412.	9.7	140*

*P < .05

N reversed the changes. In 2 dogs, MS produced increases in both Cv and Rv. Acute hemodynamic changes following MS were qualitatively similar whether or not preceded by N (1.2-10 mg).

	Part	SVR	P_{PV}	$\triangle$ Vol	P_{PA}	P_{LA}	PVR	Pair	HR
C	75	3249	9.6		24.4	7.8	657	10.4	170
MS1'	53*	2267*	14.8*	-133*	25.8	8.1	702	12.3	154
MS5'	56*	2436*	10.3	-119*	24.9	8.6	649	12.7	157*

A repeat dose of MS 1 mg/kg alone produced no changes. Histamine decreased SVR and increased P_{PV}. Histamine levels were found to increase more than 3 fold after MS but not F.

Discussion The hemodynamic effect of F was to reduce the afterload on the left heart, and increase the τ for venous return. The lack of change in P_{LA}, in the doses used, is consistent with a negligible effect on the left ventricle.

A major difference between the hemodynamic effects of F and MS in dogs lies in the acute increase in splanchnic venous resistance which may be related to histamine induced hepatic venoconstriction provoked by MS and consistent with an increased airway resistance. N up to 450 mcg/kg, did not block the effects of MS. The lack of changes in acute hemodynamic measurements with a repeated dose of MS suggests that releasable histamine was no longer available and that tachyphylaxis to the direct hemodynamic effects of MS occurred. With F, opiate receptors presumably mediate both a decreased SVR and an increased τ for venous return. While an increased Cv usually contributed to the increased τ, changes in both Rv and Cv may be influenced by neural reflexes stimulated by the fall in Part. Since Pms did not change and Cv increased, the fall in $\triangle$ Vol implies an increase in both the stressed and unstressed venous vascular volumes.

References

1 Green JF, Jackman AP, Parsons G: The Effects of Morphine on the Mechanical Properties of the Systemic Circulation in the Dog. Circ. Res. 42:474-478, 1978.