TITLE: INHIBITION OF PSEUDOCHOLINESTERASE (PCHE) ACTIVITY PROTECTS FROM COCAINE INDUCED CARDIORESPIRATORY TOXICITY (CICT) IN RATS

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INTRODUCTION: Cocaine is frequently used to infiltrate the mucous membranes in certain types of surgery. Cocaine facilitates surgery by shrinking the mucous membranes and by reducing the bleeding at the site of surgery from its vasoconstricting property. Cocaine is an ester type local anesthetic with an elimination half life of about 30 min and is considered to be metabolized primarily by an enzyme called PCHE. Some of the causes for alterations in PCHE activity include certain drugs and chemicals, liver disease, pregnancy, and genitically induced. It is logical to postulate that if PCHE is needed for the metabolism of cocaine, patients with a decreased or absent PCHE activity would be at an increased risk for CICT. The purpose of the present study is to investigate the effect of inhibition of PCHE activity on CICT.

METHODS: Fifty eight male Sprague-Dawley rats were randomly divided into two equal groups. Group 1 rats were given 1 mg/kg ISO-OMPA (a specific PCHE inhibitor) subcutaneously and group 2 rats were given an equal volume of saline. Thirty min later rats were anesthetized with intraperitoneal administration of sodium pentobarbital (40 mg/kg), a femoral vein was cannulated, and blood was collected for PCHE assay. All rats were given 10 mg/kg cocaine intravenously (iv) as the first dose (least toxic dose as determined from previous studies). Thirty min later half of the rats that survived in each group received 12 mg/kg and the other half received 13.5 mg/kg cocaine iv as a second toxic dose. Monitoring of rats during the experiment included heart rate and rhythm (EKG), and respirations. Rats were classified as survivors or fatalities at the end of 5 min following each injection of cocaine. Rats that sustained adequate ventilation, color, and heart rate were classified as survivors and rats that developed apnea, cyanosis, and agonal rhythm with no cardiac impulse were classified as dead. PCHE activity was determined by a colorimetric method. Data were analyzed by Fisher's exact test and $P < .05$ was considered significant.

RESULTS: The mean PCHE activity of groups 1 and 2 were 0.6 ± .2 and 7.3 ± .7 units, respectively ($P < .05$, Student's t-test).

	GROUP 1 RATS			GROUP 2 RATS			
Cocaine dose	Died	Total	%	Died	Total	%	P
1st 10mg/kg	5	29	17	2	29	7	NS
2nd 12mg/kg	2	11	19	6	12	50	NS
2nd 13.5mg/kg	3	13	23	10	15	67	<.03
2nd combined doses	5	24	21	16	27	59	<.005

DISCUSSION: It was previously postulated that a decrease in PCHE activity may substantially increase the risk for CICT. Our present results show that a near complete inhibition of PCHE activity did not increase the incidence of CICT. Actually the rats with a decreased PCHE activity have fewer fatalities from CICT when compared to the rats with a higher PCHE activity. The reason for this surprising finding is not obvious from this study. It is possible that one of the metabolites of cocaine formed by PCHE may be responsible for an increased incidence of fatalities in rats with higher PCHE activity. In conclusion, our results suggest that a decrease in PCHE activity does not seem to put the patients at a higher risk for acute CICT.

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TITLE: FUNCTIONAL DAMAGE OF THE CORONARY ENDOTHELIUM AFTER A SHORT DURATION OF ISCHEMIA IS REVERSIBLE.

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Coronary endothelium actively regulates the underlying smooth muscle. Mechanical removal or destruction of endothelium enhances vasoconstriction and impairs vasodilation. Coronary artery spasms are typical in variant, unstable, and post-infarction angina. We have shown previously that ischemia ranging from 10 - 30 min causes functional damage of the coronary endothelium in vitro resulting in increased contractility and impaired endothelium dependent vasodilation [1]. Such short duration of ischemia produces reversible impairment of myocardial function, known as "stunning of myocardium." We studied whether functional damage of the endothelium after a brief ischemia (15 min) was reversible following reperfusion.

In anesthetized dogs, a flow probe was placed around the left anterior descending coronary artery (LAD) for measurement of blood flow changes. A rubber band was looped around LAD for occlusion and reperfusion. Intracoronary infusions of U468944 (U4), a thromboxane mimic, acetylcholine (acetyl), an endothelium-dependent vasodilator, and nitroprusside, an endothelium-independent vasodilator, were performed. Changes in coronary blood flow before 15 min of coronary occlusion, and after 15, 30, 60, 90, and 120 min of reperfusion were recorded.

15 min of ischemia and subsequent reperfusion caused hyper-contractility to U4 which was most pronounced after 15 min reperfusion and normalized after 60 min reperfusion. Endothelium-dependent vasodilation was maximally impaired after 15 min reperfusion and gradually recovered after 90 min reperfusion (Table). Endothelium independent vasodilation was not affected by ischemia and reperfusion. The regulation of coronary tone by the endothelium was severely impaired after 15 min ischemia, but regulatory function was recovered after 60 - 90 min reperfusion.

References

1. Cardiovascular Thoracic Anesthesia Society Annual Meeting, 1990 (in press).

Table

		Control	Reperfusion				
		pre-ischemia	15	30	60	90	120
Decrease (%)	U4 2 µg	12.6 ± 2.9	36.2* ±10.1	25.0* ± 5.3	---	---	---
	U4 4 µg	23.3 ± 5.6	---	---	25.8 ± 7.3	22.5 ± 8.1	22.8 ± 7.9
Increase (%)	Acetyl 1 µg	93.8 ± 27.8	25.6* ± 9.0	55.2* ± 16	63.7* ± 23	87.8 ± 27	97.0 ± 26

- 4 µg of U4 caused extreme vasospasm in early reperfusion phase. 2 µg was tested in 15 - 30 min reperfusion.
Mean ± SEM, * $p < 0.05$