Title

Bucillamine, a diffusible antioxidant, prevents ischemia/reperfusion injury in an ex-vivo rat liver model.

Journal

TRANSPLANTATION, 69(8)

ISSN

0041-1337

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Publication Date

2000

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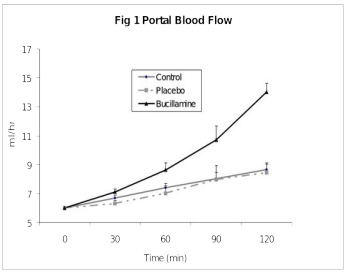
Title: Bucillamine, a diffusible antioxidant, prevents ischemia/reperfusion injury in an *ex-vivo* rat liver model

Background: Hepatic ischemia/reperfusion (I/R) injury is associated with early and late graft failure after liver transplantation. A major mechanism is the generation of highly cytotoxic reactive oxygen intermediates. This study assessed the protective efficacy against I/R injury of bucillamine [N-(2-mercapto-2-methylpropionyl)-L-cysteine], a diffusible gluthathione analogue with two donatable sulfhydryl groups, in an *ex-vivo* rat liver model.

Methods: Sprague Dawley rat livers were harvested and stored for 24h at 4˚C in UW solution and then reperfused with rat blood for 2h on an isolated perfusion rat liver apparatus. Three groups were studied (n=6 livers/group): an untreated control group, a group treated with placebo (vehicle only), and a group treated with bucillamine. Treatment groups received 10 mg bucillamine or placebo intraportally at the time of harvest and 90 mg bucillamine or placebo in the rat blood perfusate. All livers were assessed for portal vein blood flow, bile production, and plasma SGOT levels at 30 min intervals. At the end of the experiment, liver samples were collected for measurement of carbonyl proteins and lipid peroxides and blinded histological evaluation of I/R injury.

Results: Livers harvested from rats treated with bucillamine showed significantly increased portal venous blood flow ($p < 0.0001$, 120 min) (Fig. 1) and bile production (Table 1) compared with untreated or placebo-treated controls. I/R-induced hepatocyte injury, as measured by SGOT release, was significantly reduced in the bucillamine group compared with untreated or placebo-treated controls (Table 1). Histopathologic findings paralleled these results with less hepatocyte injury and lobular disarray in the bucillamine than control groups [Banff's scores 3.3±0.5, 3.2±0.7, and 1.7±0.5 (mean±SE) in the untreated, placebo-treated, and bucillamine-treated groups, resp.]. Carbonyl proteins, a protein oxidation product, and lipid peroxides were each significantly reduced in the bucillamine-treated group compared with untreated or placebo-treated controls (Table 1).



	Control	Placebo	Bucillamine	p_1**	p_2**
Bile Production (ml/2h)	0.14±0.02 *	0.07±0.02	0.39±0.01	0.0001	0.0001
SGOT (IU/L) at 120 min	206.0±5.5	218.0±25.4	124.8±7.6	0.004	0.0002
Carbonyl Proteins (nmol/mg protein)	2.00±0.11	1.29±0.24	0.42±0.14	0.0001	0.003
Lipid Peroxides (μmol/mg protein)	0.97±0.09	0.70±0.10	0.31±0.05	0.0001	0.004

*All data are Mean±SE; **p_1=Bucillamine vs. Control; **p_2=Bucillamine vs. Placebo

Conclusion: Bucillamine provides protection against I/R injury to rat livers in an *ex-vivo* model of cold ischemia followed by reperfusion. Treatment with bucillamine improved liver function, decreased hepatocyte injury, and prevented oxidative stress. Bucillamine, a diffusible antioxidant, has substantial potential for the prevention of I/R injury and its consequences in liver transplantation.

Abstracts of Transplant 2000 Meeting, Annual Scientific Meeting of the American Society of Transplant Surgeons, Chicago, IL May 13-17, 2000