Bucillamine: A Potent Thiol Donor with Multiple Clinical Applications

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ABSTRACT

Bucillamine has potential to attenuate or prevent damage during myocardial infarction, cardiac surgery and organ transplantation. Bucillamine, a cysteine derivative that contains two donatable thiol groups, is capable of replenishing the thiol group in glutathione, thereby reactivating this endogenous defense against oxidant injury. Bucillamine rapidly enters cells by the same mechanism that normally transports the amino acid cysteine. Bucillamine is a more potent thiol donor than other cysteine derivatives: approximately 16-fold more potent than N-acetylcysteine (Mucomyst®) in vivo. In addition bucillamine appears to have additional anti-inflammatory effects unrelated to its antioxidant effect. Oral bucillamine is used clinically in Asia for treatment of rheumatoid arthritis. There is a strong preclinical evidence that parenteral infusion of this agent is efficacious in acute settings characterized by inflammation and oxidative stress. In an investigator-blinded, rigorous intact dog model, consisting of 90 min of coronary artery occlusion and 48 h of reperfusion, bucillamine, given i.v. during the first 3 h of reperfusion, substantially reduced myocardial infarct size. Livers exposed to 24 h of cold ischemia were markedly protected by bucillamine in several transplantation models. In Phase I human studies in normal volunteers, bucillamine at doses up to 25 mg/kg/h i.v. for 3 h elicited no serious toxicity. On the basis of pharmacokinetic analyses of blood levels during these studies it was concluded that bucillamine, infused at i.v. doses ≥10 mg/kg/h for 3 h to humans could be expected to be therapeutically effective in myocardial infarction, organ transplantation and other acute inflammatory syndromes.