

SELECTIVE PREVENTION OF ORGAN INJURY IS SEPSIS AND SHOCK USING SELECTIVE RELEASE OF NITRIC OXIDE VULNERABLE ORGANS

This is a divisional of U.S. application No. 08/509,558 filed Jul. 31, 1995, now U.S. Pat. No. 5,714,511.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a method for the treatment of sepsis and of shock. More particularly, the present invention is directed to a method for the treatment of sepsis and shock using nitric oxide-containing compounds that selectively release nitric oxide under physiological conditions in vulnerable organs to prevent organ injury.

BACKGROUND OF THE INVENTION

Sepsis is generally understood to be the presence in the blood or tissues of various pus-forming and other pathogenic organisms or their toxins. Cecil, Textbook of Medicine 17th Ed., W. B. Saunders Company pp. 1473-1476, 1985. Serious complications arise when the infection spreads from the original site to the bloodstream. The presence of viable bacteria in the bloodstream can lead to both microbiologic complications and inflammatory complications. Microbiologic complications are known to cause direct tissue or organ damage. Inflammatory complications can result in tissue or organ damage independent of the toxins produced by the bacterium itself. The end stage of the various indications of sepsis is the systemic vascular collapse commonly known as septic shock.

Typically, treatment of sepsis has involved the use of antibiotics and anti-inflammatory agents. The therapy of shock associated with sepsis involves volume replacement as an essential component. Sufficient quantities of an appropriate solution, including, where appropriate, whole blood, are administered to the septic patient in an effort to provide the requisite volume support.

Within the last several years, it has been suggested that the release of NO might be involved in sepsis shock. Wright et al. "Protective and Pathological Roles of Nitric Oxide in Endotoxin Shock" Cardiovascular Research 26, pp. 48-57, 1992. Wright et al. conclude that the use of an inhibitor of both the Ca²⁺ dependent and Ca²⁺ independent nitric oxide synthesis in the treatment of lipopolysaccharide induced shock in anaesthetized New Zealand white rabbits was deleterious. The use of an NO donor such as S-nitroso-N-acetyl-penicillamine (SNAP) was suggested to overcome the deleterious effect of NO synthase inhibition. Interestingly, however, a Letter to the Editor by Meyer and Traber suggests that the study of Wright et al. was incomplete and that NO synthesis inhibition in a model of hyperdynamic sepsis completely reversed the alteration in hyperdynamic endotoxemia. Symington et al. "Protective Action of S-Nitroso-N-Acetylpenicillamine (SNAP) in a Rat Model of Hemorrhagic Shock" *Meth Find Exp. Clinical Pharmacol* 1992, 14(10):789-797 discuss the use of the NO donor SNAP in hemorrhagic shock and suggest that they have shown significant protective effects of SNAP in hemorrhagic shock in rats. Carey et al. "Antishock and Endothelial Protective Actions of a NO Donor in Mesenteric Ischemia and Reperfusion" *Circulatory Shock* 38:209-216 (1992) discusses the use of nitric oxide (NO) donors known as sydnonimines which are stated to spontaneously liberate NO at a physiological pH for circulatory shock. The authors conclude that the NO donor compound exhibited a protective effect in mesenteric ischemia reperfusion in cats.

The nitric oxide-releasing compounds that release NO spontaneously in physiological conditions are not entirely satisfactory because they release nitric oxide systemically. Nitric oxide in its pure form is a highly reactive gas having limited solubility in aqueous media (WHO Task Group on Environmental Health Criteria for Oxides of Nitrogen, *Oxides of Nitrogen*, Environmental Health Criteria 4 (World Health Organization: Geneva, 1977)). Nitric oxide, therefore, is difficult to introduce reliably into most biological systems without premature decomposition.

A number of compounds have been developed which are capable of delivering nitric oxide in biological systems. Such compounds include compounds which release nitric oxide upon being metabolized and compounds which release nitric oxide spontaneously in aqueous solution.

Those compounds which release nitric oxide upon being metabolized include the widely used nitrovasodilators glyceryl trinitrate and sodium nitroprusside (Ignarro et al., *J. Pharmacol. Exp. Ther.*, 218, 739-749 (1981); Ignarro, *Annu. Rev. Pharmacol. Toxicol.*, 30, 535-560 (1990); Kruszyna et al., *Toxicol. Appl. Pharmacol.*, 91, 429-438 (1987); Wilcox et al., *Chem. Res. Toxicol.*, 3, 71-76 (1990)), which are relatively stable but release nitric oxide only on activation. While this feature may be an advantage in some applications, it also can be a significant liability. For example, tolerance to glyceryl trinitrate can develop via the exhaustion of the relevant enzyme/cofactor system (Ignarro et al., *Annu. Rev. Pharmacol. Toxicol.*, 25, 171-191 (1985);

Kuhn et al., *J. Cardiovasc. Pharmacol.*, 14 (Suppl. 11), S47-54 (1989)). Also, prolonged administration of nitroprusside results in the metabolic production of cyanide, which leads to toxicity (Smith et al., "A Potpourri of Biologically Reactive Intermediates" in *Biological Reactive Intermediates IV. Molecular and Cellular Effects and Their Impact on Human Health* (Witmer et al., eds.), Advances in Experimental Medicine and Biology Volume 283 (Plenum Press: New York, 1991), pp. 365-369). S-Nitroso-N-acetylpenicillamine has been reported to release nitric oxide in solution and to be effective at inhibiting DNA synthesis (Garg et al., *Biochem. and Biophys. Res. Comm.*, 171, 474-479 (1990)). This and other S-nitrosothiols are widely considered to release NO without activation, but it has recently been shown that trace metal ions can profoundly catalyze this process (McAninly et al., *J. Chem. Soc. Chem Commun.*, 1758-59, 1993), suggesting that reports of their "spontaneous" NO generation may have depended on unnoticed catalytic effects. It has also been demonstrated that spontaneous NO release cannot account for in vitro vaso relaxation by S-nitrosothiols (Kowaluk and Fung, *J. Pharmacol., Exp. Ther.*, 255, 1256-1264, 1990.)

A class of NO donor agents that release NO truly spontaneously, i.e., without activation, is the nitric oxide-nucleophile complexes known as diazeniumdiolates, also known as NONOates, which are described in the scientific literature (e.g., Drago, *ACS Adv. Chem. Ser.*, 36, 143-149 (1962); Longhi and Drago, *Inorg. Chem.*, 2, 85 (1963). Maragos et al., *J. Med. Chem.*, 34, 3242-3247 (1991)), and in U.S. patents as referred to below. Recently, a method for treating cardiovascular disorders in a mammal with certain nitric oxide-nucleophile complexes was disclosed, e.g. in U.S. Pat. No. 4,954,526. These compounds contain the anionic N₂O₂⁻ group or derivatives thereof. See also, Maragos et al., supra. Many of these compounds have proven especially promising pharmacologically because, unlike nitrovasodilators such as nitroprusside and nitroglycerin, they release nitric oxide without first having to be activated. The only other series of drugs currently thought to be