Gö 6983: A Fast Acting Protein Kinase C Inhibitor that Attenuates Myocardial Ischemia/Reperfusion Injury

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ABSTRACT

Reperfusion injury is characterized by a decrease in endothelial release of nitric oxide within 5 min after reperfusion, increased leukocyte-endothelium interaction, and transmigration of leukocytes into the myocardium, producing cardiac contractile dysfunction. Gö 6983 is a fast acting, lipid soluble, broad spectrum protein kinase C inhibitor. When administered at the beginning of reperfusion, it can restore cardiac function within 5 min and attenuate the deleterious effects associated with acute ischemia/reperfusion. Gö 6983 may offer greater cardioprotection than other broad-spectrum PKC inhibitors in postischemic reperfusion injury because it inhibits PKCζ as well as four other isoforms. The cardioprotection is associated with decreased leukocyte superoxide release and increased endothelial derived nitric oxide from vascular tissue.

In vitro studies of human tissue showed that Gö 6983 significantly inhibited antigen-induced superoxide release from leukocytes of patients previously sensitized to tree pollen. In human vascular tissue, Gö 6983 inhibited intracellular Ca²⁺ accumulation, suggesting a mechanism for its vasodilator properties. These studies suggest that Gö 6983 would be an effective compound to use in a clinical ischemia/reperfusion setting of organ transplantation and/or cerebral ischemia where inhibiting superoxide release and vasoconstriction in postischemic tissues would allow for better restoration of organ function during reperfusion. However, given the broad-spectrum action of Gö 6983, careful titration of the dose regimen would be recommended to ensure a successful outcome in the setting of organ transplantation and/or cerebral ischemia.