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Inhibitory Effect of Selenite and Other Antioxidants on Complement-Mediated Tissue Injury in Patients with Epidemic Hemorrhagic Fever

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ABSTRACT

Results on the inhibitory effect on complement activation by sodium selenite, sodium glycyrrhizin, and a selenium–glycyrrhizin compound in hemorrhagic fever patients are presented.

Index Entries: Anti-inflammatory effect; complement activation; glycyrrhizin; hemorrhagic fever; oxygen scavengers; selenite; selenium–glycirrhizin compound.

INTRODUCTION

Epidemic hemorrhagic fever (EHF) is one of two major viral infectious diseases in China. Although it is difficult to cope with, it is a treatable disease. Its management should be based on knowledge of the current thinking about the pathogenesis of the disorder, so that patients receive the most appropriate treatment.

The steadily increasing knowledge of pathological mechanisms leading to tissue destruction in EHF has provided the basis to open up new therapeutic venues with novel pharmacological and biological agents.

These act more specifically by interfering with ongoing pathological processes than treatment principles like anti-virus vaccines and immunosuppressive agents, which have been available over the last decade.

Years of research on anti-inflammatory studies have made the author believe complement plays a central role in EHF pathogenesis.

The activation of the complement system by immune complexes also brings the concerted toxic oxygen products from activated polymorphs'

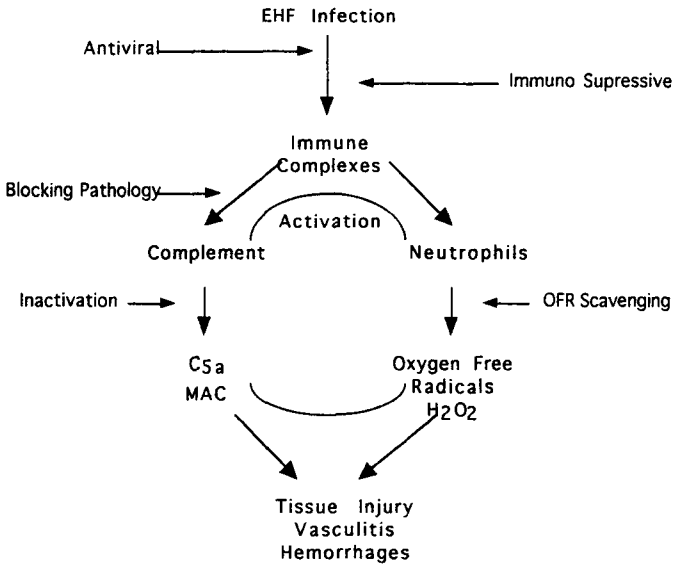

Fig. 1. Hemorrhagic fever development pathways. Treatment strategies are shown at the points where development of the disease may be stopped.

respiratory burst, resulting in further activation of complement, thus forming an amplification feedback cycle, which gives greater inflammation and tissue injury (Fig. 1).

These new insights into mechanisms of the role of immune complex in human diseases will give us new, exciting, and quite novel approaches to interventions of the inflammatory diseases that are caused by immune complexes.

It was the author's idea to inhibit in some way the complement activation with oxygen free radicals scavenging to suppress the pathology of tissue injury and inflammation in spite of the infection and favoring the cure of this disease.

During an investigation of complement-mediated tissue injury and inflammation, selenium in the form of sodium selenite was found to possess an inhibitory effect on complement activation both in vivo (Fig. 2) and in vitro *(1,2)*.

Also, glycyrrhizin, a major component of a herb licorice, which is widely used to treat chronic hepatitis in Japan *(3)*, and is a popular herbal medicine in China *(4)*, was also recognized to have a similar effect of suppressing complement activation *(4,5)*.

RESULTS

The effective inhibition of Se(II), usually begins at 0.002*M* selenite in vitro, and at 20 μg/25 g body wt mice, by iv injection in vivo.

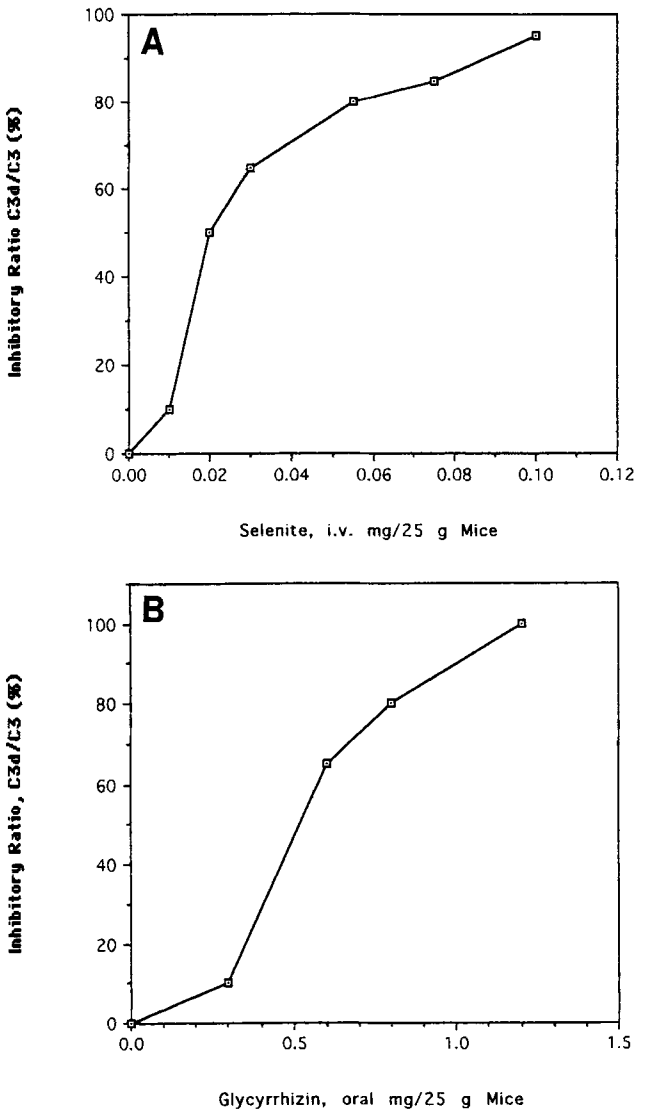

Fig. 2. In vivo tests of the inhibitory effect of endotoxin, **(A)** by iv sodium selenite, $n = 6$, **(B)** by sodium glycyrrhizin, oral, $n = 6$.

It is very interesting that both selenium and glycyrrhizin are known antioxidants, the latter also as an OFR scavenger, but that they act in a different fashion. The discovery of the new inhibiting properties of these two compounds has prompted the author to use these as blocking agents to identify the pathological mechanism the author has proposed, as well as a new therapeutic approach of hemorrhagic fever.

Guided by this hypothesis, the "anti-inflammatory" approach to treat disease in relation to immune complex formation has been success-

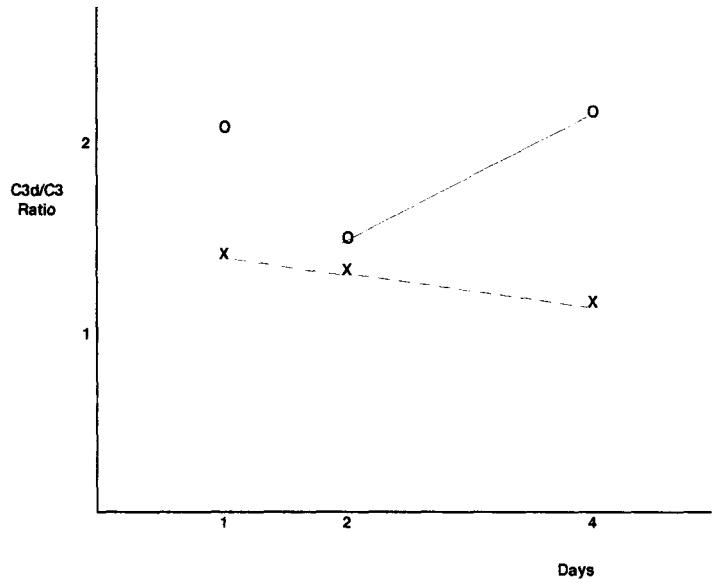

Fig. 3. Plasma complement activation estimated by immunoelectrophoretic technique for treated and untreated EHF patients. Normal C3d/C3 ratio is ≤ 1.20. -O- are values for dead subjects; no treatment was given. -X- are values for recovered subjects after treatment with sodium selenite.

fully carried out in the treatment of EHF during an epidemic episode in the Henan province by administration of sodium selenite alone.

These EHF cases were treated by multiple oral doses of 2 mg selenite/d in the first 9 d of hospitalization in addition to general management of 80 cases, including fulminant, severe, and moderate types.

Admirable results were obtained *(6)*:

1. The key role of complement activation in pathogenesis of EHF was identified (Fig. 3);
2. A remarkable therapeutic effect was observed, since the mortality of EHF fulminant cases was reduced from 100% of the untreated cases to 36.6% by treatment with selenite (Fig. 4); and
3. The inhibition of complement and platelets by selenite was indeed effective (Table 1).

Since complement activations are in close relationship with OFR activities, we expect a more efficient suppression of immune complex-mediated tissue injuries by additional checking on OFR activity with a combined seleno–glycyrrhizin compound. Therefore, further experiments on the prevention of the induction of Arthus vasculitis of skin or liver tissue in mice with a seleno–glygyrrhizin compound have been carried out successfully in animal models (Fig. 5).

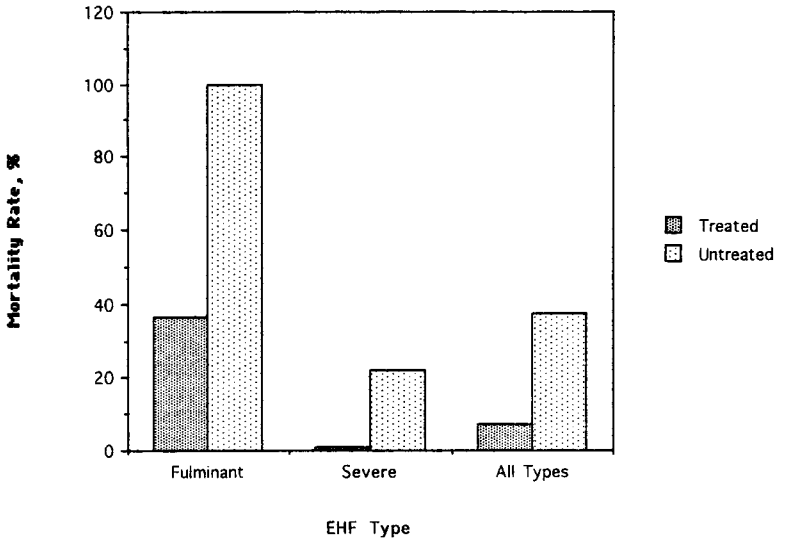

Fig. 4. Effect of treatment with sodium selenite on the mortality rate of EHF patients.

Table 1
Complement Activation Estimated by Immunoelectrophoretic Technique for Selenite-Treated and Untreated EHF Patients[a]

	C3d/C3 ratios		
	1 d	2 d	4 d
Untreated subjects	2.06 ± 0.68	1.73 ± 0.342	2.46 ± 0.63
Selenite treated	1.75 ± 0.66	1.52 ± 0.65	1.37 ± 0.42

[a]Normal C3d/C3 ratio is ≤ 1.20.

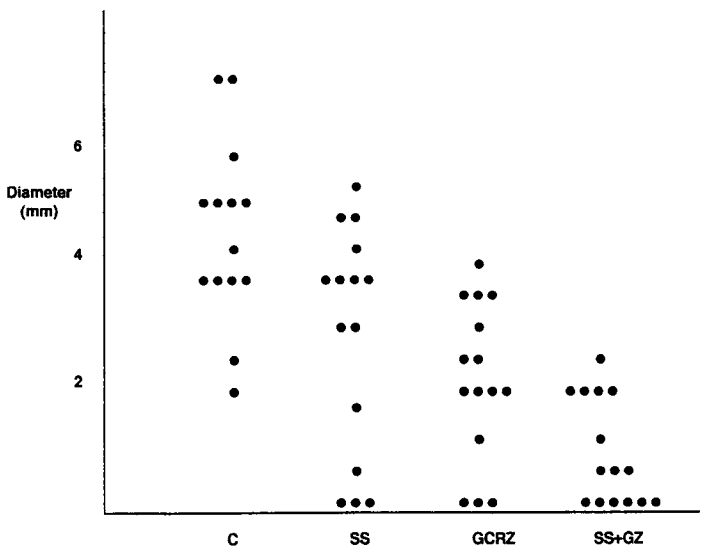

Fig. 5. Effect of treatment on arthus skin reaction. C = controls; SS = sodium selenite; GCRZ = glycyrrhizin; SS + GZ = sodium selenite plus glycyrrhizin.

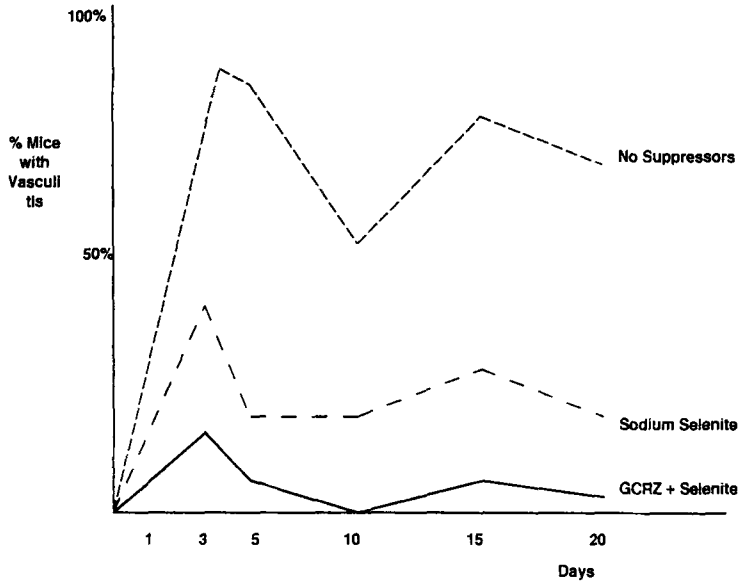

Fig. 6. Time-course effect of treatment with sodium selenite and sodium selenite plus glycyrrhizin on mice vasculitis.

Results are quite encouraging. The overall suppression of development of liver vasculitis was 30–40% better in seleno–glycyrrhizin-treated than in selenite-treated alone (Fig. 6). It indicated the potential of combined seleno-glycyrrhizin as a new type of anti-inflammatory agent with potential to treat diseases that bear similar pathogenic mechanisms to that of hemorrhagic fever.

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