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In vivo Studies of Antioxidant and Hepatoprotective Effects of Novel Bismuth (V) Metalloantibiotic in *Staphylococcus aureus* Infected Mice

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ABSTRACT

Bismuth (V) was complexed with antibiotics Chloramphenicol (CHL) and Streptomycin (STR) for synthesizing a novel metalloantibiotic (BCS). This BCS was evaluated for its relative hepatoprotective and antioxidant effects. For this adult Balb/c mice were randomly divided into six groups (A-F). Groups, B to F were challenged with ***Staphylococcus aureus*** (ATCC-33862) intraperitoneally. Group B was control infected and C, D, E and F were treated with STR, CHL, CHL+ STR ligand and BCS metalloantibiotic, respectively. The control group (A) was administered with 0.9% physiological saline adlibitum. Antioxidants enzymes like SOD, CAT, GR, GPx and GSH in serum were assayed for knowing the augmentation and treatment of installed infection. % change in enzymatic antioxidants was significant ($p<0.05$) in experimental groups than control group. Among treated group, BCS treated showed least fluctuation in all antioxidant enzymes. Change in serum AST, ALT, ALP and CPK levels were significantly different ($p<0.05$) in experimental groups compared to control group. Thus, it was concluded that the combination of this metalloantibiotic could be a potent one with less side effects in future for severe bacterial infections like MRSA.

Key words: Chloramphenicol, Streptomycin, Bismuth (V) metalloantibiotic, hepatoprotective, hepatotoxicity, antioxidants, antibiotics.

INTRODUCTION

Metal ions play a key role in the action of metalloantibiotics and are involved in specific interactions of these antibiotics with proteins, membranes, nucleic acids, and other biomolecules [1-2]. The ligand environment of transition metals can be considerably altered upon administration of a therapeutically effective dose of an antibacterial drug[1-2]. This change in balance between the metal ion and the ligand may have a profound effect upon the activity of the drug against potentially disease causing bacteria[1-2]. It has also been reported that transport of organic ligands into the cells can be facilitated by the formation of metal complexes[3].

Use of bismuth salts in formation of metalloantibiotic is a novel concept with the advent medicinal use of bismuth. Bismuth is used for the treatment of gastric ulcer has been widely reported [4-5]. According to Vertesy et al. [5], bismuth compounds are useful in peptic ulceration in three ways: Bismuth protects the stomach wall by making a physical barrier against stomach contents in the ulcer, it has positive biochemical effects on the stomach wall, and it has antibacterial activity. Binding of Bismuth to the ferric ion-binding proteins has also been reported by Guo et al. [6]. It is believed that bismuth in complex form is more stable and better tolerated than bismuth in ionic form [7-9]. Bismuth based Ampicillin and Chloramphenicol metalloantibiotics have been investigated in urinary tract infections and proved to be Bacteriostatic[7-9]. No attempt has been made for a metalloantibiotic of Bi, Chloramphenicol (CHL) and streptomycin (STR) which are currently the first choice antibiotics in developing countries and used widely in the treatment of serious bacterial infections [10-11]. A major problem in therapy with these antibiotics is their high toxicity. This relatively high toxicity causes a major limitation factor in their usefulness. The adverse toxic effects of these antibiotics may result from 1) complex formation with transition metal ions in body 2) Due to oxidative reactions subsequently promoted by the metabolites of these antibiotics 3) co-administration of transition metal chelators often associated with drugs and 4) hyper or hypo expression of enzymatic antioxidants in response to these drugs [10-11].

Thus the findings of new metal based metalloantibiotics have been largely based on ability of metals to enhance inhibitory potential of antibiotics with relatively less toxicity. A number of combinations with known antibiotics are already being recommended [12-14]. Efficacy of some therapeutic agents has been reported to have increased upon coordination to transition metals [14-15]. In past two decades, thousands of compounds have been formulated based on this well conceived idea and have been subsequently screened but few of them have successfully implemented against increasing bacterial antibiotic resistance. Some metal-based antibiotics such as bleomycin, streptonigrin, and bactracin have gained recognition and are more effective than their pure drugs [16-19]. No data is available for ligand formation of any metal ion with streptomycin and Chloramphenicol though a detailed cauterization of Cu (II) complex with streptomycin and its biological activity is suggested [14-15]. Interaction of a CHL and STR with bismuth may result in an uncharged complex which would be better absorbed through different biological membranes and would show higher bioavailability than the charged one. This may lead to enhanced levels of both the antibiotics and bismuth ions at the site of action. A preliminary work on bismuth-CHL, STR complex and its antibacterial activity against some Gram-positive and Gram-negative bacteria has been reported by us [20]. In continuation to it we present a preliminary overview of toxicity in response to this metalloantibiotics in MRSA infected mice.

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MATERIAL AND METHODS

Chemicals

Readymade solution of STR (1 mg/ml in 1 mm EDTA) and CHL (100 mg/ml in ethanol: isopropanol (95:5) were purchased from Sigma-Aldrich chemicals,