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The Protective Effects of N-Acetl-Cysteine, Oxo-Thiazolidine-Carboxylate, Acetaminophen and Their Combinations against Sulfur Mustard Cytotoxicity on Human Skin Fibroblast Cell Line (HF2FF)

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ABSTRACT

Background: Using human skin-fibroblast cell line HF2FF, the efficacy of some drugs was evaluated against sulfur mustard (SM) cytotoxicity. The drugs were the sulfhydryl containing molecule including N-acetylcysteine (NAC), 2-oxo-thiazolidine-4-carboxylate (OTC) and acetaminophen as glutathione (GSH) stimulator pathway. **Methods:** The protective effects of NAC (0.1 mM), OTC (1.8 mM), and acetaminophen (25 mM) alone or in combination with each other were evaluated on SM (180 μM)-induced cytotoxicity. NAC and OTC were applied with SM simultaneously and acetaminophen 30 min before SM exposure, incubated for 1 h and then were rinsed and incubated with fresh medium. The efficacy was evaluated by determination of cells viability, intracellular GSH level and catalase activity 1 and 24 h post SM exposure or co-treatments. **Results:** The cells viability was decreased 21.8% and 55.2%, respectively for 1 and 24 h post SM (1 h exposure) incubation. So, the 1-h SM exposure and 24-h treatment incubation were selected for evaluation. While, NAC alone treatment increased the cells viability (25%), GSH level (320%) and catalase activity (18%), the most effective combination was NAC plus OTC and acetaminophen which increased more significantly the cells viability (about 40%), GSH level (470%) and catalase activity (100%). **Conclusion:** The most effective combination was NAC (0.1 mM) plus OTC (1.8 mM) and acetaminophen (25 mM) which should be used before or concomitant with SM exposure. These drugs may reduce SM toxicity possibly by increment of GSH level and catalase activity. This efficacy needs to be confirmed by *in vivo* study. *Iran. Biomed. J. 13 (4): 149-155, 2009*

Keywords: Sulfur mustard (SM), Skin fibroblast cells, N-acetyl-cysteine, 2-oxo-thiazolidine-4-carboxylate (OTC), Acetaminophen

INTRODUCTION

Sulfur mustard (SM, 2, 2-dichlorodiethyl-sulfide) is an alkylating agent that has been used as chemical weapon [1]. SM is a highly toxic chemical agent and still remains a threat to both civilians and military personnel. Although some beneficial effects have been observed with some drugs such as vitamins C, E, niacinamide [2], amifostine [3] and hexamethylene tetramine [4, 5] on tissue culture and animal models, the antidote activity of the tested compounds have been too weak to be used as protecting agents against SM [6]. Despite many years of research on this agent, the cytotoxicity mechanisms induced by mustard and the initial events leading to the cell death is not completely understood. The proposed biochemical mechanism for mustard-induced toxicity involves the process of alkylation of cellular targets. The DNA alkylation provokes the activation of poly (adenosine di-phosphate-ribose) polymerase (PARP) resulting in a rapid depletion of NAD^+/ATP metabolites leading to cell death [6, 7]. Moreover, the oxidative stress is likely involved in mustard-induced acute toxicity following glutathione (GSH) depletion [8-10]. Indeed, alkylating agents are known to induce GSH depletion [2, 11, 12] which strongly contributes to lipid peroxidation and cell

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