ROLE OF MESNA TO REDUCE HOMOCYSTEINE LEVELS THROUGH SH/SS EXCHANGE REACTION: POSSIBLE THERAPEUTICAL APPLICATIONS IN HYPERHOMOCYSTEINEMIC PATIENTS

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Homocysteine (Hcy) is a non-protein-forming sulfhydryl amino acid involved in the metabolism of the essential amino acid L-methionine. Numerous studies have implicated elevated plasma total Hcy (tHcy) as independent risk factor for the development of atherosclerotic and occlusive vascular disease (1, 2). Despite a variety of scientific contributions, the mechanism of Hcy toxicity is still unknown, and one recent strategies of therapeutical intervention is to lower plasma tHcy by SH/SS exchange reactions (thiol echange)(3). Mesna (2-mercaptoethane-sulfonate) is a thiol widely used for the prevention of hemorrhagic cystitis caused by the oxazaphosphorines in cancer chemotherapy protocols and its administration alone and in combination with ifosfamide has been shown to reduce plasma levels of total glutathione (tGSH) and the GSH precursors cysteine (Cys) and homocysteine (Hcy) (4). However in most clinical studies, total amount of plasma thiols but not each redox species (reduced, oxidised and protein-thiol mixed disulfides) have been investigated (4, 5).
In this study, we have investigated the *in vitro* effects of mesna on major plasma thiols (Hcy, GSH, Cys and CysGly) and corresponding disulfides and protein-bound mixed disulfides. In particular the role of mesna to reduce plasma levels of homocysteine-albumin mixed disulfides, the major plasma species of Hcy, was investigated. Hcy was added and experiments were carried out to decipher the mesna action to plasma of healthy subjects (n=8) and equilibrated. Increasing concentrations range of mesna were then added and incubated at 37°C and plasma aliquots were removed at selected time intervals and concentration of all redox species of Hcy, Cys, GSH and CysGly were measured using a high-performance liquid chromatography (HPLC) method. Five-hundred micromolar mesna had a greater effect, increasing free plasma Hcy and Cys and decreasing corresponding protein-bound mixed disulfides. According to clinical computation studies carried out to know pKa value of the various thiols and other studies concerning mechanisms of albumin dethiolation by thiols (see comunication of Summa D., at this meeting), we assume that the role of mesna to detach Hcy from Hcy-albumin mixed disulfide is related to its relatively high pKa. This assay can be useful screen drugs able to reduce plasma.
Further studies are necessary to establish the safety of mesna as therapeutical intervention to reduce Hcy levels of cardiovascular and other diseases.

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