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Many ways of lung protection by low amifostine doses

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The letter by Zhengdong and co-authors raises an important point and invites discussion of the apparent controversies in our current understanding of the therapeutic application of antioxidants in the settings of sepsis and acute lung injury.

A randomized controlled study by Jepsen et al. [1] performed on 66 patients demonstrated no significant benefit of high-dose intravenous antioxidant (480 mg/kg *N*-acetylcysteine per day). In turn, administration of antioxidants (procysteine, *N*-acetylcysteine) at moderate doses, such as 70 mg/kg *N*-acetylcysteine or 63 mg/kg procysteine per day, accelerated recovery from ALI and elevated the cardiac index, although it did not change the mortality rate [2]. Another randomized controlled study of 51 ARDS patients demonstrated that enteral nutrition supplemented by antioxidant vitamins (vitamin C, vitamin E, β -carotene, taurine, and L-carnitine) improved oxygenation and reduced both the duration of ventilator support and ICU stay [3].

Opposite effects of high and low doses of antioxidants on LPS-induced lung injury have been also demonstrated in a rat model [4] which showed that, in contrast to low dose (275 mg/kg in 48 h), high-dose *N*-acetylcysteine treatment (550 and 950 mg/kg in 48 h) resulted in a significantly smaller number of surviving animals. This difference was also associated with a decrease in the lung's pool of reduced glutathione [4], indicating an imbalance of endogenous redox equilibrium. In fact, inhibition of ROS production induced by high doses of antioxidants may contribute to the propagation of bacterial infection and sepsis, as ROS play an essential role in antibacterial defense.

Our study shows added beneficial effects of chronic treatment with low dose amifostine due to induction of manganese superoxide dismutase (Mn-SOD) gene expression and protein production. The Mn-SOD gene codes for an inducible antioxidant enzyme localized in the mitochondria that catalyzes the dismutation of superoxide radicals to oxygen and hydrogen peroxide. Thus, Mn-SOD induction by low doses of amifostine stimulates endogenous

mechanisms for regulating ROS production, leading to a more precise control of local tissue redox balance in comparison to acute intravenous antioxidant administration.

It is important to note that biphasic mechanisms of antioxidant administration extend beyond conditions associated with inflammation and sepsis. Administration of low dose amifostine in vivo (50 mg/kg) was much more effective in preventing spontaneous metastases development in a mouse model than were higher doses of 100, 200 and 400 mg/kg [5]. These effects were also linked to a four-fold elevation of an angiogenesis inhibiting factor, angiostatin, over control levels in the plasma of animals treated with a dose of 50 mg/kg every other day for 6 days, while no elevation after treatment with 200 mg/kg was observed [5].

Taken together, these findings suggest that the low dose effectiveness of amifostine can be tied to the redox environment of the cell and appears to be effective at low rather than high doses. In summary, several studies including this work conclude that too much or too little of an antioxidant will be ineffective, and the optimum amount will be specific for the particular pathologic process being targeted. These findings suggest important clinical implications of low concentration antioxidant therapies in the treatment of lung pathologies associated with redox imbalance.

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