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Title:

INCREASING SPUTUM LEVELS OF GAMMA-GLUTAMYLTRANSFERASE MAY IDENTIFY CYSTIC FIBROSIS PATIENTS WHO DO NOT BENEFIT FROM INHALED GLUTATHIONE

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What was your research question?

The present study was aimed to clarify whether the presence of increased levels of gamma-glutamyltransferase (GGT) – an enzyme which is secreted by inflammatory cells, capable of degradating glutathione (GSH) – in sputum of cystic fibrosis (CF) patients might represent a contraindication to therapeutic application of GSH inhalation treatments.

Why is this important?

Inhalation treatments with GSH (a primary antioxidant that protects the airways) have become popular and aim to restore bronchial fluid levels of GSH, which is consumed during inflammatory processes. The results attained so far from clinical studies, however, remain disappointing, mainly because of the limited anti-inflammatory effects produced by such treatments. Our study predicted that a reason for such disappointing results might be due to the increased levels of GGT that are often found in the CF lungs. It has been shown (in cultured cell experiments in the laboratory) that during GGT-mediated degradation of GSH - besides consuming exogenously administered GSH - production of metabolites (*i.e.* reactive oxygen species and other reactive compounds), having a pro-inflammatory and harmful action, may occur! Therefore, it is important to clarify whether GSH inhalation therapies are truly beneficial, ineffective or even – in selected conditions – potentially dangerous.

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What did you do?

We determined GGT activities in sputum samples obtained from a previously published clinical trial, which assessed the effects of inhaled GSH in over 150 CF subjects. Here, patients were randomized to receive GSH (73 people) or placebo (80 people) every 12 hours for 6 months. The study concluded that GSH inhalation neither produced changes in markers of oxidation or inflammation, nor produced clinically relevant improvements in average lung function. In our current study, we measured GGT activities in sputum samples from the same patients, and re-evaluated the clinical and biochemical responses in relation to decreasing or increasing GGT activities (over the 6-month observation period).

What did you find?

Our analysis showed that GSH treatment produced a significant – but small – improvement in the level of inflammatory cytokines in sputum, but only in subjects presenting with decreasing GGT levels in sputum, (i.e. a reduction in inflammation) during the period of observation. On the contrary, in patients whose lung inflammation was worsening (caused by increasing neutrophil infiltration that, resulted in increasing sputum GGT activities), GSH inhalation produced adverse, paradoxical pro-oxidant effects, as shown by increased protein oxidation. These effects could be mediated through sputum GGT. Therefore, the results suggest that GSH inhalation should not be further recommended for usage.

What does this mean and reasons for caution?

Our analysis demonstrates that neutrophilic inflammation in CF airways is correlated with varying GGT activity in sputum. Differentiating patients with increasing and decreasing GGT activities may discriminate subjects with resolving inflammation (therefore, more likely to benefit from inhaled GSH) from those with worsening inflammation, in which GSH might aggravate lung damage. Currently, there are no biomarkers available that readily indicate decreasing or increasing inflammation in the airways. Notably, the determination of GGT activity in sputum might represent such a biomarker. Further investigation is, however, required to corroborate this interpretation.

What's next?

It is important to verify whether the inhalation of drugs capable of inhibiting GGT activity minimizes the degradation of inhaled GSH, thus allowing to achieve the benefits expected from the antioxidant and anti-inflammatory actions of GSH.

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