MUCOLYTICS IN COPD: THE PLOT THICKENS?

Sir,

In his clinical opinion[1] of the systematic review by Poole and Black,[2] Gleadhill points out that the role of mucolytics in COPD still remains to be clarified.

Indeed, the term mucolytic may be a misnomer, as none of these agents has been shown to have mucolytic properties *in vivo*. For example, N-acetylcysteine (NAC) is rapidly inactivated at the airway surface which may explain its lack of effect when given as an aerosol. It is therefore important to distinguish between administering these agents as aerosols where there is a lack of evidence, and as oral agents where they may act, but by different mechanisms.

Therefore, although mucolytic mechanisms are well described, antioxidant mechanisms would be an alternative means by which such agents may be of benefit in COPD and other lung disease. N-acetylcysteine is one of the few drugs to show a beneficial (albeit modest) effect in idiopathic pulmonary fibrosis (IPF) in the IFIGENIA study.[3] In this study, NAC was used at high dose (600mg td) comparable with that shown to replete intracellular glutathione levels in IPF), i.e. with the intention of being an anti-oxidant.[4] Imbalances of oxidative stress are well described in IPF.[5]

In the BRONCUS trial quoted by Gleadhill, one-third of the dose was used (600mg od) compared to the IFIGENIA study, but there was a benefit (albeit limited to a sub-group) in reduction in exacerbations in the inhaled steroid naïve cohort.[6] It should be noted, however, that this was a subgroup analysis in an industry-funded study which was not planned at the time of study, design limiting its significance. Could it be that NAC (and other cysteine-containing mucolytics referred to in the meta-analysis[2] quoted) are achieving their limited benefit here via an antioxidant action in COPD too? It should be noted that any such meta-analysis will be subject to publication bias again reducing its significance. Nevertheless, this is biologically plausible as oxidative stress is well described in COPD, although the relationship with airflow obstruction is not entirely clear.[7]

Future definitive studies, not subject to the problems alluded to above, should investigate the effects of NAC at an antioxidant dosage in COPD, coupled with assessments of changes to glutathione levels and oxidative activity in bronchoalveolar lavage cells. This should help clarify the relative benefits of mucolysis and antioxidant mechanisms in COPD. This may indeed widen the indications for 'mucolytic' therapy in COPD.

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Editor's Note: 'rapidly inactivated at the airway surface'. The pharmacokinetics of N-acetylcysteine (NAC) have been under intense scrutiny since at least 1978. In 1991, David Flenley's group in Edinburgh[1] published one of the definitive papers which showed that after oral dosing at 600mg per day for 5 days, NAC could not be detected in plasma or bronchoalveolar lavage samples at 1–3hrs. However, glutathione, the antioxidant in question was detectable in both plasma and lavage fluid. This, along with many other papers, shows NAC to be rapidly deacetylated, regardless of the route of administration, and that resulting cysteine is transformed to reduced glutathione, raising the levels of glutathione in plasma and the airways. Others have shown that IV NAC restores the glutathione levels in patients with pulmonary fibrosis but has no effect in normals.[2] Using a variety of methods, but rarely direct, others have shown inhaled NAC to reduce the adhesive properties of mucus, and raise antioxidant levels in both the airways and the blood. NAC is also used as a detoxifying agent where the thiol grouping in cysteine combines with the toxic agent (e.g. paracetamol) speeding urinary secretion.[3]

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