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Letter to the Editor

On the use of acetylcysteine as a mucolytic drug

DEAR EDITOR,

Acetylcysteine (N-acetyl-L-cysteine or NAC) is considered to be a mucolytic drug; however this activity is not well documented [1,2]. There is apparently a strong placebo effect reinforced by Pavlovian conditioning if NAC had been administered together with efficient expectorants or inhalations. It was pointed out that all positive findings on NAC in chronic obstructive pulmonary diseases have come from studies either investigating relatively small numbers of patients, or conducted in patients possibly not representative of the wider population [3]. The large Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS) trial showed that NAC is ineffective in preventing deterioration of the lung function in patients with chronic obstructive pulmonary disease (COPD) [4]. It was concluded that there had been no randomized controlled trials demonstrating a benefit from inhaled NAC in the treatment of any airway diseases [5-8], and that no data have convincingly demonstrated an improvement of mucus expectoration, while there is a risk of epithelial damage when NAC is administered via aerosol [8]. At the same time, a systematic review found that the treatment with mucolytics reduced the frequency of exacerbations of COPD [9], while some studies included in the review were with NAC. These findings were supported by a pharmaco-epidemiologic study [10], although there was a concern that the benefit had actually been the result of a bias [11]. A 2013 Cochrane review found no evidence to recommend the use of either nebulized or oral NAC in patients with cystic fibrosis [6]. It was reported on the mucolitic efficiency of NAC against bacterial biofilms on the tonsils [12,13], probably because it is technically easier to achieve an efficient concentration in the nose and throat region compared to bronchi.

There have been in vitro studies reporting that NAC at relatively high concentrations lowers viscosity of sputum [14-18]. It should be commented that theoretically, depending on concentrations, cysteine and NAC might not only lower but also enhance the viscosity of sputum. The mucolytic effect of NAC is explained as its thiol (sulfhydryl) groups "hydrolyze disulfide bonds of mucins and other proteins" [5]. Both cysteine and acetylcysteine have a thiol group; two cysteine molecules can unite and build one cystine molecule with a disulfide bond. If cysteine is added, the cysteine-cystine equilibrium (including both free cysteine/cystine and their residua within proteins and other molecules) may shift to the right according to the law of mass action i.e. more disulfide bond would be built. The same might be true for NAC, which, given per os, is deacetylated to cysteine [19]. The matter should be clarified by independent experiments with sputum and other mucous substances. Efficiency of NAC is particularly doubtful if the substance is given per os. NAC is not detected in airway secretions and bronchoalveolar lavage fluid, while cysteine concentration did not increase in the lavage fluid following an oral intake of NAC [2,8,19,20]. This is not surprising as NAC is rapidly metabolized and incorporated by proteins [8,21]. Slight increase in radioactivity of bronchial secretions after the oral intake of 35S-NAC [22] does not prove that there was active NAC in the bronchial lumen.

A separate topic is the use of NAC for the treatment of microbial infections accompanied by the formation of biofilms. Antibiotic resistance of bacteria in biofilms contributes to the chronicity of infections [23]. Biofilms have been demonstrated to be responsible for both acute and chronic conditions of the upper respiratory tract, sinusitis, otitis media, tonsillitis and adenoiditis [24]. Difficulties of biofilm eradication with systemic antibiotics have led to consider non-antibiotic therapies including NAC. Evidence from in vitro studies indicates that NAC has antibacterial properties, enhances potencies of antibiotics and interferes with the biofilm formation [25-27]. The question is how to achieve an efficient concentration of NAC in the bronchial contents. As discussed above, this hardly can be expected from an intake per os. The encouraging experimental findings need to be tested using inhalation as a route of NAC administration [25], bearing in mind possible adverse effects [8].

Apart from the direct biochemical action discussed above, NAC was supposed to exert antioxidant and anti-inflammatory effects [28,29]. Data on the anti-inflammatory activity of NAC are limited [30] and the mechanism is not readily understandable. Antioxidants affecting reactive oxygen species may have both harmful and beneficial effects. Generation of reactive oxygen species is a normal phenomenon in the course of aerobic metabolism [31]. Free radicals are not invariably toxic; some of them are necessary for the physiological functioning [32]. The redox status is maintained in equilibrium under the influence of various

factors [33,34]. The artificial support of the antioxidant status is not necessarily beneficial [33]; more details and references are in [35]. In any case antioxidant effects of NAC are not directly related to its supposed mucolytic activity.

In conclusion, there are reasons to doubt effectiveness of NAC as a mucolytic agent beyond the placebo effect especially for the oral intake. The matter can be clarified e.g. by in vitro viscosimetry of sputum with NAC concentrations comparable to those under different conditions in vivo, and measurements of NAC concentration in expectorated sputum from patients receiving the substance per os.

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