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The sulphoxidation of *S*-carboxymethyl-L-cysteine in COPD

To the Editors:

Mucolytics, such as *S*-carboxymethyl-L-cysteine, have a role to play as an adjunct in the treatment of chronic obstructive airway disease, but their apparent unreliability has led to divided opinion concerning their usefulness [1–3]. The failure to achieve any measurable benefit with some patients presumably reflects underlying interindividual differences within the patient cohort, and not that the drug itself is without efficacy. In this respect, one major topic affecting clinical efficacy of a drug is its disposition and fate following administration, and, in particular, those factors that influence its subsequent metabolism and deactivation.

The metabolic fate of *S*-carboxymethyl-L-cysteine, an extensively used and widely available mucoactive drug, is now known to be complex. Detailed and rigorous studies in humans have revealed that the biotransformation of the drug varies widely within the same individual, with little sulphoxide (sulphur oxygenated) metabolites being produced following night-time administration [4]. This seemingly trivial observation is crucial, as recent work indicates that this drug functions as a free radical scavenger [5, 6] and that, in this respect, the sulphide (parent compound) is the active species with the sulphoxide metabolites (already oxidised) being inactive. Thus, a night-time intake of the drug should be more beneficial to the patient than daytime administration. However, this diurnal variation in metabolism (deactivation) is overlaid on an underlying genetic polymorphism that gives the patient population a spread of *S*-carboxymethyl-L-cysteine sulphoxidation capacities [7] (fig. 1). Those individuals who are relatively efficient sulphur oxidisers will rapidly produce inactive oxygenated metabolites, whereas those who have a relative deficiency in this process will be exposed to the active sulphide for a longer period of time, effectively mimicking the night-time dosing situation. In efficient sulphoxidisers, the standard dose of the drug may well have little effect. The underlying enzymology of these reactions is not yet clear, but two cytosolic enzymes, cysteine dioxygenase and phenylalanine 4-hydroxylase, have been implicated [8].

It is evident that a ''broad brush stroke'' approach to therapy with this particular mucolytic agent will not work for everyone. The recognition that the same dose of *S*-carboxymethyl-L-cysteine will not be equally effective for all patients should enable this part of the therapeutic regimen to be tailored to each individual patient, or subgroup, of patients. Removing or withholding treatment because it appears ineffective in some subjects is manifestly incorrect for that proportion of the

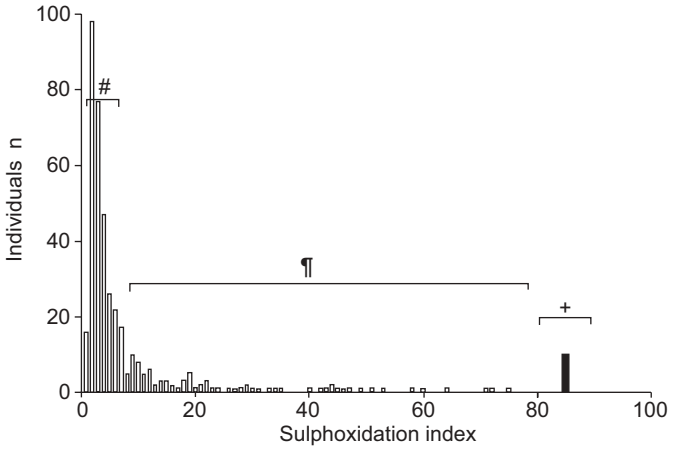

FIGURE 1. Distribution of *S*-carboxymethyl-L-cysteine sulphoxidation capacities for 401 subjects (*S*-carboxymethyl-L-cysteine was dosed *p.o.* at 09:00 h and urine was colleted from 09:00–17:00 h) expressed as a sulphoxidation index (SI; ratio sulphides/sulphoxides). The population can be divided into three sub-groups as follows. #: extensive metaboliser phenotype, 65.8% population (SI<6); ¶: intermediate metaboliser phenotype, 31.7% (SI 6–80); +: poor metaboliser phenotype, 2.5% (SI>80).

patient population for whom benefit may be gained. Some form of practical screening prior to mucolytic therapy would permit the correct dosage to be assigned.

We would welcome correspondence concerning the efficacy, or otherwise, of *S*-carboxymethyl-L-cysteine in the treatment of chronic obstructive pulmonary disease.

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Urinary incontinence in patients with bronchiectasis

To the Editors:

The psychosocial impact of bronchiectasis is frequently underestimated as chronic productive cough is often embarrassing for the patient. In addition, in many females, cough may precipitate an episode of urinary incontinence. We have found that patients with bronchiectasis are often reticent to discuss their incontinence issues with any healthcare professionals and, as such, go untreated. We conducted an audit of the female attendees of a mixed severe asthma/bronchiectasis clinic to determine whether there were any unmet healthcare needs.

Female patients attending the Manchester Severe Asthma Service (Manchester, UK), a tertiary referral clinic for the diagnosis and management of severe asthma and bronchiectasis, were approached to participate. Data were collected on age, menopausal status and parity (vaginal or caesarean). Prevalence of incontinence and its impact on quality of life was assessed using the Incontinence Quality of Life questionnaire (I-QoL) [1]. Severity of incontinence was measured by assessing frequency of incontinence (regardless of severity) and worst degree of urinary leak on any occasion. Patients were clinically classified as having asthma, bronchiectasis, chronic cough, or any combination of these three. Previous access to gynaecological services and requests for referral was audited.

In total, 80 consecutive patients completed the audit questionnaire, of which 75 were suitable for analysis (mean (range) age, 47 (18–73) yrs). Of the 75 patients, 43 (57%) had bronchiectasis (with or without asthma).

The overall prevalence of urinary incontinence (at least 1 episode·week^{-1}, regardless of severity) in females attending the