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Pharmacokinetics and Bioavailability of Reduced and Oxidized N-Acetylcysteine

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Summary. The pharmacokinetics and bioavailability of N-acetylcysteine (NAC) have been determined after its intravenous and oral administration to 6 healthy volunteers.

According to a randomized cross-over design each subject received NAC 200 mg i.v. and 400 mg p.o., and blood samples were collected for 30 h.

Reduced NAC had a volume of distribution (V_{SS}) of 0.59 $l \cdot kg^{-1}$ and a plasma clearance of 0.84 $l \cdot h^{-1} \cdot kg^{-1}$. The terminal half-life after intravenous administration was 1.95 h. The oral bioavailability was 4.0%.

Based on total NAC concentration, its volume of distribution (V_{SS}) was 0.47 $l \cdot kg^{-1}$ and its plasma clearance was 0.11 $l \cdot h^{-1} \cdot kg^{-1}$. The terminal half-life was 5.58 h after intravenous administration and 6.25 h after oral administration. Oral bioavailability of total NAC was 9.1%.

Key words: N-acetylcysteine; pharmacokinetics, bioavailability

N-acetylcysteine (NAC), which is considered to be a mucolytic [1] or a mucoregulatory [2] drug, is used in the treatment of chronic bronchitis [3-5] and other diseases complicated by the production of a viscous mucus. In addition, NAC has been found useful in the treatment of paracetamol intoxication [6], and as a chemoprotective adjunct in cancer therapy [7].

In plasma NAC can be present in its intact, reduced form as well as in various oxidized forms. It can be oxidized to a disulphide, N,N'-diacetylcystine, and it can form mixed disulphides by reacting with other low molecular weight thiols such as cysteine and glutathione. NAC can be oxidized by reaction with the thiol groups of plasma proteins. It should be kept in mind that this is not the same kind of protein binding as that exhibited by other drugs. The structures of NAC and some of its oxidation products are shown in Fig. 1.

There are several bioanalytical methods for the determination of NAC in plasma [8-12], of which those by Cotgreave and Moldéus [11], and Johansson and Westerlund [12], permit determination of all the forms of NAC mentioned above. The pharmacokinetics of NAC has not been described in detail until recently, largely due to the lack of sensitive and specific bioanalytical methods. Earlier studies in animals and man used radiolabelled NAC and thin layer chromatography for the separation and identification of NAC and its metabolites [13-15]; cysteine and cystine were identified as the major metabolites of NAC. Inorganic sulphate was the

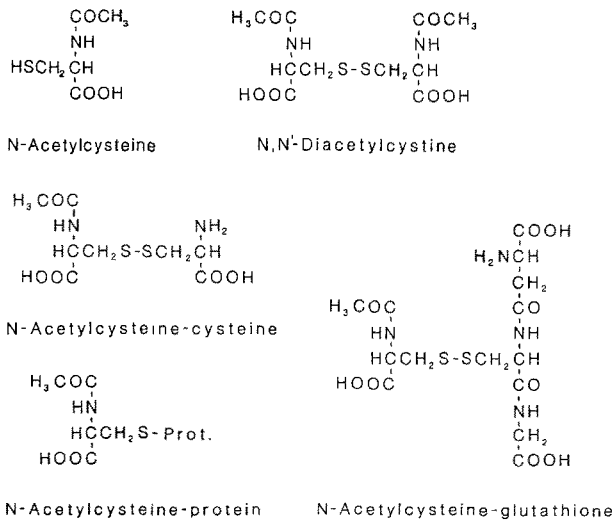

Fig. 1. Structure of NAC and some of its oxidation products