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Pharmacokinetics of N-Acetylcysteine in Man

L. Borgström[1], B. Kågedal[2], and O. Paulsen[3]

[1] Research and Development, Pharmacokinetics Laboratory, AB Draco, Lund
[2] Department of Clinical Chemistry, University Hospital, Linköping, and
[3] Department of Clinical Pharmacology, University Hospital, Lund, Sweden

Summary. N-Acetylcysteine was given intravenously and as three fast dissolving and one slow-release formulation, on separate occasions, as a single dose of 600 mg to 10 fasting (5 men and 5 women) healthy volunteers. Blood and urine were sampled for the following 12 h.

Renal clearance constituted around 30% of total body clearance, which was 0.21 l/h/kg. Volume of distribution was 0.33 l/kg, consistent with distribution mainly to extracellular water. The late elimination half-life was 2.27 h and the mean residence time 1.62 h.

The slow-release tablet resulted in a flattened plasma concentration-time curve typical of slow release formulations, while the other three oral formulations were rapidly absorbed.

The oral availability of N-acetylcysteine varied between 6 and 10%, with the slow-release tablet having the lowest and the fast dissolving tablet the highest availability.

Key words: N-acetylcysteine; bioavailability, slow-release formulation, pharmacokinetics

For more than 20 years, N-acetylcysteine (NAC), an endogenous product of cysteine, has been in clinical use as a mucolytic agent administered by inhalation. NAC disrupts disulphide bonds in mucus, making it less viscous [1], and is also utilized as an effective antidote in paracetamol poisoning [2]. NAC is reported to offer protection against doxorubicin toxicity [3] and to reduce ifosfamide- and cyclophosphamide-induced cystitis [4-5]. The use of NAC in the treatment of bronchitis was previously limited to inhalation therapy, which sometimes caused local irritation. But in the last ten years, clinical trials have shown that oral NAC has a good clinical effect on the viscosity of bronchial mucus [6-9]. The presence of a thiol group in N-acetylcysteine explains its tendency to bind to reactive compounds and to cysteine and other endogenous, sulphhydryl-containing molecules in mucus, tissue and plasma.

Extensive clinical multicentre trials have confirmed the value of oral NAC in the long-time treatment of chronic bronchitis [8]. The exacerbation rate in patients was significantly reduced by a dose of 200 mg NAC twice daily for 6 months [8-9]. In the trials hitherto performed dosage levels and dose intervals have been chosen arbitrarily, since pharmacokinetic information has largely been lacking.

Studies with radioactive NAC in man have shown that the maximal radioactive concentration in plasma is achieved 2-3 h after oral administration [10], and between 13 and 38% of an oral radioactive dose is recovered in urine within 24 h. Some radioactivity can be detected in bronchial secretions.

Maddock [11] administered 400 mg NAC to healthy volunteers and found an increase in what, without further support, was called the plasma free (ultrafiltrable) acetylcysteine concentration. The maximal concentration occurred at 1 h and the mean elimination half-life was 1.4 h. An increase in other sulphhydryl group-containing molecules was also observed.

Recently, new methods for the determination of N-acetylcysteine in plasma have appeared [12-15], and a few pilot studies with NAC have illustrated their usefulness.

The aim of the present study was to assess the primary and secondary pharmacokinetic parameters of NAC given intravenously to man, and to compare the rate and extent of availability of four different oral NAC-formulations.

Material and Methods

The study was approved by the local Ethics Committee. It was in accordance with the Declaration of Helsinki. Written informed consent was given by each volunteer.

Subjects

Ten healthy volunteers (5 men and 5 women) participated in the study. Their ages varied between 29 and 44 years and their weight from 54 to 90 kg. The subjects did not take any other drugs or drink alcoholic beverages during the study.

Acetylcysteine Formulations

One intravenous and four different oral formulations of NAC were studied. The solution for infusion, Mucomyst (Tika), containing NAC 200 mg/ml was diluted with an equal volume of saline before infusion.

The four oral formulations were: Fabrol (Inpharzam), Mucomyst (Tika), NAC-Plain (Draco) and NAC-SR (Draco). Fabrol is a granulate to be dissolved in water before intake, and Mucomyst is an effervescent tablet. NAC-Plain is a fast dissolving tablet and NAC-SR is a slow-release tablet in which the slow-release properties are achieved by dispersing the NAC grains in an insoluble matrix.

Procedure

The study was open, randomized and cross-over. There was a wash-out period of at least 3 days between the experimental days. All subjects fasted from 10 p.m. on the day before. They arrived at the clinic on the morning of the study day. Two hours after drug intake a standardized breakfast was served [16].

The intravenous infusion (600 mg; 3676 μmol) was given over 5 min into an antecubital vein in the arm not used for blood sampling.

The oral formulations were given as a single dose of 600 mg (3676 μmol). Fabrol and Mucomyst were dissolved in 100 ml of water before intake. Afterwards the drinking glass was rinsed with an additional 20 ml water, which was swallowed. NAC-Plain and NAC-SR were taken together with 120 ml water.

Blood for NAC analysis was sampled at the following scheduled times: 0, 20, 40 min, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after the start of the administration. Urine was collected in one pool for 0–12 h after drug intake. On a separate day urine was sampled during 0–12 h to determine the amount of endogenously excreted NAC. The individual background values were subtracted from the amount excreted after dosing before calculating the renal clearance and amount excreted in urine.

Analysis of NAC in Plasma and Urine

Blood samples 10 ml were collected through an indwelling antecubital vein catheter into tubes containing 0.1 ml 17% EDTA (K3), and were immediately centrifuged. Plasma 3 ml was mixed with 0.6 ml trichloroacetic acid (200 g/l) to precipitate the proteins. After mixing, the tubes were left standing for 15 min and after a second centrifugation the clear supernatant was transferred to new tubes and kept at −20 °C until analyzed by HPLC for its concentration of non-protein-bound NAC according to a previously described method [14]. The method measures NAC not-covalently bound to plasma after reduction of disulphide bridges of low-molecular weight compounds, e.g. N,N′-diacetylcystine or N-acetylcysteine-cysteine mixed disulphide. Urine was appropriately diluted [17] and NAC was determined by a procedure similar to that for plasma NAC determination.

Pharmacokinetic Calculations

Maximal plasma concentration (C_{max}), was defined as the highest experimental plasma concentration obtained, and t_{max} was the time for C_{max}.

The elimination half-life ($t_{½}$), was calculated on the descending slope of the plasma concentration-time curve (C,t-curve) after intravenous administration.

The area under the C,t-curve (AUC) was calculated according to the trapezoidal rule. All areas were calculated over the first 12 h and, when necessary, extrapolated to infinity. The extrapolated areas were calculated as C_{12}/k, where k is the individual elimination rate constant derived from the intravenous experiment, and C_{12} is the plasma concentration after 12 h. The area under the first moment of the C,t-curve (AUMC), defined as the area under the curve of the product of time, t, and plasma concentration, C_p, from zero time to infinity, was also calculated up to 12 h with the aid of the trapezoidal rule. The extrapolated AUMC was calculated as $C_{12}/k^2 + 12 \cdot C_{12}/k$.

Mean residence time (MRT) is the mean time for drug molecules to transit through the body. It was calculated as AUMC/AUC.

Volume of distribution (V_{ss}) after the intravenous dose was calculated as

$$\frac{\text{Dose} \cdot \text{AUMC}}{(\text{AUC})^2} - \frac{\text{Dose} \cdot \text{T}}{2 \cdot \text{AUC}}$$

where T is the infusion time, in this case 5 min. All doses used in the calculations are the doses actually given.

Total body clearance (CL) after intravenous administration, was calculated as dose divided by AUC.

Renal clearance (CL_R) was calculated after the intravenous experiment as amount of NAC excreted in urine divided by the corresponding AUC-value.

Bioavailability, $F_{(plasma)}$, was calculated as AUC (oral)/AUC (i.v.). Bioavailability was also calculated by dividing the amount of NAC excreted in urine after oral intake by that excreted after intravenous infusion, $F_{(urine)}$.

Statistical Analysis

Differences between the oral formulations were evaluated by analysis of variance and two-sided paired Student's *t*-test. The level of significance was set at $\alpha = 0.05$.

Results

Primary Pharmacokinetics After i.v. Infusion

The subjects complied well with the study protocol, and almost all blood samples were taken within 3 min of the scheduled time. In three cases when the time deviation slightly exceeded 3 min, a new value at the scheduled time was calculated by linear interpolation.

Urine was sampled according to the scheduled time ±10 min, except in one case when the urine sampled between +1 and +4 h was lost and a missing value had to be given in the statistical analysis. Renal clearance and urinary availability values from one subject were excluded as for unknown reasons the amount of NAC found in urine after intravenous administration was only 10% of the mean of the other subjects.

The mean plasma concentration of N-acetylcysteine versus time (C,t-curve) after intravenous infusion is shown in Fig. 1, and the calculated individual pharmacokinetic parameters are given in Table 1.

The volume of distribution (V_{ss}) was 0.327 l·kg^{-1}, with very little interindividual variation. Elimination from plasma could be approximated with a monoexponential phase, half-life 2.27 h, after about 2 h and after 12 h virtually no N-acetylcysteine was found in plasma.

Total body clearance was 0.207 l·h^{-1}·kg^{-1}, or 242 ml·min^{-1} for a person weighing 70 kg. The renal

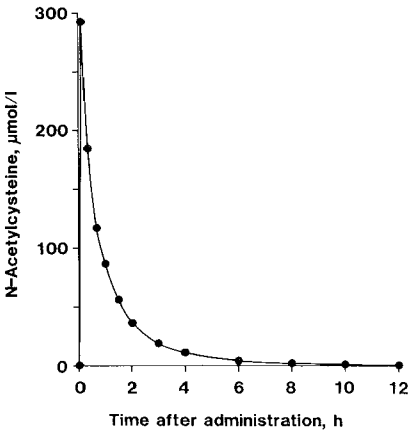

Fig. 1. Mean plasma concentrations of NAC after intravenous administration of 600 mg (3676 µmol) to 10 subjects

Table 1. Pharmacokinetic parameters after intravenous administration of 600 mg (3676 µmol) NAC as Mucomyst solution within 5 min. (CL = total body clearance; CL_R = renal clearance; V_{ss} = volume of distribution at steady state; $t_{½}$ = elimination half-life; MRT = mean residence time; Ae (0–12) = amount excreted in urine during 0–12 h)

Subject	CL (l·h^{-1}·kg^{-1})	CL_R (l·h^{-1}·kg^{-1})	V_{ss} (l·kg^{-1})	$t_{½}$ (h)	MRT (h)	Ae (0–12) (% of dose)
1	0.201	0.066	0.388	1.94	1.72	31.8
2	0.219	0.043	0.334	1.89	1.57	30.9
3	0.226	0.067	0.361	1.97	1.64	29.3
4	0.190	-	0.282	2.20	1.52	(2.4)
5	0.198	0.050	0.330	2.22	1.71	24.9
6	0.216	0.070	0.350	2.39	1.66	32.2
7	0.193	0.066	0.348	2.80	1.84	33.4
8	0.241	0.064	0.337	2.62	1.44	26.4
9	0.199	0.051	0.299	2.07	1.54	25.3
10	0.191	0.044	0.293	2.60	1.58	26.7
Mean	0.207	0.058	0.337	2.27	1.62	29.0
±SD	0.017	0.011	0.027	0.32	0.12	3.2 (n=9)

part of the clearance was 68 ml·min^{-1}. Thus, approximately 70% of the total clearance was non-renal.

Plasma Concentration After Oral Intake

The mean plasma C,t-curves after oral intake are shown in Fig. 2. The low C_{max} value for NAC-SR can be observed. The other oral formulations resulted in similar C,t-curves.

The differences in C_{max} and t_{max} illustrate the slow release of active drug from NAC-SR (Table 2). These differences between NAC-SR and any of the other oral formulations were statistically significant. As could be expected for a slow release formulation, the MRT of NAC-SR was significantly higher than for the other oral formulations, and as mentioned above, this can also be seen in the flattened appearance of the C,t-curve (Fig. 2). The three rapid formulations all had very similar MRT values, indicating that dissolution of those formulations was not rate-limiting in the overall absorption process.

Bioavailability and Urinary Excretion

Bioavailability, $F_{(plasma)}$, of the different oral formulations calculated from areas under the curves was in close conformity with the corresponding figures obtained from urinary excretion, $F_{(urine)}$ (Table 3). Analysis of variance showed a significant difference between the four formulations, the slow release tablet having the lowest bioavailability. Collectively, bioavailability after oral intake was low, with individual values ranging from 3.4 to 19.8%, and mean formulation values from 6.4 to 10.0%.

Details of spontaneous endogenous urinary excretion of NAC are given in Table 3 for all the subjects together, and with the increase in urinary output obtained after exogenous NAC-administration. As can be seen, i.v. administration of 600 mg increased

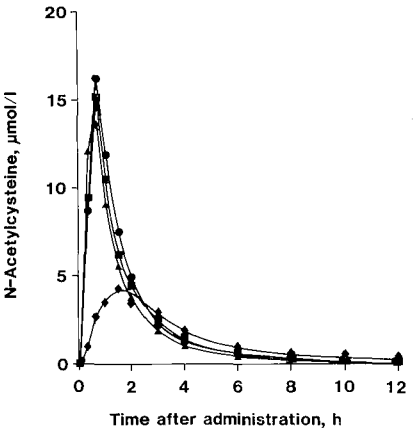

Fig. 2. Mean plasma concentrations of NAC after oral administration of four different NAC-formulations (600 mg; 3676 µmol) to 10 subjects. ▲—▲ Fabrol, ■—■ Mucomyst, ●—● NAC-Plain, ◆—◆ NAC-SR

Table 3. Individual amounts (µmol) of N-acetylcysteine excreted after intravenous and oral (four different formulations) administration of 600 mg (3676 µmol) N-acetylcysteine. Urine was collected for 12 h after drug administration during daytime. The amount excreted endogenously was determined on another day over a similar sampling interval

Subject	Endogenously excreted amount	Formulation				
		i.v.	Fabrol	Mucomyst	NAC Plain	NAC SR
1	10.1	1183	117	101	122	98
2	29.4	1165	111	104	106	107
3	9.5	1148	78	80	104	60
4	30.3	(112)	130	148	137	114
5	21.5	996	141	148	118	67
6	33.8	1329	118	132	-	117
7	39.4	1389	124	153	147	86
8	51.5	1105	96	109	140	102
9	24.8	973	70	77	87	95
10	20.0	1101	132	132	213	182
Mean	27.0	1154	112	118	130	103
±SD	12.8	137 (n=9)	23	28	36	33

Table 2. Pharmacokinetic parameters after oral intake of 600 mg (3676 µmol) N-acetylcysteine in 4 different formulations. Mean ± SD; n=10. (C_{max} = maximal plasma concentration; t_{max} = time for C_{max}; MRT = mean residence time; $F_{(urine)}$ = bioavailability calculated from urinary excretion; $F_{(plasma)}$ = bioavailability calculated from plasma concentration, time-curve)

Formulation	C_{max} (µmol·l^{-1})	t_{max} (h)	MRT (h)	$F_{(urine)}$ (%)	$F_{(plasma)}$ (%)
Fabrol	15.0 ± 7.2	0.67 ± 0.16	2.34 ± 0.49	7.7 ± 2.8	9.1 ± 3.0
Mucomyst	16.0 ± 7.9	0.65 ± 0.33	2.17 ± 0.34	8.2 ± 2.7	8.3 ± 2.5
NAC Plain	16.9 ± 7.5	0.75 ± 0.21	2.30 ± 0.42	10.1 ± 4.2	10.0 ± 2.2
NAC SR	4.7 ± 2.2	1.90 ± 0.61	4.40 ± 0.80	7.2 ± 3.8	6.4 ± 1.7

[a] In one subject the amount of N-acetylcysteine excreted in urine after i.v. administration (see Table 3) for unknown reasons was around 10% of the mean of the other subjects. The low value resulted in an improbable oral availability. The mean value of $F_{(urine)}$ was therefore based on data from 9 subjects

the output about 40 times, while the increase due to oral intake was about four times the endogenous amount.

Discussion

Few studies of the plasma concentrations and pharmacokinetics of NAC in man are available. Pharmacokinetic studies of NAC have been hampered by the lack of suitable analytical procedures to determine the compound in plasma, and were previously confined to work with NAC labelled with ^{35}S [10].

The maximal ultrafiltrable free NAC concentration in plasma after oral intake of 400 mg N-acetylcysteine was estimated by Maddock [11] to 0–36 $\mu mol \cdot l^{-1}$. This finding contrasts with the results obtained by Lewis et al. [15]; following derivatization no free level could be detected by HPLC, even after an oral dose of 800 mg. However, after oral administration of 9.9–13.7 g to human subjects, Krenzelok et al. [18] found a maximal free NAC concentration of 9.3 to 17.6 $mg \cdot l^{-1}$ (57–108 $\mu mol \cdot l^{-1}$).

No previous intravenous data are available, but from Table 2 it can be seen that the maximal value of about 300 $\mu mol \cdot l^{-1}$ after 600 mg was about 20-times that obtained after oral intake of a similar dose. The half-life of elimination, 2.27 h, is comparable to reported values [12, 16]. After intake of the three different fast dissolving oral formulations, the mean t_{max} varied between 0.65 and 0.73 h, as in earlier findings [12, 14]. The method used by Morgan et al. [12] did not include a protein precipitation step, and so their values may include some protein-bound NAC. As discussed earlier [14], their results after oral intake are rather similar to those obtained here after allowing for differences in dosing.

Using capillary gas-liquid chromatography for measuring total NAC in plasma, Frank et al. [13] showed a typical serum concentration-time curve in a subject receiving 1.6 $mmol \cdot l^{-1}$ (260 mg) NAC during 6 h. After cessation of the infusion, they obtained a maximal value of 20 $\mu mol \cdot l^{-1}$, which reverted to baseline after a further 10 h. The decrease is in accordance with the finding that virtually no NAC was found in plasma 12 h after oral intake, except after the intake of slow-release tablets.

The volume of distribution was 0.327 $l \cdot kg^{-1}$. As NAC is a hydrophilic compound and to some extent is probably bound to other components in plasma, this value is in good accord with distribution in extracellular water.

The total body plasma clearance was 242 ml/min for a person weighing 70 kg and approximately 70% of it was non-renal. The extraction ratio of a drug across a particular eliminating organ can be calculated by dividing its clearance by the flow through the eliminating organ [19]. If it is assumed that the renal plasma flow is 550 $ml \cdot min^{-1}$, the renal extraction ratio for NAC was 0.12. If the major part of the non-renal extraction were hepatic and the hepatic plasma flow is assumed to be 675 $ml \cdot min^{-1}$, the hepatic extraction ratio was 0.26. Thus, NAC is a drug with a low extraction ratio and can be assumed to behave like similar drugs with respect to changes in blood flow etc. [20].

It has been shown in rats [21] that only a small amount (3%) of radioactive NAC is excreted in faeces, even after i.v. and oral administration. The low availability after oral administration is probably due to fast metabolism in the gut wall and liver. The almost complete absorption leaves a large amount of NAC for in vivo metabolism, e.g. for cellular uptake, deacetylation to cysteine [22] and synthesis of glutathione [23] or other sulphur compounds. Rodenstein et al. [10], after oral administration of 100 mg ^{35}S-labelled NAC, obtained the maximum concentration rather later [11–14, 18], and showed that a substantial amount of radioactivity still remained in plasma after 24 h. Metabolic products, still radioactively labelled, may recirculate or have a lower clearance than NAC.

The clinical relevance of the low oral availability of NAC is not clear and may have different implications for treatment of chronic bronchitis and of paracetamol poisoning. In a study by Grassi et al. [24] on chronic bronchitis, NAC was given intravenously (500 mg per day), intramuscularly (600 mg per day) and orally (600 mg per day). The main finding was a faster onset of action after intravenous than after intramuscular or oral dosing. The clinical effects after 6 days of treatment, however, were similar.

The low bioavailability of NAC after oral intake may imply that higher oral than intravenous doses should be given in paracetamol poisoning. According to the current recommendation of the Swedish Poison Information Centre, Karolinska Hospital, Stockholm, for antidote purpose, it is recommended to give similar amounts of NAC irrespective of the mode of administration: 140–150 $mg \cdot kg^{-1}$ initially, with 50–70 $mg \cdot kg^{-1}$ every 4th hour for 24–28 h. Thus, oral administration of NAC seems to be clinically effective in spite of its low bioavailability. It is made possible by the common latent period of some hours after paracetamol intake before symptoms of toxicity, including vomiting, develop. Another question is whether a sufficient amount of antidote will be available after oral intake. However, as indicated above, a major part of NAC may be metabolized during its first passage in the gut wall and liver, and

oral NAC in fact offers prompt availability of thiol groups needed for glutathione synthesis in the hepatic cells where the need is highest. In that case, it might be appropriate promptly to give acetylcysteine orally in paracetamol poisoning [18]. Such formulations may be more readily at hand than i.v. solutions.

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Lars Borgström
Pharmacokinetics Laboratory
AB Draco
Box 34
S-221 00 Lund, Sweden