DOSE DEPENDENT PHARMACOKINETICS OF N-ACETYLCYSTEINE AFTER ORAL DOSING TO MAN

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ABSTRACT

The pharmacokinetics after oral administration of 200, 600 or 1200 mg of N-acetylcysteine (NAC) were studied in 10 healthy subjects. Normalized maximal plasma concentration was significantly higher after a 600 mg dose than after a 200 mg dose. Bioavailability of NAC significantly increased with increasing dose. Time for maximal plasma concentration also increased with increasing dose. The observations can be explained by a capacity-limited presystemic elimination of NAC. In an extension of the study, 600 mg of NAC was given twice a day for 5 days and the plasma concentrations were followed after the morning dose on day 6. No differences in the pharmacokinetic parameters were observed in comparison with the single 600 mg dose. This indicates that the beneficial clinical effects observed after repeated dosing cannot be ascribed to an accumulation of NAC in plasma.

KEY WORDS    N-acetylcysteine    Pharmacokinetics    Dose-dependence    Elimination    Human

INTRODUCTION

N-Acetyl-L-cysteine (NAC) has long been used as a topically applied mucolytic agent, and recently it has been shown that repeated oral administration of NAC has a good clinical effect on chronic bronchitis.1-5 The number of exacerbations and exacerbation days are reduced and, as a consequence, the number of days of sick leave has also been reduced. The underlying mechanism after topical and oral administration is probably not the same.6,7

The pharmacokinetics of NAC after single intravenous and oral administration have been evaluated in healthy volunteers.8 When used in therapy, NAC is given as repeated doses and the effects of NAC will take some days to evolve. This has raised the question as to whether the processes for absorption or elimination of NAC are saturable, in the clinical dose range. An
acute effect could be studied by administration of single oral doses of different sizes, and a chronic influence by giving repeated doses.

MATERIAL AND METHODS

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

Volunteers

Ten healthy volunteers (5 men and 5 women) participated in the study. Their age varied between 30 and 45 (mean 36) years and their weight from 55 to 91 (mean 69) kg. The volunteers included in the present study have earlier taken part in another study with NAC. In that study different oral formulations and an intravenous dose of 600 mg were given. The present study is a continuation of that study and the values from the effervescent tablet and the intravenous dose are used for comparison.

Study drugs

An effervescent tablet formulation of NAC (Mucomyst, 200 mg, Tika, Sweden) was used in the study.

Study design

The general outlines of the study were similar to the earlier reported pharmacokinetic study from which the intravenous values, used in the bioavailability calculations, were extracted. In short, the study was divided into two parts, single doses and repeated administration. In the first part, 200, 600 or 1200 mg of NAC was given as a single dose. The 200 and 1200 mg doses were randomized and crossed-over, while the 600 mg dose was given before the two other doses. In the second part, 600 mg of NAC was given twice a day for 5 days, and on study day 6 the plasma concentrations were followed during one dosing interval. On the experimental days the subjects arrived at the clinic in the morning after fasting since 10 pm the evening before. The study drugs were dissolved in 150 ml of water before intake. A standardized breakfast was served 2 h after administration of the drug. Blood for NAC analysis was sampled at the following scheduled sampling times: 0, 20, 40 min, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after the start of the administration. NAC in plasma was determined according to the method of Kågedal et al. In short, the method measures the total of free NAC and NAC generated after reduction of disulphide bridges of low-molecular weight compounds, e.g. N, N-diacyl cystin or N-acetylcysteine-cysteine mixed disulphides in protein-free samples.
Pharmacokinetic calculations

Maximal plasma concentration, $C_{\text{max}}$, was the highest experimental plasma concentration and $t_{\text{max}}$ was the time for $C_{\text{max}}$. The area under the curve for plasma concentration versus time ($C$, $t$-curve), $\text{AUC}_c$, was calculated according to the trapezoidal rule during the first 12 h. Extrapolation of AUC to infinity was made by $C_{12}/\lambda$ where $C_{12}$ is the plasma concentration after 12 h and $\lambda$ is the elimination rate constant calculated on the descending slope of the plasma concentration curve after intravenous administration.

Bioavailability, $F$, was calculated as $(\text{AUC}_{\text{oral}}/\text{AUC}_{\text{iv}}) \cdot (\text{Dose}_{\text{iv}}/\text{Dose}_{\text{oral}})$. All doses used in the calculations are the actual doses administered.

Statistics

Differences were evaluated with analysis of variance (ANOVA) and paired two-sided Student's $t$-test. Level of significance was set at $\alpha = 0.05$.

RESULTS

Single doses

The plasma concentrations were normalized to a given dose of 100 mg NAC and the resulting mean $C$, $t$-curves are given in Figure 1. Mean (± SD) $C_{\text{max}}$ and $t_{\text{max}}$ after the three different doses, as well as bioavailability are given in Table 1.

In order to compare different doses, the actual $C_{\text{max}}$ values were normalized to a dose of 100 mg NAC. Normalized $C_{\text{max}}$ differed significantly (ANOVA: $p<0.001$) between the three treatments. A further analysis with the $t$-test revealed that $C_{\text{max}}$ after the 200 mg dose was significantly lower than after the 600 mg dose ($p<0.001$) and the 1200 mg dose ($p<0.001$). The difference between the 600 and 1200 mg doses did not reach significance ($p=0.244$).

The difference between the actual $t_{\text{max}}$ values was significant (ANOVA: $p<0.001$), with the lowest dose showing the smallest values. All three interdose differences also reached significance ($p<0.01$).

Table 1. Mean pharmacokinetic parameters ± SD obtained after oral administration of 200, 600, and 1200 mg of NAC as a single dose, and after repeated administration of 600 mg NAC twice a day to 10 healthy volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>200 mg</th>
<th>600 mg</th>
<th>1200 mg</th>
<th>600 mg repeated</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µmol L$^{-1}$)*</td>
<td>1.64 ± 0.89</td>
<td>2.67 ± 1.68</td>
<td>2.99 ± 1.20</td>
<td>2.27 ± 1.00</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (min)</td>
<td>28 ± 13</td>
<td>39 ± 19</td>
<td>52 ± 25</td>
<td>41 ± 22</td>
</tr>
<tr>
<td>$F$ (%)†</td>
<td>7.6 ± 2.2</td>
<td>8.3 ± 2.5</td>
<td>11.6 ± 2.8</td>
<td>8.3 ± 2.3</td>
</tr>
</tbody>
</table>

*The given $C_{\text{max}}$ values were normalized to a given dose of 100 mg NAC.
†$F$ is bioavailability.
Bioavailability of NAC increased (ANOVA: $p<0.001$) with increasing doses. A further analysis with t-test revealed that the 1200 mg dose differed from both the 200 mg ($p<0.001$) and the 600 mg ($p<0.01$) dose.

Repeate dosing

The mean plasma concentration time curve after repeated dosing is given in Figure 2 as is the corresponding single dose curve. Maximal plasma concentration, $C_{\text{max}}$, was normalized to an administered dose of 100 mg and is given in Table 1 as is $t_{\text{max}}$ and the bioavailability after repeated dosing.

Repeated dosing of NAC did not result in any changes in $C_{\text{max}}$, $t_{\text{max}}$, or bioavailability.

DISCUSSION

Single doses

There was a prolongation in $t_{\text{max}}$ as the dose was increased from 200 over 600 to 1200 mg, and in another study, where 4000 mg was administered as a single oral dose to three volunteers, $t_{\text{max}}$ occurred after 120 min; a result which supports and extends the present findings.
Figure 2. Mean NAC plasma concentrations after single and repeated administration of 600 mg of NAC a day as an effervescent tablet to 10 healthy volunteers (--- single dose, --- repeated dosing)

Maximal plasma concentration, $C_{\text{max}}$, and bioavailability gradually increased when the given dose was increased from 200 to 1200 mg. In addition, $C_{\text{max}}$ after a single 4000 mg dose in another study was $3.46 \mu\text{mol l}^{-1} 100 \text{mg}^{-1}$, a value higher than after the 1200 mg dose in the present study.

The observed prolongation in $t_{\text{max}}$, when giving higher doses, could be the result of a delayed stomach emptying, a saturation of a capacity-limited absorption, or a saturation of a capacity-limited presystemic elimination mechanism. Gastric residence time was probably the same after all administrations as the three doses were all taken in the fasting state with the same amount, 150 ml, of water. Amino acids are absorbed over the gut wall by active processes, and NAC could possibly be absorbed through the same active transport system as cysteine, since the two substances have a similar chemical structure. When higher doses of NAC are given, the absorption mechanism could be partially saturated and the rate of absorption consequently decreased which would result in a delayed $t_{\text{max}}$, after the higher NAC-doses. If the rate of absorption governs the $t_{\text{max}}$-value, a prolongation in $t_{\text{max}}$ would have been accompanied by a decrease in the dose-normalized maximal plasma concentration, which was not seen.

NAC undergoes a high degree of first-pass elimination and saturation of a capacity-limited presystemic elimination would increase the rate of absorption.
This would result in a prolongation of $t_{\text{max}}$ and an increase in $C_{\text{max}}$, both of which were observed. The present results thus are in accord with a partial saturation of a presystemic elimination process.

The concomitant presence of a capacity-limited absorption cannot however be ruled out. The observed non-linear increase in $C_{\text{max}}$ and bioavailability after increasing oral doses could also be the result of a capacity-limited systemic elimination process. The calculated late elimination half-lives were 4-1, 2-4, and 2-4 h after the 200, 600 and 1200 mg doses, respectively. Thus the systemic elimination of NAC does not seem to be non-linear in the concentration range studied.

**Repeated dosing**

As the dosing interval (12 h) was equal to 5 elimination half-lives no accumulation of plasma concentration was expected; about 97 per cent of the given dose should have been eliminated before the succeeding dose. As can be seen in Figure 2, repeated dosing of NAC did not induce any changes in the observed plasma concentration time curve. This is in good accord with the findings of Moldéus et al.\(^7\) Thus, the observed clinical effects after repeated dosing of NAC cannot be correlated to an accumulation of drug in plasma.

Collectively, there was a prolongation in $t_{\text{max}}$ and an increase in $C_{\text{max}}$ and bioavailability of NAC when higher single oral doses were given. The prolongation in $t_{\text{max}}$ and the increase in $C_{\text{max}}$, as well as the increased bioavailability could be explained by the saturation of a capacity-limited process in the presystemic elimination of NAC. No differences between a single dose and repeated dosing were observed.

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**REFERENCES**