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Pharmacokinetics of oral noscapine

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Summary. The relative bioavailability in 20 healthy volunteers of 100 mg, 200 mg and 300 mg tablets of noscapine and 200 mg as a solution has been assessed in a four-way cross-over study, with repeated administration of the 200 mg dose to assess intraindividual variability. There was a disproportionate increase in the AUC of noscapine tablets, as a 3-fold increase in dose produced a 9-fold rise in AUC. This dose-dependency could mainly be attributed to saturable first-pass metabolism of the drug. Administration of noscapine as a solution resulted in a significantly higher maximal concentration at an earlier time-point and a higher AUC than the corresponding dose as tablets. Repeated administration of noscapine tablets and solution yielded higher AUC on the second dosing occasion. No cause for this carry-over effect was found, and the contribution of remaining noscapine was negligible. The terminal half-life of noscapine, which was independent of formulation or dose size was 4.5 h. Both inter- and intraindividual variability in noscapine kinetics were very high, e.g. 73% and 51% CV of the AUC for the 200 mg tablet.

Key words: Noscapine; pharmacokinetics, bioavailability, dose dependency, oral administration, inter- and intra-individual variability, adverse events

Noscapine is an isoquinoline alkaloid obtained from opium, which lacks sedative, euphoric, analgesic or respiratory depressant properties (Martindale 1977). The only pronounced pharmacological effect of noscapine is cough suppression, for which it has been used for about 30 years. The antitussive effect has been documented in animals (Winter and Flataker 1954, Idänpään-Heikkilä 1967), healthy volunteers (Bickerman et al. 1957, Empey et al. 1979) and patients with chronic cough (Matthys et al. 1985). A central site of action is indicated from its effect on electrically induced cough (Balint and Rabloczky 1968) and from radioligand binding studies, where noscapine binds to specific sites (Karlsson et al. 1988, Karlsson and Neil 1988) and enhances dextromethorphan binding to its binding sites (Craviso and Mushaccio 1983), possibly by an allosteric mechanism.

Noscapine is eliminated by metabolism and has a relatively low bioavailability due to a substantial first-pass loss (Dahlström et al. 1982). The consequential high variability in plasma concentrations may have clinical implications, although no data are available to describe the concentration-response relationship. The present study was undertaken to assess both the extent of inter- and intra-subject variability in serum noscapine concentrations, as well as the influence of formulation and dosage size on the bioavailability of noscapine.

Subjects and methods

Subjects

Twenty healthy male volunteers, mean age 24 y (range 21 to 34 y), participated in the study. Their mean weight was 74 kg (range 63 to 88 kg), and no individual deviated more than 10% from normal body weight. The participants were healthy on clinical examination and routine blood chemistry tests performed prior to commencing and after completion of the study. A debrisoquine metabolism test was performed after selection of the participants, and subjects were classified as slow or extensive metabolisers (Steiner et al. 1988). No concomitant medication was allowed for 2 weeks prior to or during the study. All subjects gave written informed consent to their participation in the study, which was conducted according to the Declaration of Helsinki. It was approved by the Ethical Committee at Uppsala University.

Study design

The study was a randomized cross-over study in which the subjects received tablets containing 100 mg, 200 mg and 300 mg noscapine base as hydrochloride (50 mg tablet, Noskapin, ACO AB, Sweden) and 200 mg noscapine base as an aqueous solution (5 mg/ml, ACO AB, Sweden), on four different occasions a week apart. The four weeks constituted the four periods of the study. Twelve of the subjects were randomly selected to receive a repeat dose of 200 mg as tablets and the aqueous solution 1–2 days after the first dose. In those periods in which two doses administered, only the results of the first dose were used for comparison with doses in other periods. After an overnight fast, the subject took the tablet doses together with 250 ml water at room temperature, or the aqueous solution with 210 ml water, at 08.00 to 09.00 h. Four h later a standardised lunch was served. An indwelling intravenous catheter was inserted in the cubital vein for blood sampling. Blood samples (10 ml) were withdrawn before and at the following times after drug administration: 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 9 and 12 h. Thirty min after the collection the blood was centrifuged at 500 g for 10 min, and the serum was stored at −20°C until analysed.

Drug analysis

The serum concentrations of noscapine and its metabolites cotarnine, narcotoline and nor-noscapine (N-desmethyl-noscapine) were determined by a coupled column liquid chromatographic method (Johansson et al. 1988). Sample work-up employed protein precipitation for noscapine levels > 10 ng/ml, and extraction into 1% heptafluorobutanol in methylenchloride for levels < 10 ng/ml. The day-to-day vari-

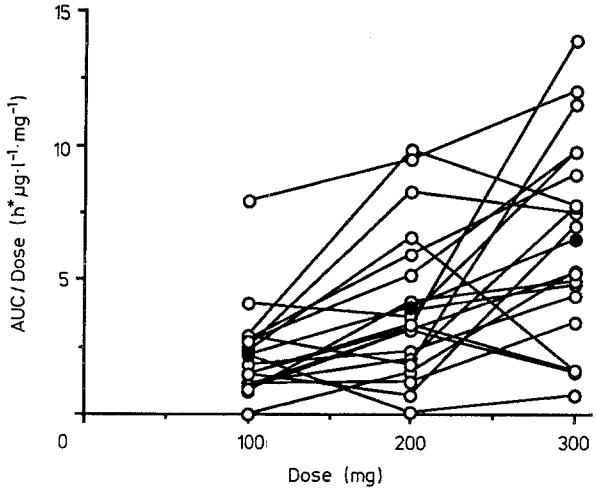

Fig. 1. Dose-corrected AUC vs dose for noscapine tablets; individual estimates (○), mean value (●)

ability of the analysis was 22%, 9.5% and 5.5% at 2.7, 15 and 250 ng/ml, respectively. The lowest concentration that could be determined was 2.5 and 3 ng/ml for noscapine and nor-noscapine, respectively. Cotarnine and narcotoline could be determined at about similar concentrations, but they were not detected in the serum samples.

Data analysis

Serum concentration-time profiles for each subject after each treatment were characterized in terms of the peak drug concentration in serum (C_{max}), the time to peak concentration (t_{max}), the area under the serum concentration-time curve extrapolated to infinity (AUC) and the half-life of the terminal decline in the serum concentration ($t_{1/2}$). AUC between time zero and the last time-point was calculated according to the log-linear trapezoidal rule. The slope of the terminal elimination phase (λ_z) was calculated by log-linear regression of three or more measurements, based on the highest coefficient of correlation (r^2), and it was used to calculate the extrapolated fraction of the total AUC (Gibaldi and Perrier 1982). In 15 data-sets (12 from the 100 mg dose) in which the last sample(s) contained drug concentrations below the determination limit, the extrapolated AUC was also calculated, assuming the first sample below the determination limit to be at that limit. This was done to avoid possible underestimation of the extrapolated AUC from such data-sets.

Statistical calculations

The entire data were divided into two parts which were treated separately: (1) data-sets resulting from all the tablet administrations except the repeated 200 mg dose, and (2) data-sets from the administration of 200 mg doses, both as tablets and solution. Three-way analysis of variance (subject, dose and period) was used in testing the AUC of noscapine, and the other parameters were tested by two-way analysis of variance (dose and subject). Hypothesis testing was performed by Friedman statistics and Wilcoxon's signed rank test for t_{max}. The three-way analysis of variance was performed with the statistical package BMDP, and Statview™ was used for the other tests. The significance level was set at $P < 0.05$, unless otherwise stated. Intraindividual CV was obtained as $\sqrt{\hat{\sigma}^2}/\hat{\mu}$, where $\sqrt{\hat{\sigma}^2}$ was obtained as $\sum_{i=1}^{n} (d_i - \bar{d})^2/2n$, d being the difference between the first and second observations from the repeated 200 mg dose.

Results

Subjects

All subjects were considered extensive metabolisers of debrisoquine. No clinically significant change in blood chemistry was detected in the tests performed after completion of the study.

Dose Proportionality

Dose proportionality was assessed by giving three different doses of tablets of noscapine; 100 mg, 200 mg, and 300 mg. The dose-corrected AUC (AUC/dose) showed a significant increase with increasing dose (Table 1), and there was an approximately linear relationship between dose and AUC/dose, so that a 3-fold increase in dose, from 100 mg to 300 mg, resulted in a 9-fold increase in AUC (Fig. 1). There was a increase over the entire dose range as indicated by the differences both between the 100 mg and 200 mg doses ($P = 0.003$), and between the 200 mg and 300 mg doses ($P = 0.01$). The mean extrapolated fraction of AUC was about 10%, with no marked difference between the dose levels. The choice of method to calculate the extrapolated AUC for data-sets with the last sample(s) below determination limit did not result in changes on the hypothesis testing. There was a 4- and 6-fold increase in C_{max}, accompanied by a slightly longer t_{max}, when increasing the dose from 100 mg to 200 and 300 mg, respectively. The interindividual CVs of the AUCs were 77%, 70% and 58% for the 100 mg, 200 mg and 300 mg doses, respectively. Corresponding values for C_{max} were 132%, 92% and 60%. The effect of period was not significant for AUC ($P = 0.4$). The disposition characteristics of

Table 1. Pharmacokinetic parameters of noscapine and nor-noscapine after 100, 200 and 300 mg noscapine as tablets ($n = 19$)

Parameter	Change with increasing dose	*P*-values	Mean (SD)			Unit
			100 mg	200 mg	300 mg	
AUC/Dose	Increase	*** < 0.0001	2.19 (1.69)	3.97 (2.87)	6.57 (3.86)	h* µg·l⁻¹·mg⁻¹
C_{max}/Dose	Increase	** 0.0027	1.29 (1.7)	1.97 (1.80)	2.88 (1.78)	ug·l⁻¹·mg⁻¹
t_{max}	NS		0.88 (0.34)	0.96 (0.35)	1.09 (0.49)	h
AUC(m)/Dose	Increase	*** 0.001	0.89 (0.63)	1.31 (0.85)	1.57 (0.78)	h* µg·l⁻¹·mg⁻¹
C_{max}(m)/Dose	NS		0.62 (0.50)	0.74 (0.55)	0.67 (0.32)	ug·l⁻¹·mg⁻¹
t_{max}(m)	NS		0.84 (0.32)	0.92 (0.40)	1.13 (0.48)	h
AUC(m)/AUC	Decrease	*** < 0.0001	0.39 (0.09)	0.30 (0.08)	0.26 (0.12)	–
C_{max}(m)/C_{max}	Decrease	*** < 0.0001	0.53 (0.19)	0.40 (0.18)	0.28 (0.14)	–
t_{max}(m)/t_{max}	NS		1.01 (0.15)	0.95 (0.15)	1.03 (0.21)	–

NS = Not Significant ($P > 0.05$)

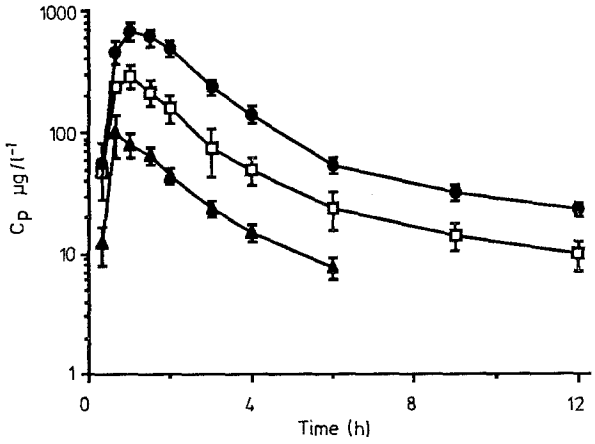

Fig. 2. Serum concentrations of noscapine (Mean, SEM) after doses of tablets of 100 mg (▲) 200 mg (□) and 300 mg (●)

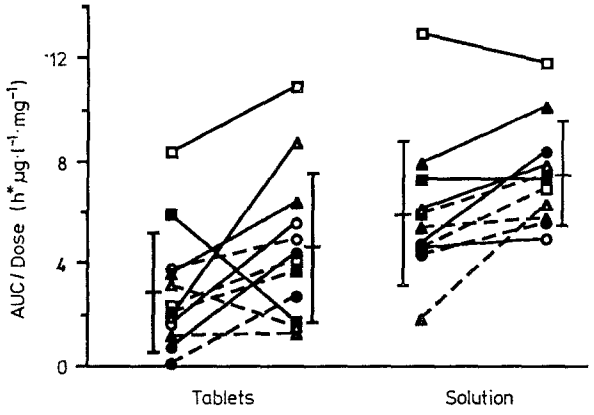

Fig. 3. Individual AUCs for replicated 200 mg doses. AUC for the first dose of each formulation are given to the left. All subjects have different combinations of symbols and lines. Mean (SD) is shown as a vertical bar

noscapine in the post-absorption phase were similar for the different sized doses (Fig. 2). The terminal half-life of noscapine, as determined from all data-sets with the last sample above the determination limit, was 4.5 (2.2) h.

A previously unknown metabolite, nor-noscapine, was detected in serum from all the subjects. Nor-noscapine showed its maximal concentration at the same time as noscapine, and the ratio between metabolite and noscapine was approximately constant in the post-absorption phase. The mean metabolite/noscapine ratio (SD) in all individual samples obtained between 2 and 12 h was 0.31 (0.14) (range 0.07–0.83; $n = 360$). The variability in AUC and C_{max} of nor-noscapine was similar to that of noscapine, whereas their ratio showed markedly less variation (Table 1).

Tablet vs solution

To assess the influence of formulation, noscapine 200 mg was given as tablets and as a solution. Noscapine in solution was significantly more rapidly absorbed, yielding a higher maximum concentration and a larger AUC than when given as tablets (Table 2). Further, the variability in the observed parameters was markedly lower for the solution, with inter- and intraindividual CV in AUC of 37% and 16%, compared to 73% and 51% for the tablets. Corresponding CV values for C_{max} were 41% and 32% for the solution and 79% and 71% for the tablets. The terminal half-life did not differ between the two formulations.

When noscapine 200 mg was repeated one or two days after the first dose, changes in several parameters were observed (Table 3). The most pronounced was an increase in the AUC of the tablets and solution (Fig. 3). The increase could not readily be explained by the presence of residual noscapine, as pre-administration serum concentrations were below the determination limit. The contribution of such a low level of noscapine to the concentration-time profile could not explain the increase found in the AUC.

Side-effects and drop-out

The spontaneously reported side-effects were headache (6 occasions), tiredness (2) and nausea/tiredness (1), as reported by 6 of the volunteers. The side effects occured after the noscapine solution (on 4 occasions), the 100 mg (2), 200 mg (1) and 300 mg (2) tablet doses. One subject withdrew from the study after completing Period 2 due to acute illness not related to the intake of noscapine.

Discussion

The results suggest that the main factor governing the nonlinearities encountered is the dose-dependent availability of orally administered noscapine. The reported plasma clearance of 1.5 l/min [Dahlström et al. 1982] makes extensive first-pass loss of drug plausible, and supports the conclusion that the main increase in dose-corrected AUC is likely to result from more drug escaping

Table 2. Difference in pharmacokinetic parameters of noscapine and nor-noscapine after 200 mg noscapine administered as tablets and as solution ($n = 19$)

Parameter	Soln vs Tabl	*P*-values	Mean (SD)		Unit
			Tabl	Soln	
AUC/Dose	Higher	*** < 0.0001	4.21 (2.91)	6.64 (2.30)	h* µg·l⁻¹·mg⁻¹
C_{max}/Dose	Higher	*** < 0.0001	2.03 (1.62)	4.06 (1.66)	ug·l⁻¹·mg⁻¹
t_{max}	Lower	** < 0.01	0.96 (0.40)	0.57 (0.18)	h
AUC(m)/Dose	Higher	*** 0.0004	1.23 (0.75)	1.69 (0.57)	h* µg·l⁻¹·mg⁻¹
C_{max}(m)/Dose	Higher	*** < 0.0001	0.69 (0.47)	1.07 (0.32)	ug·l⁻¹·mg⁻¹
t_{max}(m)	Lower	** < 0.01	0.92 (0.40)	0.56 (0.16)	h
AUC(m)/AUC	Lower	* 0.017	0.33 (0.15)	0.27 (0.06)	–
C_{max}(m)/C_{max}	Lower	** 0.0026	0.46 (0.28)	0.29 (0.10)	–

Table 3. Changes in pharmacokinetic parameters of noscapine and nor-noscapine after 200 mg noscapine tablets and solution repeated within 2 days ($n = 11$)

Parameter	Formulation	Change with 2nd dose	*P*-value	Mean (SD)		Unit
				1st dose	2nd dose	
AUC/Dose	Soln	Increase	* 0.011	5.95 (2.81)	7.46 (2.02)	h* ug·l^{-1}·mg^{-1}
	Tabl	NS		2.87 (2.32)	4.64 (2.94)	
C_{max}	Soln	NS		3.67 (1.83)	4.47 (1.47)	ug·l^{-1}·mg^{-1}
	Tabl	NS		1.17 (1.18)	2.29 (1.36)	
t_{max}	Soln	NS		0.58 (0.16)	0.58 (0.22)	h
	Tabl	NS		0.89 (0.27)	1.0 (0.49)	
AUC(m)	Soln	NS		1.54 (0.56)	1.75 (0.53)	h* ug·l^{-1}·mg^{-1}
	Tabl	NS		0.96 (0.70)	1.37 (0.64)	
C_{max}(m)	Soln	NS		1.01 (0.31)	1.09 (0.27)	ug·l^{-1}·mg^{-1}
	Tabl	Increase	* 0.037	0.48 (0.35)	0.8 (0.4)	
t_{max}(m)	Soln	NS		0.53 (0.18)	0.64 (0.11)	h
	Tabl	NS		0.83 (0.38)	0.88 (0.46)	
AUC(m)/AUC	Soln	NS		0.27 (0.07)	0.24 (0.05)	–
	Tabl	NS		0.38 (0.19)	0.35 (0.13)	
C_{max}(m)/C_{max}	Soln	NS		0.30 (0.08)	0.27 (0.06)	–
	Tabl	NS		0.58 (0.28)	0.46 (0.31)	

NS = Not Significant ($P > 0.05$)

first-pass loss due to saturation of liver/gut wall enzymes by high portal concentrations during the absorption phase. The lower variability in AUC and C_{max} found with higher doses and higher absorption rates may also be explained in the context of saturable first-pass metabolism, as the fraction available would be increased.

The disproportionate increase in AUC with the dose of noscapine invalidates any calculation of bioavailability based on relative AUCs, and the availability of small doses will be underestimated if such a procedure were adopted. For certain special cases methods exist to determine the fraction of dose available, even if there are nonlinear kinetics [Martis and Levy 1973, Rubin and Tozer 1984]. Unfortunately, these methods are not applicable to a drug such as noscapine, with multiexponential disposition and several unknown metabolic pathways. A plausible explanation for the higher bioavailability of noscapine administered as a solution than as a tablet is a higher rate of absorption from the former and saturable first-pass loss. A possible cause of the increase in AUC and C_{max} when the 200 mg dose of noscapine was repeated is the presence of one or several slowly eliminated metabolites, which competes both with noscapine and nor-noscapine for the same metabolic pathway(s). Another possible cause of a lower rate of metabolism would be depletion of co-factors required by the metabolizing enzymes by the first dose of noscapine.

Intra- and interindividual variability

The differences in AUC within and between subjects can be ascribed to variability in bioavailability and/or clearance. For a drug with high hepatic clearance and saturable first-pass metabolism, its bioavailability will be dependent not only on the intrinsic metabolism and hepatic blood flow, but also on the rate of absorption. A high absorption rate will yield high portal drug concentrations, leading to enzyme saturation and a small loss in the first pass, whereas the same dose absorbed over a longer period may suffer high first-pass loss via the relatively unsaturated hepatic enzymes. The absorption rate of drugs often varies considerably, both between and within individuals, which offers one plausible explanation for the large variability of AUC.

Nor-noscapine

The decline of the nor-noscapine concentrations paralleled that of noscapine, indicating formation rate limited elimination of the metabolite. The pharmacological effects of nor-noscapine do not appear to have been studied, so any therapeutic significance, of the metabolite cannot be assessed. Noscapine metabolites in blood have not previously been analysed, and what knowledge there is comes from urine data. About ten metabolites identified there accounted for less than 20% of the dose given [Tsunoda and Yosimura 1979 and 1981]. The relative importance of the nor-noscapine pathway in the elimination of noscapine cannot be assessed. The renal excretion of intact noscapine is negligible [Vedsö 1961, Tsunoda and Yosimura 1981]. Nor-noscapine may be renally excreted, although secondary metabolism seems more likely, since at least five different pathways of noscapine metabolism apply to nor-noscapine as well [Tsunoda and Yosimura 1979 and 1981].

The decline in the AUC-ratio (nor-noscapine/noscapine) with increasing dose denotes a saturable mechanism of nor-noscapine formation. This was also demonstrated by the lower C_{max}-ratios at higher doses, as well as the lower C_{max}-ratios for the solution than for the tablets. The magnitude of the increase in dose-corrected AUC of noscapine with dose suggests that major metabolic pathway(s) must exhibit nonlinearities during the first pass of the drug. Thus, either nor-noscapine must be a major metabolite of noscapine, or nonlinearities in other metabolic pathways must be present.

With nonlinear formation from noscapine and linear elimination of nor-noscapine, increasing doses of the parent drug should result in decreasing values of $C_{max(m)}$/dose and $t_{max(m)}$. However, these parameters were constant and increased with dose, respectively. This is compatible with saturability both of the formation and elimination of nor-noscapine. The higher $AUC_{(m)}$ of nor-noscapine after administration of the solution than of the same dose as tablets further supports saturable elimination of the metabolite.

Terminal half-life of noscapine

The terminal half-life of noscapine was, 4.5 h, much longer than the previously reports of 2.2 h [Dahlström et al. 1982] and 1.7 h [Haikala et al. 1986]. In those studies serum was collected for 6 h after dosing, which accounts for the discrepancy between the estimates. However, the true terminal half-life is probably even longer than 4.5 h, since the terminal decline deviated from log-linearity in the present data. The reported plasma clearance of noscapine of 1.5 l/min [Dahlström et al. 1982] is probably overestimated by at least 10%–15%, due to extrapolation from a too short a half-life.

Therapeutic implications

The doses used here exceeded the recommended single dose of 50 mg t.d.s. Dose-dependency of kinetics always raises questions about the effect of over-dosing. Although nonlinear systems do not readily lend themselves to extrapolation, there is some basis for cautious predictions, under the assumption that the disproportionate increase in AUC can largely be attributed to an increase in the bioavailability. Dahlström et al. (1982) found that the absolute availability of 150 mg of a similar tablet of noscapine was about 30%. As the concentrations resulting from the intravenous dose in that study were at least 5-fold higher than those from oral dosing, this bioavailability may be an underestimate. However, from the suggested absolute availability of $\geq 30\%$, and the approximately linear relationship between dose and bioavailability in the dose range studied, a bioavailability of $\geq 60\%$ can be calculated for the 300 mg dose. At increasing doses above 300 mg, availability must rapidly approach unity or the rate of increase in bioavailability must decline.

The therapeutic importance of three observations made here, the disproportionate increase in AUC, the longer true terminal half-life and the carry-over effect, could be evaluated in a study involving measurements at steady state.

No concentration-effect relationship has been established for noscapine. In spite of this, it seems plausible that the large variability in pharmacokinetics observed, would have therapeutic implications. As the variability even increased at lower doses, therapeutic failure of noscapine may result from the production of subtherapeutic concentrations.

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