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ORIGINAL ARTICLE

Preclinical pharmacokinetics and bioavailability of noscapine, a tubulin-binding anticancer agent

Ritu Aneja · Neerupma Dhiman · Jyoti Idnani · Anshumali Awasthi · Sudershan K. Arora · Ramesh Chandra · Harish C. Joshi

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Abstract
Background Noscapine, a naturally occurring antitussive phthalideisoquinoline alkaloid, is a tubulin-binding agent currently in Phase I/II clinical trials for anticancer therapy. Unlike currently available antimitotics such as taxanes and vincas, noscapine is water-soluble, well tolerated, and shows no detectable toxicity.
Objective The goal was to develop a simple, sensitive, quantitative, selective, and less time-consuming high-performance liquid chromatography (HPLC) method for determination of noscapine and to study its pharmacokinetics in mice models.
Method Noscapine was extracted from mice plasma using the protein-precipitation method and detected using a reversed-phase C8 column with mobile phase consisting of 35% acetonitrile and 65% ammonium acetate buffer (pH 4.5) at 232 nm wavelength. Pharmacokinetic studies of noscapine were performed in mice following intravenous bolus at 10 mg/kg and oral administrations at 75, 150, and 300 mg/kg.
Results The standard curves for noscapine estimation were linear between 390 and 50,000 ng/ml (lower limit of quantification was 390 ng/ml) and the recovery was ~80%. Following 10 mg/kg intravenous dose, mean plasma concentrations of 7.88 μg/ml were achieved at 5 min in mice and declined with undetectable levels at 4 h. The mean total body clearance was 4.78 l/h. The mean volume of distribution (V_d) was 5.05 l. Non-compartmental analysis yielded the mean area under the plasma concentration–time curve (AUC) for noscapine as 53.42, 64.08, and 198.35 h μg/ml reaching maximum plasma concentrations (C_{max}) of 12.74, 23.24, and 46.73 μg/ml at a t_{max} of 1.12, 1.50, and 0.46 h at the linearly increasing dose levels.
Conclusion A rapid and simple HPLC/UV method for the quantification of noscapine in plasma has been developed to study pharmacokinetics of noscapine at tumor-suppressive doses in the mouse. Since orally available anticancer drugs are rare, therefore, noscapine, an innocuous agent, having a mean oral bioavailability of 31.5% over the studied dose range merits its further advancement in humans for anticancer therapy.

Keywords Noscapine · Pharmacokinetics · HPLC/UV

R. Aneja (✉) · H. C. Joshi
Laboratory for Drug Discovery and Research,
Department of Cell Biology,
Emory University School of Medicine,
615 Michael Street, Atlanta, GA 30322, USA
e-mail: raneja@emory.edu

N. Dhiman · R. Chandra
BR Ambedkar Center for Biomedical Research,
University of Delhi, Delhi 110007, India

J. Idnani · A. Awasthi · S. K. Arora
Preclinical Pharmacokinetics and Metabolism Laboratories,
Lupin Research Park, Pune 411042, India

Introduction

Highly dynamic mitotic spindle microtubules are among the most successful targets for anticancer therapy [1–3]. Microtubule-targeted drugs, including paclitaxel and vinca alkaloids, are thus widely used in current chemotherapy regimes [4]. However, despite their impressive clinical successes, several problems associated with existing anticancer therapeutics remain, such as toxicities including myelosuppression,

peripheral neuropathy, alopecia, and gastrointestinal toxicity; susceptibility to the development of drug resistance; poor bioavailability that results in a need for prolonged intravenous infusions and frequent hospital visits, and sparse solubility usually necessitating the use of agents (for example, cremophor) that cause undesirable side-effects [5–9]. It is, thus, necessary that new tubulin-binding drugs are discovered and developed that are non-toxic and have improved pharmacological profiles.

Our laboratory has discovered a novel microtubule-binding chemotherapeutic agent [10] that overcomes many of the limitations associated with other tubulin-binding anticancer drugs. This agent, noscapine (Fig. 1), is a commonly used antitussive agent available worldwide that lacks sedative, euphoric, analgesic, and respiratory depressant properties [11]. The precise mechanism for the antitussive effects of noscapine remains unknown. Cough suppression was the only pronounced pharmacological effect of noscapine known for more than 30 years. In the last 8 years, we have demonstrated that noscapine: (a) binds to tubulin and alters its conformation and assembly properties [10]; (b) interferes with microtubule dynamics [12, 13]; (c) does not significantly change the microtubule polymer mass even at higher concentrations [12, 14]; (d) arrests a variety of mammalian cells including drug-resistant variants in mitosis and targets them for apoptosis [10, 14–17]; and (e) inhibits progression of murine melanoma, lymphoma, glioblastoma, and human breast tumors implanted in nude mice with no detectable toxicity to the rapidly dividing cells and post-mitotic cells such as neurons [10, 12, 16, 17]; (f) does not inhibit primary humoral and cellular immune responses in mice [17]; (g) can be orally administered bypassing parenteral injections and intravenous infusions that can be complicated by anaphylactic responses and infection at the injection site causing pain, thrombosis of blood vessels, or embolisms [10, 12, 16, 17].

Although orally available anticancer drugs are rare, it is unique that noscapine can be administered orally to successfully regress tumor volumes in mice [10, 12, 16, 17]. We have been able to show that noscapine is active against tumor cells that have become resistant to currently available anticancer drugs due to p-glycoprotein overexpression and other drug efflux pumps of the ATP-binding drug transporter family [14]. These efflux pumps also play a role in modulating the oral bioavailability and pharmacokinetics of drugs [18, 19]. Given that other microtubule drugs are better substrates for various ABC transporters that can alter drug distribution due to their faster elimination, noscapine being a poor p-glycoprotein substrate is unique among currently available chemotherapeutic drugs. We were thus inquisitive to study the bioavailability and pharmacokinetic profiles of tumor-suppressive dosages of noscapine. Though the pharmacokinetics of low antitussive doses of noscapine has been previously described [20–22], the then available methods involved for the analysis of noscapine in plasma and urine included fluorometric [23, 24] gas and thin-layer chromatographic [25, 26], and liquid chromatographic techniques [27, 28]. Those techniques involved multiple extraction and purification steps and were, therefore, labor-intensive, and time-consuming and ran a risk of losing some amounts during the multiple steps involved. Recently, Zhu et al. reported a liquid chromatography–tandem mass spectrometric method for the simultaneous determination of methylephedrine and noscapine in human plasma [29]. This study involved the highly sensitive LC-MS/MS method, due to the low antitussive doses of noscapine given to the subjects. Here, we present a new, simple, sensitive, selective, quantitative, and less time-consuming reversed-phase HPLC method for the determination of tumor-suppressive dosages of noscapine in mice plasma. The feasibility for oral administration and its non-toxic attributes might offer noscapine as an anticancer drug of the future. Given the importance of pharmacokinetic evaluation in the drug development process, we employed the HPLC method to evaluate the pharmacokinetic parameters and bioavailability in male and female mice upon oral and intravenous administration of noscapine.

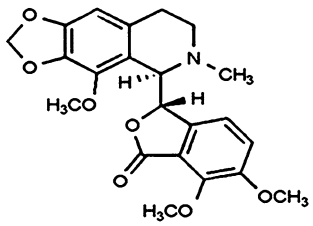

Fig. 1 Molecular structure of noscapine

Materials and methods

Chemicals

Noscapine was obtained from Sigma Aldrich (St Louis, MO, USA). In order to increase the solubility of noscapine to the cancer chemotherapeutic doses, we synthesized its hydrochloride salt, which is equally effective in preclinical studies as the parent-free base, noscapine.

The purity of the noscapine salt was 98.5% as assessed by HPLC. Acetonitrile and methanol (HPLC grade), and other chemicals, analytical grade, were purchased from J.T. Baker and Merck.

Instrumentation and chromatographic conditions

A high-performance liquid chromatography (HPLC) system consisted of Shimadzu instruments equipped with a Shimadzu LC-10 AT pump and a SPD-10A UV detector. The analytical column used was LiChrospher @ 60 RP select-B (C8) reversed-phase column (4 mm × 125 mm) packed with 5 μm particles. The column temperature was maintained at the room temperature (25°C). The mobile phase consisted of ammonium acetate:acetonitrile (65:35). The pH of the 20 mM ammonium acetate was adjusted to 4.5 using glacial acetic acid. The solution was filtered and degassed by vacuum filtration through a 0.22-μm membrane filter before use and was freshly prepared for each run. The flow rate of the mobile phase was adjusted to 1 ml/min. The wavelength of detection was 232 nm and the detector was set at 0.005-absorbance unit, full scale.

Animal dosing and sampling

Swiss albino mice used for the pharmacokinetic study were bred and maintained in the Animal Facility of Lupin Research Park, Pune. All procedures involving animals were in accordance with protocols approved by the Institutional Animal Ethics Committee and were reviewed by the Committee for the Purpose of Control and Supervision of Experiments on Animals. A total of 216 Swiss albino mice (108 males and 108 females) with an average weight of 25 g were used for the oral and intravenous pharmacokinetic study. For each dose level, 27 mice (male or female) were randomly divided into 9 groups of 3 animals each corresponding to the time points of blood collection. Although this gives us three mice per time point per dose per gender for analysis, but to ensure that our systemic error is acceptable we had analyzed each sample in triplicates and seen no variation (at 95% confidence level). The animals were housed in an environment with a 12-h light and 12-h dark cycle at a constant temperature (22°C) and had free access to standard laboratory feed and water. Mice were acclimatized to this environment for 1 week prior to the experiments. On the day of the experiment, animals were fasted for 3 h before the experiment; however, water was available ad libitum. Noscapine was administered orally by gavage at a dose of 75, 150, and 300 mg/kg. The intravenous dose was 10 mg/kg. The noscapine solution for administration to mice via the oral and intravenous routes was prepared by dissolution of the noscapine salt in phosphate buffer (pH 4.5). Plasma levels of noscapine were monitored for 24 h after dosing. Samples were collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after oral administration and 0, 0.083, 0.25, 0.5, 0.75, 1, 2, 4, and 6 h after intravenous administration of the drug. Approximately 750 μl of blood was collected from the retro-orbital vein into polypropylene microcentrifuge tubes containing 25 μl of 20 mM sodium citrate. The blood samples were centrifuged at 4,600 rpm for 15 min at 4°C, and the plasma was separated. Plasma samples were stored at −80°C until analysis.

Preparation of calibration standards and quality control samples

The selectivity of the method was ascertained by analyzing human plasma from six different sources for potential interferences from endogenous compounds. The human plasma sample finally chosen for spiking was the one that offered no significant interferences from endogenous substances at the retention time of noscapine. Standard stock solution of noscapine was prepared in acetonitrile and the working solutions for calibration standards and quality control (QC) samples were derived from the stock solution at final concentrations ranging from 8 to 1,000 μg/ml. Calibration curves were prepared by spiking 50 μl of the working solution to 950 μl of blank drug-free human plasma to obtain plasma samples ranging from 0.39 to 50 μg/ml. The plasma samples were deproteinized with three volumes of acetonitrile and plasma concentration of spiked noscapine was analyzed using the HPLC method. Plasma samples were quantified using the peak area which was plotted against noscapine concentrations and standard curves in the form of $y = A + Bx$ were calculated using weighted ($1/x^2$) least square linear regression. Excellent linearity was obtained over the chosen concentration range and the correlation coefficients for the calibration regression curves were 0.99 or greater. In the current method, the lower limit of quantification was 0.39 μg/ml, at which the peak (response) was identifiable, discrete, and reproducible with a precision of 20% and an accuracy of 80–120%. All QC samples used in the validation and during the pharmacokinetic study were prepared in the same way as calibration standards before analysis. Plasma concentrations of QC samples were 1.2, 12.02, and 20.04 μg/ml. The spiked plasma samples (standards and QCs) were extracted on each analytical batch along with the

unknown samples. To account for matrix effects between human and mouse plasma and to ensure that there is no bias by quantitating mouse plasma off of a human plasma calibration curve, a mini-validation including the mouse QC samples was performed that demonstrated acceptable accuracy and precision. For noscapine, the predicted concentration of the QC samples was within 15% of the nominal concentration, indicating acceptable assay performance.

Method validation

Intra-day variability was assessed at three concentrations [1,200, 12,000, and 20,000, namely the low quality control (low QC), medium quality control (med QC), and high quality control (high QC), respectively] by injecting five replicates of each concentration on the same day. Similarly, the inter-day variability was assessed at these three different concentrations by injecting five replicates of each concentration on four different days. Accuracy was determined by comparing the calculated concentration using calibration curves to nominal concentration. Precision was expressed using the coefficient of variance (CV). As summarized in Table 1, the intra-day mean accuracies varied from 90.90 to 106.14% over the 1,200–20,000 ng/ml concentration range of noscapine, the corresponding precision ($n = 5$) varied from 1.23 to 4.23%. The inter-day mean accuracies varied from 104.42 to 105.75% and the corresponding precision ($n = 20$) varied from 3.39 to 3.73%. Thus the method showed good accuracy and precision.

Analysis of pharmacokinetic data

Plasma-concentration data were analyzed with standard non-compartmental methods using the WIN NONLIN software version 4.1. Composite plasma concentration–time profiles were constructed for both male and female mice. The following pharmacokinetic parameters were assessed: $t_{1/2}$ (h), t_{max} (h), C_{max} (μg/ml), AUC_{last} (h μg/ml), AUC_{inf} (h μg/ml), CL (ml/h), V_d (ml). The area under the curve (AUC_{last}) was calculated by the linear trapezoidal rule up to the last sampling point with detectable levels with extrapolation to infinity (AUC_{inf}) by the equation: $AUC_{last} + C/k_e$ where k_e represents the terminal disposition rate constant. k_e was calculated from the slope of data points in the final log linear part of the drug-concentration–time curve by weighted least square linear regression analysis. The terminal disposition half-life ($t_{1/2}$) value was calculated using the equation: $t_{1/2} = 0.693/k_e$. The total body clearance (CL_{tot}) was calculated as the dose/AUC_{inf}. The apparent volume of distribution (V_d) was calculated as CL_{tot}/k_e. Maximum plasma concentration (C_{max}) and the time to maximum concentration (t_{max}) following oral administration were estimated by recording directly from experimental observations. The bioavailability was calculated using the formula, $F = (AUC_{iv} \cdot Dose_{po}/AUC_{po} \cdot Dose_{iv})100$.

Table 1 Accuracy and precision of QC samples

Analysis day	Nominal concentration (μg/ml)		
	Low QC (1,200 ng/ml)	Med QC (12,000 ng/ml)	High QC (20,000 ng/ml)
Day 1 ($n = 5$)			
Intra-day mean	1,235.38	1,3091.48	21,256.93
±SD	50.52	550.01	898.95
CV%	4.09	4.20	4.23
Mean accuracy %	97.05	90.90	93.72
Day 2 ($n = 5$)			
Intra-day mean	1,273.21	12,533.31	21,228.32
±SD	48.02	367.73	869.51
CV%	3.77	2.93	4.10
Mean accuracy %	106.10	104.44	106.14
Day 3 ($n = 5$)			
Intra-day mean	1,250.40	12,445.19	20,534.80
±SD	23.39	200.37	252.34
CV%	1.87	1.61	1.23
Mean accuracy %	104.20	103.71	102.67
Day 4 ($n = 5$)			
Inter-day mean	1,253.00	12,689.99	21,006.68
±SD	42.47	473.58	764.54
CV%	3.39	3.73	3.64
Mean accuracy %	104.42	105.75	105.03

Results and discussion

The discovery of the anticancer property of a non-toxic antitussive agent, noscapine has recently drawn considerable attention and its medicinal chemistry is being actively explored to design more potent analogs with improved pharmacological profiles [30–35]. Following our work, the lead compound, noscapine is in Phase I/II clinical trials for non-Hodgkin's lymphoma or chronic lymphocytic leukemia refractory to chemotherapy at the University of Southern California. Since the pharmacokinetic evaluation is an important component of the preclinical drug development process, we sought to investigate the pharmacokinetics and bioavailability of this well-tolerated non-toxic anticancer drug.

Although several reports describing the pharmacokinetics of noscapine using liquid chromatographic methods are available [20–23], these methods are limited due to tedious multiple extraction and purification steps involved. Even so, a recent report by Zhu et al. describes a sensitive LC-MS/MS method for the determination of noscapine in a multicomponent formulation, but the low noscapine doses in the formulation (16 mg) are conducive to its antitussive effects. The tumor-suppressive dose regimes of noscapine are much higher than the antitussive dosages and have not been a subject of study so far. Therefore, we realized the need to develop an adequately sensitive, specific, and selective method for the determination of chemotherapeutic dose regimes of noscapine in plasma, which is not cumbersome and is time-effective. The simple and fast assay method was then successfully employed to an oral and intravenous pharmacokinetic study. The HPLC method was optimized with respect to the effect of certain variables including the selection of the organic phase, the concentration of the buffer to achieve good retention times, and the pH of the mobile phase. There was a need to slightly modify the mobile phase composition for achieving a clean area where there were no observable plasma interferences in the retention time region of noscapine. According to the retention time, peak height, and peak asymmetry factor, the suitable conditions of the mobile phase were established as consisting of ammonium acetate:acetonitrile (65:35) at a pH 4.5. Under these chromatographic conditions, symmetrical and well-resolved peaks were obtained for noscapine. A typical chromatogram of blank (noscapine-free) human plasma is displayed in Fig. 2a. Figure 2b depicts a representative chromatogram of noscapine spiked in human plasma. There were no interfering peaks from endogenous compounds at the retention time region of noscapine, which is clearly evident by the well-separated noscapine peak at a retention time of 4.52 min. Figure 2c shows a representative chromatogram of a study sample, where mice plasma was obtained after oral noscapine administration.

Since the chromatographic method was developed for application to a pharmacokinetic study, the standardization and development of an extraction method was another important component of the undertaken study. After several trials, we found that the one-step protein-precipitation method using acetonitrile as a solvent for precipitating proteins and solubilizing noscapine was satisfactory. Next, the extraction efficiency of noscapine from plasma was determined for each standard concentration from validation standards. The mean recovery for noscapine from mice plasma was found to be about 80% using acetonitrile. The extent of recovery of noscapine was found to be consistent, precise, and reproducible when analytical results for extracted samples at three concentrations (low, medium, and high) were compared with

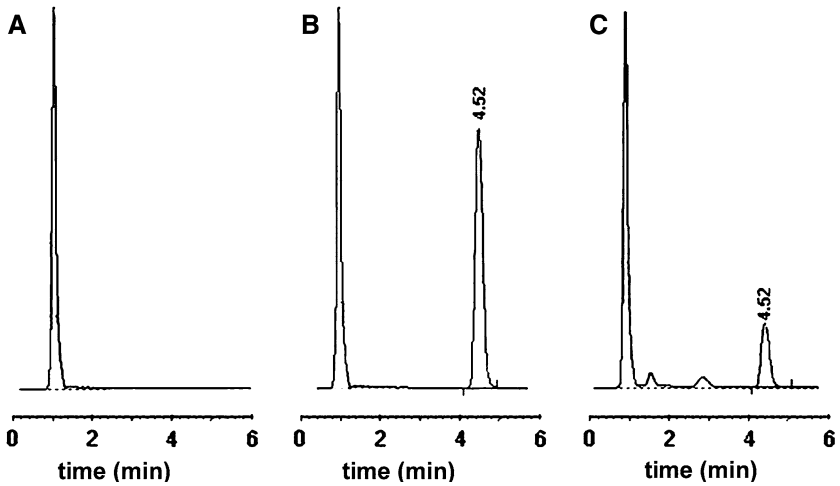

Fig. 2 High-performance liquid chromatograms of acetonitrile extract of **a** blank human plasma, **b** human plasma spiked with noscapine depicting retention time of 4.52 min at a mobile phase of composition (ammonium acetate:acetonitrile, 65:35, pH 4.5), and **c** mice plasma obtained after oral noscapine administration

standards representing 100% recovery. Thus the extraction method was suitable for the analysis of noscapine in plasma samples. Using this assay, we reliably measured noscapine in mice plasma over a wide range of concentrations from 0.39 to 50 μg/ml using 200 μl of mice plasma samples. The linearity between 0.39 and 50 μg/ml was determined using the least square regression equation. The lowest limit of quantification for noscapine under these conditions was 0.39 μg/ml.

Pharmacokinetics upon oral administration of noscapine in mice

The plasma concentration–time profiles of noscapine were studied at three single dose levels (75, 150, and 300 mg/kg) for both male and female mice upon oral administration to establish the linearity of dose responsiveness and are shown in Fig. 3a–c. Figure 3d depicts a composite of all three oral doses with mean data values of parameters from male and female mice. All the three doses were well tolerated and mice did not show any signs of discomfort. The pharmacokinetic parameters of noscapine in mice obtained upon oral administration at the three different doses are summarized in Table 2. As can be seen clearly in Table 2, noscapine was easily absorbed, reaching a C_{max} of 13.37, 24.48, and 49.47 μg/ml at a t_{max} of 1.08, 1.75, and 0.33 h upon oral administration of 75, 150, and 300 mg/kg noscapine, respectively, in male mice. Similarly, at the linearly increasing dose levels, the C_{max} in female mice was 12.18, 22.00, and 44.00 μg/ml at a t_{max} of 1.17, 1.25, and 0.59 h. The AUC_{last} at 75 and 150 mg/kg for both male and female mice was comparable; however, the AUC_{last} at 300 mg/kg was approximately threefold higher as compared to the two lower doses. The lack of proportional relationships of the AUC values as a function of dose possibly suggests that a saturable or non-linear behavior may be occurring over the studied dose range. The half-life ($t_{1/2}$) of the drug for both male and female mice was comparable at 75 and 300 mg/kg, but was lower at the median dose of 150 mg/kg. Since half-life represents a hybrid parameter influenced by the primary pharmacokinetic clearance (CL) and volume of distribution (V_d), it is possible that a stationary half-life might result from changes in both CL and V_d that cancel out changes in half-life. Overall, our results from the oral study clearly indicate that noscapine absorbs quickly in mice at all dose levels ($t_{max} < 2$ h) and is distributed rapidly and widely. The percent bioavailability was comparable at 75 and 300 mg/kg; however, it was higher at 150 mg/kg for both male and female mice. Furthermore, our data reveals absence of any gender-related differences at the three oral dose levels included in the study.

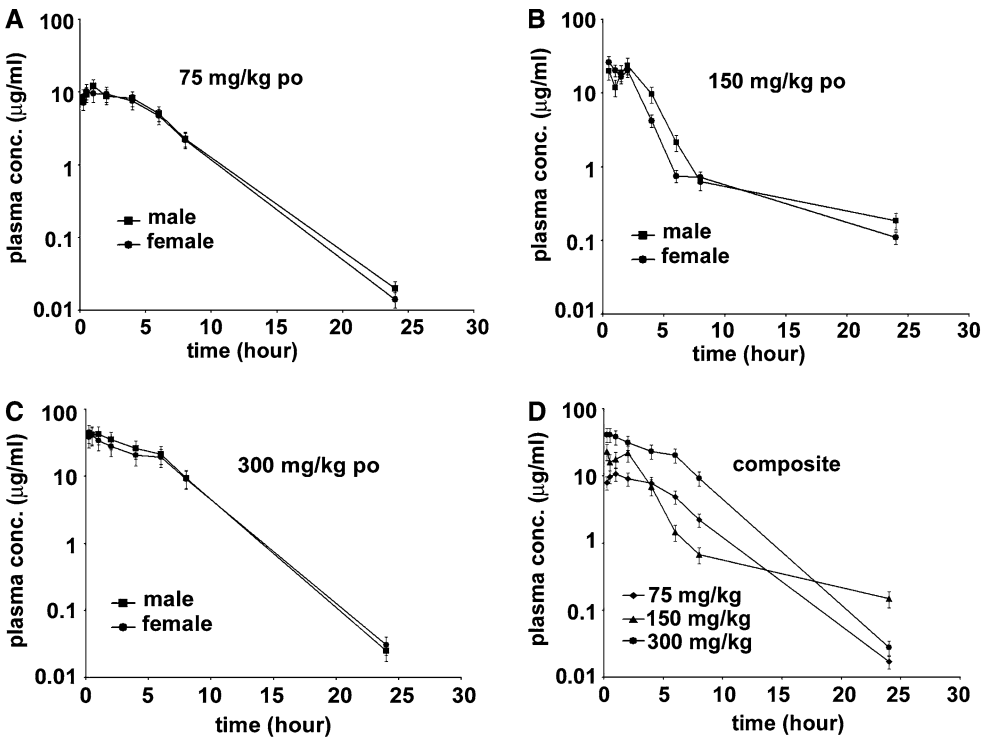

Fig. 3 Plasma concentration–time profile of noscapine in male and female mice upon oral administration of **a** 75 mg/kg, **b** 150 mg/kg, and **c** 300 mg/kg noscapine. **d** Mean composite plasma concentration–time profile for all three oral doses

Table 2 Pharmacokinetic parameters of noscapine upon oral administration ($n = 3$) in male and female mice

Properties	Dose					
	75 mg/kg		150 mg/kg		300 mg/kg	
	Male	Female	Male	Female	Male	Female
C_{max} (μg/ml)	13.37 ± 2.2	12.18 ± 2.4	24.48 ± 2.7	22.00 ± 3.3	49.47 ± 2.3	44.00 ± 2.2
t_{max} (h)	1.08 ± 0.8	1.17 ± 0.7	1.75 ± 0.3	1.25 ± 0.4	0.33 ± 0.14	0.59 ± 0.3
$t_{1/2}$ (h)	2.91 ± 0.3	3.02 ± 0.2	1.47 ± 0.3	0.99 ± 0.23	2.52 ± 1.2	2.65 ± 1.1
AUC_{last} (h μg/ml)	54.55 ± 9.4	52.29 ± 17	67.23 ± 6.1	60.93 ± 7.4	215.20 ± 18.2	181.5 ± 15
AUC_{inf} (h μg/ml)	71.50 ± 8.3	68.92 ± 17.5	81.35 ± 9.9	61.99 ± 7.4	257.48 ± 31	223 ± 18
Bioavailability (%)	23.98 ± 3.2	21.55 ± 2.9	42.22 ± 4.2	47.90 ± 4.7	26.68 ± 3.8	26.63 ± 3.5

The data are presented as mean ± SD ($P < 0.05$)

Table 3 Pharmacokinetic parameters of noscapine upon intravenous administration ($n = 3$) in male and female mice

Properties	Dose: 10 mg/kg (iv)	
	Male	Female
$t_{1/2}$ (h)	0.39 ± 0.1	1.05 ± 0.3
AUC_{last} (h μg/ml)	2.10 ± 0.2	1.66 ± 0.2
AUC_{inf} (h μg/ml)	2.29 ± 0.2	1.98 ± 0.4
Volume of distribution (V_d) (l)	2.60 ± 0.9	7.50 ± 1.2
Clearance (l/h)	4.40 ± 0.5	5.16 ± 0.9

The data are presented as mean ± SD ($P < 0.05$)

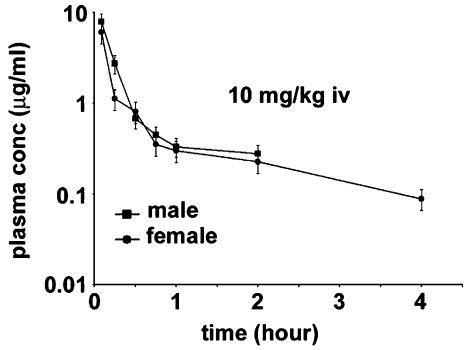

Fig. 4 Plasma concentration–time profile of 10 mg/kg intravenously administered noscapine in male and female mice

Pharmacokinetics upon intravenous administration of noscapine in mice

The plasma concentration–time profiles of noscapine at the single dose level of 10 mg/kg for both male and female mice upon intravenous administration are shown in Fig. 4. The pharmacokinetic parameters of noscapine in mice obtained upon intravenous administration at the single dose are shown in Table 3. Our results show that the plasma concentration–time curve of noscapine is characterized by a steep decline during the first 1 h. This rapid distributive phase is followed by a terminal elimination phase with a mean half-life of about 0.39 h for male mice and 1.05 h for female mice. Our data show that the total body clearance (CL) was rapid (4.40 ± 0.5 l/h for male mice, and 5.16 ± 0.9 l/h for female mice), indicating fast removal of noscapine from the plasma. As expected from the rapid clearance rates, plasma noscapine levels declined quickly and noscapine was almost undetectable after 3–4 h of infusion. The drug half-life ($t_{1/2}$; 0.39 ± 0.1 h for males, 1.05 ± 0.3 h for females) and the volume of distribution (V_d; 2.6 ± 0.9 l for males, 7.5 ± 1.2 l for females) clearly reflects gender-related differences in pharmacokinetics upon intravenous administration. Table 4 shows composite mean data of male and female mice for all doses (both intravenous and oral) studied. A comparison of the oral AUC_{inf} data at the three different doses to the intravenous data collected at 10 mg/kg indicated the mean percent oral bioavailability of noscapine as 22.76, 45.05, and 26.6% at

Table 4 Mean pharmacokinetic parameters of noscapine in mice (calculated using composite data of male and female mice)

	Dose (mg/kg)			
	10 mg/kg (iv)	75 mg/kg (po)	150 mg/kg (po)	300 mg/kg (po)
C_{max} (μg/ml)	–	12.74	23.24	46.73
t_{max} (h)	–	1.12	1.50	0.46
$t_{1/2}$ (h)	0.72	2.96	1.23	2.58
AUC_{last} (h μg/ml)	1.88	53.42	64.08	198.35
AUC_{inf} (h μg/ml)	2.14	70.27	71.67	240.24
Volume of distribution (V_d)	5.05	–	–	–
Clearance (l/h)	4.78	–	–	–
Bioavailability (%)	–	22.76	45.06	26.65

75, 150, and 300 mg/kg, respectively ($P < 0.05$). Our results thus indicate that the best oral bioavailability in both male and female mice is achieved at 150 mg/kg and the mean bioavailability of noscapine was ~30–32% across the studied dose range.

There also has been an increasing interest in developing anticancer drug formulations that selectively target the malignant tissue, thereby increasing drug-efficacy while decreasing the occurrence of side-effects related to wide and non-specific body distribution. Thus studies in our laboratory are underway to investigate various noscapine formulations (both liposomal and microsphere based) to improvise the bioavailability and other pharmacokinetic characteristics such as volume of distribution, total body clearance, etc. to maximize the therapeutic efficacy without compromising the quality of life. However, one should not ignore the challenges and potential risks in implementing these approaches in the actual therapy.

Conclusion

An efficient HPLC/UV method for quantification of noscapine in plasma has been developed. This method has been validated and applied for the preclinical pharmacokinetic study of noscapine in mice plasma. Besides its low cost and convenience, the feasibility for oral administration of noscapine precludes chances of concerning hypersensitivity reactions encountered during infusions of other currently available insoluble chemotherapeutic agents that utilize vehicle agents with several undesirable characteristics. Since biologically inactive doses minimize antitumor responses, the therapeutic efficacy of an anticancer drug is directly related to its bioavailable dose. Thus, the oral bioavailability of noscapine offers further support for its clinical advancement as a novel chemotherapeutic agent.

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