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Pulmonary delivery of a dopamine D-1 agonist, ABT-431, in dogs and humans

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Abstract

The purpose of this study was to evaluate the feasibility of intrapulmonary delivery of ABT-431, a selective D1 receptor agonist. Following intratracheal instillation of the drug solution, the lung bioavailability was found to be approximately 75% in dogs. An aerosol suspension formulation was then developed by dispersing the drug in tetrafluoroethane, HFC-134a, with the aid of poloxamer 124 and vitamin E. This ABT-431 MDI aerosol formulation showed about 40% of the particles emitted from the valve and actuator system to be under 5 μm in diameter. Also, the primary package (15 mL aluminum container, DF10/ACT-150 valve, and Micron-4-actuator with the orifice 0.4 mm) was satisfactory for accurate and reproducible dosimetry. Using tracheostomized beagle dogs, the C_{max} following tracheal administration of 5 mg aerosolized ABT-431 was found to be 13.3 ± 0.9 ng ml^{-1} and the AUC_{0-24} was estimated at 33.2 ± 10.6 h ng ml^{-1}. The lung bioavailability of the aerosolized drug was 34% compared to intravenous injection in dogs. In humans, results from a single rising dose study demonstrated that rapid absorption of ABT-431 following oral inhalation administration resulted in a dose-dependent increase in the area under the plasma-time curve at dosage levels between 3.3 and 13.2 mg. There is a possibility of up to 25% absorption of the drug from human lung. Thus, pulmonary bioavailability of ABT-431 is significantly greater than that of oral administration. Also, these findings suggest that small and lipophilic compounds, especially with hepatic first pass effect, may be effectively delivered systemically using oral inhalation aerosols.

Keywords: Dopamine D-1; Agonist; ABT-431; Metered-dose inhalation; Pulmonary absorption; Pulmonary bioavailability

1. Introduction

A-86929 is a potent and selective agonist to dopamine receptor D-1 and is under evaluation for the treatment of Parkinson's disease (Shiosaki et al., 1996; Brefel et al., 1997) The diacetyl

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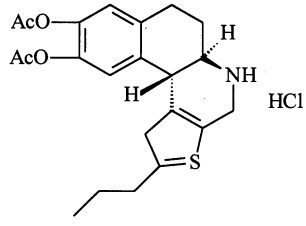
prodrug, ABT-431 (Fig. 1), was synthesized in an attempt to improve the chemical stability and bioavailability of A-86929. The diacetyl prodrug, when administered to humans, was found to immediately convert to A-86929 in the body. However, ABT-431 is subject to extensive 'first pass' effect and thus the oral bioavailability is less than 3.5%, when dosed as a solution. Chen et al. (1998) have reported that the bioavailability of ABT-431 in humans can be improved by gingival administration of bioadhesive tablets, which included an effective solubility enhancer for the drug. The intrapulmonary route of administration represents an alternative to oral administration, as well as an effective means of avoiding the hepatic 'first pass' clearance (Hoover et al., 1992). In addition, the lung has a large surface area available for absorption. Thus, intrapulmonary administration could be an attractive route for improving the bioavailability of ABT-431. The objectives of this study were: (1) to explore the absorption characteristics of ABT-431 from the lung by intratracheal instillation of the drug solution; (2) to develop a metered dose inhalation (MDI) aerosol of ABT-431 in a non-chlorofluorocarbon propellant, HFC-134a; and (3) to assess the pulmonary delivery and bioavailability of aerosolized drug in dogs and humans.

2. Materials and methods

2.1. Materials and equipment

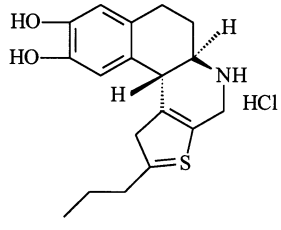
The following materials were used in this study: ABT-431 (lot no. 14-220-AL and 12-177-AL used



ABT-431

(-) -trans 9,10-acetoxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride

Molecular formula $C_{22}H_{26}NO_4SCl$; Molecular weight: 435.97



A-86929

(-) -trans 9,10-hydroxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride

Fig. 1. Chemical structure of A-86929 and ABT-431.

as reference standard, Pharmaceutical Products Division, Abbott Laboratories); and tetrafluoroethane, HFC-134a (lot 02-933-AL, DuPont). All other chemicals and reagents were either AR or HPLC grade materials and used as received. A Marple–Miller cascade impactor was used to determine the particle size distribution of the inhalation aerosol formulations. Drug assays were performed using an HPLC system consisting of a Spectra Physics HPLC pump and auto sampler, a UV detector, and a Spectra Physics integrator.

2.2. Intratracheal absorption of ABT-431

2.2.1. In vivo intratracheal instillation

Six tracheostomized beagle dogs weighing 8.9 to 10.6 kg were randomly divided into two groups (I and II) with each group containing three dogs. A two-way crossover design with a 1-week washout period was used for both groups of dogs. A solution containing 2.0 mg ml^{-1} of ABT-431 was prepared by dissolving the drug in a mixed solvent of water-ethanol (9:1) immediately before dosing. Half milliliter of this drug solution was instilled into the trachea of each dog in group I. The same solution was administered IV to the group II dogs. This translated to A-86929 doses of 0.1 mg kg^{-1}. Serial blood samples were collected at 0, 0.25, 0.5, 1, 2, 4 and 6 h after single intratracheal (IT) instillation, or following IV administration. The plasma samples were separated and assayed for drug concentration. The data was then normalized for differences in dog weight based on a nominal dose of 0.1 mg kg^{-1}.

2.2.2. Blood sample processing and drug analysis

A 0.5 ml plasma sample was combined with 0.1 ml of the internal standard (A-83114) solution, and mixed with 5 ml of a 1:1 (v/v) hexane: tert-butylmethyl ether solution. The resulting mixture was shaken at low speed for approximately 20 min, and centrifuged at 3000 rpm for 10 min. The aqueous layer was aspirated to waste, and the organic phase transferred to a test-tube and evaporated to dryness with a gentle stream of nitrogen at room temperature. The sample was then reconstituted with 0.30 ml of HPLC mobile phase and analyzed via HPLC.

A reversed-phase HPLC assay with electrochemical detection was used to determine the concentration of A-86929 in the plasma samples. The chromatographic conditions were as follows: column: Phenomenex Prodigy® 5 ODS column (250×4.6 mm, 120 Å, 5μm); flow rate: 0.6 mL min^{-1}; mobile phase: CH_3CN:CH_3OH: aqueous buffer (26:4:70 v/v/v); buffer: 0.05 M KH_2PO_4 and 80 mg mL^{-1} of EDTA.

The ratios of the observed peak heights of the analyte to those of the internal standard from the standard curve samples were subjected to weighed linear regression against the theoretical plasma concentrations to derive a standard curve. For each set of blood samples, a calibration curve (0.313 to 80.16 ng ml^{-1}) was constructed with spiked standards and used for the calculation of the sample concentrations. The measured concentrations were calculated by interpolating the observed ratios of the unknown samples to the standard curve. This method could detect and quantitate 0.313 ng ml^{-1} of A-86929 (the low limit of quantitation) using 1 ml of plasma, with a coefficient of variation (CV) within 5.5%.

2.3. Pulmonary absorption of aerosolized ABT-431

2.3.1. Formulation

A suspension MDI formulation containing poloxamer 124, vitamin E, and 25 mg ml^{-1} ABT-431 in HFC-134a was prepared and used in this study with a batch size of 10 kg. Reduction of dispersed drug particle size was achieved by a cryogenic, continuous bead milling system (Adjei et al., 1997). Milling was deemed complete when approximately 90% of the slurry volume particles were 10 μm or smaller in diameter and the mean volume diameter was 5 μm or smaller.

2.3.2. Primary packaging, dosimetry of MDI formulation

Primary packaging for the MDI formulation consisted of a 150 μl metering valve (DF10/ACT/kematal, Valois, Le Neuborg, France), a 15 mL epoxy phenolic lined aluminum container (Safet Embamet, St. Florantine, France), and Micron-4 actuators (TAP Holdings, Inc., Deerfield, IL).

Valve delivery was examined by measuring the dose of drug delivered per spray throughout a canister. After priming, the formulation was sprayed two times while immersing the valve stem in a beaker containing ethanol. The contents of the solution were then gently swirled to solubilize the drug, and the resulting solution diluted with acetonitrile-water solution (1:1) and assayed for drug content using the HPLC method described below Section 2.3.4.

Ex-actuator dose was evaluated using a proposed USP Dosage Unit Sampling Apparatus (USP Advisory Panel, 1994). Parts of this apparatus, including the vacuum connector, filter membrane, sample collection tube and mouthpiece adapter, were assembled as described in the literature. The valve was initially activated by spraying two times to waste. After the two priming sprays, each container was gently shaken and the appropriate number of sprays discharged into the sampling apparatus through the mouthpiece adapter, with the vacuum pump running at 30 ± 1.5 L min^{-1}. One minute later, the next shot was delivered to the apparatus. This process was repeated until a total of three sprays were delivered. Sixty seconds after delivering the third spray, the inhaler was detached from the Dosage Unit Sampling Apparatus, and disconnected from the vacuum. The filter and interior of the apparatus were rinsed with the sampling solvent (50% acetonitrile in water) and diluted to a final volume of 50 mL. Drug content in the final sample solution was analyzed using HPLC. For each aerosol can tested, a total of three doses were collected and analyzed, i.e., dose 1 (sprays 3-5), dose 2 (sprays 30-32), dose 3 (sprays 58-60). The means and standard deviations of the respective ex-actuator doses were calculated and used to evaluate intra-can dose uniformity of batches utilized in the investigation. Drug residues retained on the actuator components were rinsed off with sampling solution and diluted to a final volume of 25 mL for quantitation using the HPLC methodology described below Section 2.3.4.

2.3.3. Particle size analysis by Marple-Miller cascade impactor

A Marple-Miller five-stage impactor was used to determine the aerodynamic particle size of the MDI formulation (Ganderton et al., 1996). The container was primed five times before ten actuations were discharged into the cascade impactor. The valve stem, actuator, entry port, cascade stages 1–5, and the terminal filter (5 μm PVC membrane) were rinsed with the solvent and collected separately for HPLC analysis. A computer software 'Impactplot' (Nephele Enterprises, Version 1.0) was used to calculate the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). The test was performed on three individual containers.

2.3.4. ABT-431 HPLC assay

ABT-431 was analyzed using a reverse phase HPLC method, a C_8 column (4.6×250 mm, 5 μm), and 4-nitrobenzophenone as an internal standard. The mobile phase consisted of 0.2% perchloric acid aqueous solution:acetonitrile (55:45 v/v). Elution of the HPLC column was performed at a flow rate of 1.0 ml min^{-1} with the mobile phase; the column eluate was monitored by absorbance at 230 nm. The concentration of ABT-431 in the samples was calculated from the HPLC peak area ratios relative to the internal standard. The standard solution of ABT-431 and the internal standard solution (4-nitrobenzophenone) were approximately 100 μg ml^{-1} and 140 μg ml^{-1}, respectively. Results were expressed as μg ABT-431 per spray or μg A-86929 equivalent per spray.

2.3.5. In vivo studies in dogs

Intrapulmonary absorption of ABT-431 was assessed in tracheostomized beagle dogs weighing about 10 kg. Appropriate numbers of sprays of the MDI formulation were delivered via the tracheal stoma. An actuator device (Micron 4) was modified by removal of the main plastic body to enable stem insertion into the dog trachea for delivering the dose (Adjei et al., 1990). Drug was administered at a dose of 5 mg ABT-431 per dog. Absolute bioavailability estimates were made using about 0.1 mg kg^{-1} ABT-431 given by intravenous injection. Blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8 and 12 h after dosing.

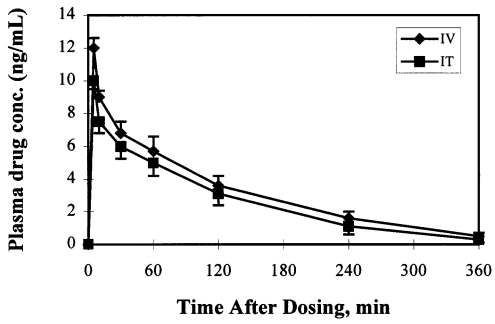


Fig. 2. Mean plasma concentration-time profiles following administration of single doses of ABT-431 to beagle dogs (0.1 mg kg^{-1}, $n = 6$). IV: intravenous injection; IT: intratracheal instillation.

Plasma concentrations of A-86929 equivalents were determined via the HPLC method described in Section 2.3.2 and plotted as a function of sampling time after drug administration. Areas under these plasma concentration–time curves (AUC) were estimated using trapezoidal approximation.

2.3.6. Clinical studies

This was a Phase I, double blinded, placebo-controlled, single center, sequential dose study. Twelve healthy adult male subjects were randomized to receive ABT-431 MDI aerosol or placebo (in a 5:1 ratio) on six consecutive days. The study consisted of a single period, where drug or placebo was administered as an oral inhalation in an escalating dose fashion on days 1 through 5, and intravenously (IV) on day 6; one dose was administered on the morning of each of the six study days. Number of sprays actuated by subjects were one actuation (1.7 mg) for day 1, two actuations (3.3 mg) for day 2, four actuations (6.6 mg) for day 3, eight actuations (13.2 mg) for day 4, and 12 actuations (19.8 mg) for day 5, respectively. Blood samples were obtained in EDTA collection tubes for determination of plasma A-86929 concentrations at specified times following drug administration. No blood samples were taken for pharmacokinetic evaluation at day 1 for one actuation (1.7 mg dose).

The blood samples were immediately stored at 4°C or below and the plasma was separated by centrifugation within 1 h after sample collection. Plasma A-86929 concentrations were determined using an HPLC method with electrochemical detection as described in Section 2.3.2. The pharmacokinetic parameters of A-86929 after single oral inhalation rising doses and an intravenous dose of the drug were estimated using standard noncompartmental methods. The peak plasma concentration (C_{max}) and time to reach the peak concentration (T_{max}) were taken directly from the plasma concentration-time data. The terminal rate constant (β) was determined by linear regression of the natural log-transformed plasma concentrations in the terminal phases. The AUC from time zero to the time of the last measurable concentration (AUC_t) was calculated by the linear trapezoidal rule using the measured concentration data. The extrapolated AUC from t to infinity ($AUC_{t-\infty}$) was estimated by dividing the last measurable plasma concentration (C_{last}) by β. The AUC from time zero to infinity (AUC_∞) was estimated by adding $AUC_{t-\infty}$ to AUC_t.

3. Results and discussion

3.1. Intratracheal absorption of ABT-431

The mean blood concentrations following a single IV administration of 0.1 mg kg^{-1} of A-86929 equivalent in groups of six dogs is shown in Fig. 2. Data after intratracheal (IT) instillation of equivalent single doses of drug in groups of six dogs are also shown in the same figure. Estimates of the pharmacokinetic parameters for each of the respective treatments are listed in Table 1. The bioavailability of the IT doses was estimated using area under the plasma concentration versus time curve through infinity time ($AUC_{0-\infty}$).

Following IT instillation of the drug solution, A-86929 concentrations in plasma increased rapidly, with maximum concentrations (C_{max}) attained within 0.1 h after dosing (see Table 1). The concentration–time curve from IT instillation was similar to that observed with IV injection (Fig. 2). Considering the low aqueous solubility of ABT-431, these results are rather surprising and indicate that the lung might provide for rapid

absorption of lipophilic compounds such as ABT-431. Thus, following pulmonary instillation, ABT-431 is well absorbed in a rapid manner. The mean absolute bioavailability following IT delivery of 0.1 mg kg^{-1} A-86929 equivalent was estimated to be $74.6\% \pm 19.4$ (Table 1). The IT instillation study demonstrated that ABT-431 can be systemically absorbed through deep lung in dogs and thus intrapulmonary delivery of the drug is feasible using an inhalation aerosol formulation.

3.2. Pulmonary absorption of aerosolized ABT-431

3.2.1. Formulation development

Tetrafluoroethane, HFC-134a, is a gas with a boiling point of approximately 26.5°C (Dalby et al., 1990; Gupta et al., 1997) which is a very non-polar solvent with extremely poor solubility characteristics when subjected to high pressure and low processing temperatures. Since HFC-134a is immiscible with most conventional surfactants used in MDI formulations, it also demonstrates poor dispersion qualities. For this reason, various excipients were screened to assess their effects on the quality of ABT-431 suspensions in HFC-134a. A selected formulation with good dispersion properties (e.g., good homogeneity and no distinct separation for 1 week) and acceptable chemical stability (i.e., no drug loss at room temperature over 3 month) was further characterized for functional performance, i.e. particle size distribution, dosimetry and drug content uniformity.

3.2.2. Particle size

Particle size of aerosolized products determines the extent as well as the pattern of drug deposition in the respiratory tract. Particles in the size range of 1–5 μm are believed to be most efficiently deposited in the peripheral lung (Hickey and Evans, 1996; Gupta, and Hickey, 1991). Mass distribution data for ABT-431 MDI aerosol formulation from Marple–Miller cascade impactor is given in Fig. 3. Approximately 40% of the particles emitted from the valve and actuator system are ≤ 5 μm in diameter and are considered to be respirable particles. The fraction of particles retained in the actuator was less than the respirable particles. The mass median aerodynamic diameters (MMAD) for two batches of the product were 4.5 ± 0.4 and 4.1 ± 0.8 μm, respectively. Similar profiles of mass particle distribution were observed between the two batches of ABT-431 MDI aerosol.

3.2.3. Dose delivery: through-can drug content uniformity

A 10 ml fill volume of product formulation should theoretically deliver a total of 66 sprays as the spray volume is determined by the valve capacity, i.e. 150 μl. Because a fraction of the nom-

Table 1
Summary after intravenous and intratracheal dosing of ABT-431 solution to dogs[a]

Parameters	IV	IT Instillation
$T_{1/2}$	1.5	1.3
Vc (1 kg^{-1})	5.7 ± 1.3	–
Vβ (1 kg^{-1})	13.3 ± 5.8	–
CLp (1 $hr \times kg^{-1}$)	5.8 ± 2.1	–
$AUC_{0-\infty}$ (ng hr mL-1)	19.3 ± 7.4	14.7 ± 6.6
C_{max} (ng mL-1)	–	9.9 ± 4.1
T_{max} (hr)	–	0.1 ± 0.1
F (%)	100	74.6 ± 19.4

[a] Plasma concentrations normalized to a 0.1 mg A-86929 equivalent per kg dose in each dog. Data are expressed as mean ± S.D, ($n = 6$).

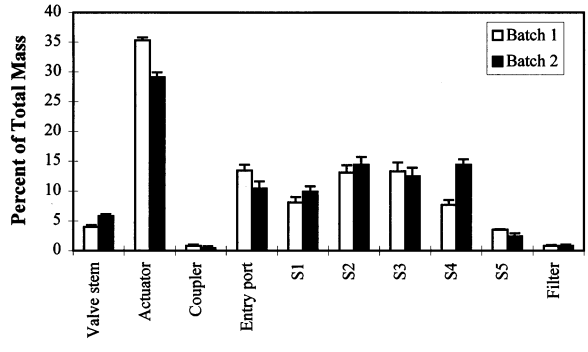


Fig. 3. Patricle mass distribution of ABT-431 MDI aerosol formulation by Marple–Miller cascade impactor ($n = 3$). Stage 1 = 10 μm, Stage 2 = 5 μm, Stage 3 = 2.5 μm, Stage 4 = 1.25 μm and Stage 5 = 0.625 μm.

Table 2
Ex-actuator dose delivery of ABT-431 MDI aerosol formulation

	A-86929 (mg per 3 sprays)				
	Cans	Spray 3–5	Sprays 30–32	Sprays 58–60	Grand mean ± SD
Actuator orifice 0.4 mm					
Actuator retention	6	3.31 ± 0.30	2.98 ± 0.21	3.09 ± 0.35	3.13 ± 0.30
Ex-actuator dose[a]	6	4.52 ± 0.34	4.70 ± 0.36	4.47 ± 0.54	4.56 ± 0.40[b]
% Actuator retention					40.7
Actuator orifice 0.5 mm					
Actuator retention	6	4.22 ± 1.00	3.70 ± 0.35	3.74 ± 0.49	3.88 ± 0.66
Ex-actuator dose[a]	6	3.91 ± 0.20	3.11 ± 0.57	3.68 ± 0.81	3.57 ± 0.64
% Actuator retention					52.1

[a] ANOVA test among doses of sprays 3-5, sprays 30-32 and sprays 58-60: $p > 0.05$ indicates no significant differences in intra-can doses.

[b] t-test: $p < 0.05$ compared with 0.5 mm of the actuator orifice indicates significant differences at the 5% level.

inal fill is dead volume and thus undeliverable, the actual number of emitted sprays should be less than the theoretical calculation. Ex-valve dosimetry results indicated a 10-mL fill volume consistently delivered 60 sprays of product formulation, beyond which a sharp 'tail-off' commenced. In addition, drug potency assays in these samples (two batches) ranged between 101.9 and 110.0% A-86929 equivalents, with typical specification ranging from 75 to 125% label claim. These results indicate that the valves used for the product provide satisfactory functional performance.

The amount and uniformity of active ingredient available to patients (ex-actuator dose) using MDI products is a critical performance variable for therapeutic inhalation aerosol products. Many factors are capable of having an impact on the ex-actuator dose delivery of an aerosol product, including formulation, particle size distribution of all solids dispersed in the product, delivery valve and actuator. In particular, device geometry such as the actuator orifice diameter influences the distribution of drug particles in the plume, subsequently affecting variability and control of ex-actuator dosimetry of the formulation (Adjei et al., 1996). Ex-actuator dose delivery and actuator retention data on ABT-431 aerosol formulation included in this investigation are summarized in Table 2. Using an actuator with 0.4 mm orifice diameter, the average ex-actuator A-86929 dose was 4.56 mg per three sprays. Results for the beginning (sprays 3–5), the middle (sprays 30–32) and the end doses (sprays 58–60) from six randomly selected canisters were 4.52, 4.70 and 4.47 mg of A-86929 equivalents, respectively. These results demonstrate that the ex-actuator drug content from this formulation is about 60% of the nominal labeled dose. Thus, about 40% of the nominal dose delivery is retained in the actuator. It is noteworthy that there were no statistically meaningful differences between the beginning, middle and end doses, suggesting good intra- and inter-can dose uniformity.

For actuators with 0.5 mm orifice diameter, a higher percentage of the nominal dose was retained in the actuator (i.e. about 52% compared with 40% for actuators with 0.4 mm orifice diameter). The dosimetric results (Table 2) suggest that intra- and inter-can dose uniformity is satisfactory based upon a 75 to 125% product specification limit. However, drug thru-put would be more favorable if ABT-431 aerosol is packaged with an actuator configured with 0.4 mm orifice diameter.

3.2.4. In vivo absorption of aerosolized ABT-431 in tracheotomized dogs

In a two-way cross-over study involving six tracheostomized dogs, the plasma drug concentrations over 24 h following inhalation aerosol administration of 0.5 mg kg^{-1} A-86929 equivalent

Table 3
Bioavailability and pharmacokinetic parameters of ABT-431 following inhalation delivery to dogs[a]

Parameters	IV	MDI
$T_{1/2}$	1.6	2.0
C_{max} (ng mL^{-1})	–	13.3 ± 0.9
T_{max} (hr)	–	0.1 ± 0.1
$AUC_{0-\infty}$ (ng hr mL^{-1})	97.2 ± 2.4	33.2 ± 10.6
F (%)	100	34.3 ± 4.0

[a] Plasma concentrations normalized to a 0.5 mg A-86929 equivalent per kg dose in each dog. Data are expressed as mean ± S.D. ($n = 6$).

were compared with those after IV administration of the drug (0.1 mg kg^{-1}). The results of this study are displayed in Table 3. Following inhalation aerosol administration, A-86929 concentrations in the plasma increased rapidly, with maximum concentrations (C_{max}) attained within 20 min after dosing (see Table 3). The C_{max} values following inhalation aerosol administration were estimated to be 13.3 ± 0.9 ng ml^{-1}. The absolute bioavailability calculated from $AUC_{0-\infty}$ was 34.3 ± 4.0% in comparison of IV injection. Thus, the aerosol formulation demonstrated fast onset of drug absorption and good bioavailability in dogs as also shown by the IT instillation study.

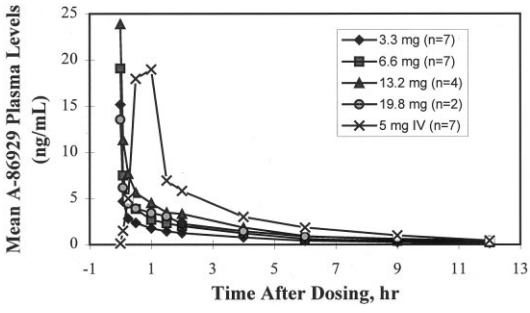


Fig. 4. Mean plasma concentration-time profiles following I.V. and inhalation delivery of ABT-431 to humans.

3.2.5. In vivo absorption and pharmacokinetics of aerosolized ABT-431 in humans

Plasma concentration time profiles for ABT-431 following single oral inhalation rising doses and an intravenous dose in humans are shown in Fig. 4 with the corresponding values tabulated in Table 4. As seen in Table 4, the time for peak plasma A-86929 concentrations to occur was less than 10 min for all doses similar to values observed in dogs. Peak concentrations following MDI oral inhalation occurred much earlier than after a 1 h intravenous infusion. Thus, absorption of A-86929 in human lung was rapid for all doses. The mean plasma AUC values increased with increasing dose to 13.2 mg (eight actuations). A linear dose-response relationship following pulmonary delivery of ABT-431 was observed within the dose range of 3.3–13.2 mg and the regression coefficient of AUC versus dose was 0.9993. The mean AUC for the 19.8 mg dose (12 actuation) could not be fitted into the line. Also, the bioavailability decreased as the number of actuations was increased. From two to 12 actuations, the mean bioavailability decreased from 24.9 to 8.4%. Since the aqueous solubility of the drug was lower, saturation or physiological changes in the absorption barrier as a result of the drug accumulation in deep lung surface could deter the drug across the airway to the systemic circulation and hence decrease the drug absorption at the higher dose levels. Nevertheless, the lung bioavailability of ABT-431 MDI aerosol is higher than that of

Table 4
Noncompartmental pharmacokinetic parameters for A-86929 in humans (mean ± SD)

Route	Dose (mg)	n	T_{max} (h)	C_{max} (ng mL^{-1})	$AUC_{0-\infty}$ (ng h mL^{-1})	$T_{1/2}$ (h)	F (%)
Inhalation	3.3	6	0.09 ± 0.19	15.2 ± 16.2	10.6 ± 4.3	3.2 ± 0.7	24.9 ± 4.2
Inhalation	6.6	6	0.07 ± 0.03	19.1 ± 13.3	16.1 ± 5.6	3.2 ± 0.5	19.8 ± 3.9
Inhalation	13.2	4	0.15 ± 0.04	24.2 ± 29.9	26.0 ± 21.8	3.2 ± 0.8	18.0 ± 8.6
Inhalation	19.8	2	0.18 ± 0.18	13.6 ± 13.5	22.5 ± 7.8	5.5 ± 1.2	8.4 ± 5.8
IV	5	7	0.67 ± 0.32	19.4 ± 4.7	42.7 ± 10.6	4.3 ± 1.5	–

the oral solution (3.5%) and sublingual tablets (< 13%) in humans (Chen et al., 1998).

4. Conclusions

Results from this study indicate that ABT-431 is rapidly absorbed following IT instillation to the dog lungs. The absolute pulmonary bioavailability at the dose of 0.1 mg kg^{-1}, against IV controls, was estimated to be about 75%. Furthermore, an HFC-134a based MDI aerosol formulation of ABT-431 was successfully developed. The formulation demonstrated reproducible dose delivery in vitro with approximately 40% of particles delivered from the device less than 5 μm in size. The actuator retention of the drug was dependent on the size of diameters of the actuator orifice. An actuator with 0.4 mm of orifice demonstrated an ex-actuator dose which was approximately 60% of ex-valve dose. In contrast, the ex-actuator dose decreased to approximately 50% of ex-valve dose with a 0.5 mm actuator orifice. In dogs, ABT-431 aerosol formulation demonstrated rapid onset and good absorption of the drug from lung. The absolute pulmonary bioavailability of aerosolized drug was approximately 30% in comparison with IV injection in dogs. In humans, rapid absorption of ABT-431 following oral inhalation administration resulted in a dose-dependent increase in the area under the plasma-time curve at dosage levels between 3.3 and 13.2 mg. Bioavailability of ABT-431 decreased with increasing dose and the data suggested a possibility of up to 25% absorption of the drug from lung following administration as an oral inhalation aerosol in humans. These findings suggest that small and lipophilic compounds, like ABT-431, may be effectively delivered systemically using inhalation aerosols.

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