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Short Communication

The Pharmacokinetics of Butylscopolamine in Camel Plasma after Intravenous Administration

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Abstract

Camels are commonly administered butylscopolamine (BSA), an antimuscarinic quaternary ammonium derivative, to reduce spasms in the smooth muscles of their urinary and gastrointestinal tracts. However, its presence in body fluids after racing is prohibited by animal racing authorities. The current study aimed to conduct a pilot pharmacokinetic study of BSA in healthy camels. The goal was to obtain initial pharmacokinetic parameters and use these parameters to predict plasma concentrations from the dose and clearance. This will help advise on a withdrawal time for BSA administration before camel racing. The pharmacokinetics of BSA were evaluated in three healthy camels after a single intravenous dose of 0.2 mg/kg body weight. Sensitive liquid chromatography with tandem mass spectrometry was used for the quantification of BSA and the internal standard, ipratropium, in plasma. BSA concentration versus time data were best described by a two-compartment open model. The pharmacokinetic parameters (median and range) were as follows: terminal elimination half-life was 2.29 (1.48–2.46) h, plasma clearance was 1,018.5 (772.4–1,024.0) mL/h/kg, volume of distribution at steady state was 931.9 (700.0–1,068.7) mL/kg, Cmax was 443.9 (351.1–443.9) ng/mL, and Tmax was 0.5 (0.25–0.75) h. BSA's irrelevant plasma concentration was estimated to be 20 ng/mL. Consequently, it can be concluded that plasma would not contain BSA at the screening level of 20 ng/mL at the usual dose of 0.2 mg/kg body weight 24 h before camel racing.

Introduction

Buscopan is a combination medication consisting of two active ingredients: dipyrone (500 mg/mL), a non-steroidal anti-inflammatory drug, and butylscopolamine (BSA), an antimuscarinic quaternary ammonium derivative of scopolamine. The peripheral muscarinic receptor-binding drug BSA has an anticholinergic effect that prevents smooth muscle contraction in the gastrointestinal, biliary, and genitourinary tracts, thereby reducing bowel movement or colicky pain. Besides its use for symptomatic relief, butylscopolamine is also used in diagnostic procedures such as magnetic resonance imaging (MRI) of the abdomen and pelvis.[1–3] However, a recent study found that continuous IV butylscopolamine was no more effective than a placebo at relieving pain in individuals with renal colic.[4] Nonetheless, BSA is commonly administered to camels to alleviate spasms in the smooth muscles of the urinary and gastrointestinal tracts.[5,6] BSA is given as an intravenous injection due to the low oral absorption of quaternary ammonium compounds. It distributes and takes effect quickly.[5,7] BSA rarely causes negative effects on the central nervous system because its low lipid solubility makes it difficult to penetrate the blood-brain barrier.[5] BSA is excreted largely unchanged in urine, whereas dipyrone is metabolized to methylaminoantipyrine, aminoantipyrine, and formylaminoantipyrine.

BSA's pharmacokinetics (PK) have been previously investigated in horses and dogs,[8–10] but despite its widespread use in camels, no such reports exist. The current study's objectives were to determine the PK of BSA following the intravenous administration of Buscopan Compositum and to provide guidance on the recommended detection window prior to camel racing.

Materials and methods

BSA and ipratropium bromide, used as the internal standard, were purchased from Sigma Aldrich (St. Louis, MO, USA) with a purity of around 98%. All chemicals and solvents, also from Sigma Al-

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drich, were of analytical grade or HPLC grade. Oasis HLB solid-phase extraction cartridges (3 CC, 60 mg) were provided by Gulf Scientific Corporation in Dubai, United Arab Emirates.

Animals

In this investigation, three male camels (Camelus dromedarius), aged 5–7 years and weighing between 400 and 500 kg, were used. The camels were maintained in open pens and were fed high-quality hay and Lucerne (alfalfa) once per day, with unlimited access to water. The study protocol was approved by the UAE Ministry of Agriculture's Veterinary Department.

Treatment

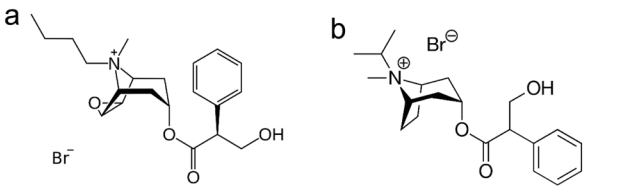
Buscopan Compositum (Boehringer Ingelheim, 55216 Ingelheim am Rhein, Germany), equivalent to 4.0 mg/mL of BSA, was administered as an intravenous injection at a dose of 0.2 mg/kg body weight. Venous blood samples (7 mL) were drawn from the jugular vein into heparinized blood tubes at 0, 5, 10, 15, 30, and 45 m, and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 12, 24, and 48 h. Blood samples were immediately placed on ice, and plasma was separated by centrifugation at 4,500 ×g at room temperature for 10 m. The collected plasma was frozen at −20°C prior to BSA and ipratropium analyses. Extraction and liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis of plasma BSA and ipratropium were performed as reported previously.[6] However, the employed LC-MS/MS was an Agilent 1200 series HPLC system with a binary gradient pump (Agilent Technologies, Palo Alto, CA, USA) and an autosampler coupled to a 5500 QTrap mass spectrometer (Applied Biosystems, Foster City, CA, USA). A gradient mode at 35°C was employed with a Phenomenex Kintex C18 column (2.6 µm, 2.1 mm × 50 mm) connected to a Phenomenex pre-column filter (KrudKatcher ULTRA, 2.0 µm Depth Filter × 0.004 in ID). The mobile phase consisted of Solvent A (0.1% formic acid in water) and Solvent B (0.1% formic acid in methanol). Initially, 40% Solvent B was used in a linear gradient at 0.3 mL/m, increasing to 90% at t = 3 m. At t = 4.0 m, the gradient was reset to 40% Solvent B and remained stable for 7.5 m before the next injection. The nebulizer gas and heater gas were set to 45 and 55 psi, respectively, with the source in positive ESI mode at 500°C. The collision gas was set to medium, the curtain gas to 22 psi, and the ion spray voltage to 5,500 V. The resolution was set to unit mass for both product ions in Q3 and precursor ions in Q1. The internal standard and analyte were detected using a single time segment in the MRM mode, with a scan time of 50 ms for each transition. For BSA, the mass transitions m/z 360.3 to 138.1 and m/z 360.3 to 103.1 were used, and for ipratropium, m/z 332.3 to 121.4 and m/z 332.3 to 194.2, were utilized to selectively monitor precursor ions and corresponding product ions. Reference material infusion was employed to optimize the SRM transitions, declustering potentials, collision energies, and collision cell exit potentials for both BSA and ipratropium. Data processing was performed using Analyst software (Version 1.5.1). The analytes from the plasma were extracted using Oasis HLB solid-phase extraction cartridges. The cartridges were conditioned with 2 mL of methanol and 2 mL of water before the samples were loaded. After being cleaned with 2 mL of 5% (v/v) methanol in water, the cartridges were dried for 5 m at 20 mm Hg. The analytes were eluted with 2 mL of methanol. The eluent was evaporated under a nitrogen stream at 40°C, reconstituted in 100 µL of mobile phase, and analyzed by LC-MS/MS.

Pharmacokinetic analysis

The least-squares nonlinear regression analysis programme (WinNonLin Standard edition, version 4.0.1, Pharsight, Sunnyvale, CA, USA) was used for the PK analysis of the plasma BSA concentrations in each animal. Both one-compartment and two-compartment models were tested to determine the best fit for the data from intravenous delivery. Weighting was accomplished using the following formula:

$$\text{var}\,(t) = \frac{1}{Y}\,\text{observed}^2$$

where var(t) is the variance of the residual error of drug concentration at time "t" and Y observed is the observed drug concentration at time "t". The best fit was determined based on Akaike and Schwarz criteria,[11,12] analysis of residual plots, and the correlation matrix. Calculations were performed on individual data.



Butylscopolamine bromide
Molecular formula: $C_{21}H_{30}BrNO_4$
Average mass: 440.371 Da
ChemSpider ID: 16736107

Ipratropium bromide
Molecular formula: $C_{20}H_{30}BrNO_3$
Average mass: 412.368 Da
ChemSpider ID: 3615

Fig. 1. The chemical structures of (a) Butylscopolamine and (b) the internal standard ipratropium bromide (ChemSpider: http://www.chemspider.com).

Statistical calculations

Statistical analyses of the data were conducted using Statistica software (version 5.5) to obtain descriptive statistics. PK parameters are reported as mean, standard deviation (SD), median, and ranges.

Results and discussion

Deuterated BSA was not available for this study. However, using ipratropium bromide as an internal standard, which has a similar chemical structure to BSA (Fig. 1), resulted in accurate quantification. The ideal method for extracting quaternary ammonium derivatives (QADs), which are ionic compounds with a persistent positive charge, is to use a weak cation exchanger, typically a carboxy phase.[13] The positively charged quaternary nitrogens of QADs interact with the negatively charged moiety group of the cation exchanger during the extraction process. In an acidic environment, the protonation of the carboxy group releases the quaternary cations. This is suitable for the extraction of analytes (such as QADs) whose permanent positive charge is not modified by pH alterations. Clearly, such extraction techniques require careful attention to pH manipulation. However, we used Oasis HLB extraction cartridges (CBA 500 mg, Biotage), which are strongly hydrophilic, reversed-phase, water-wettable polymers that are stable from pH 0–14. The sorbent maintains high retention capacity even if it runs dry after conditioning, resulting in efficient and consistent performance, and it is simple to use.

By spiking pooled drug-free camel plasma from 10 camels, the method was validated for BSA and ipratropium at three QC levels (1.5, 10, and 50 ng/mL). Validation runs were conducted over three days. Two replicates of the QC samples and one set of calibration standards were used in each validation run (n = 18 total values

Table 1. Pharmacokinetic parameters of butylscopolamine following intravenous administration to three healthy camels at a dose of 0.2 mg/kg body weight

	$AUC_{0-\infty}$ (ng h^{-1} · mL)	$T_{½\alpha}$ (h)	$T_{½\beta}$ (h)	Cl (mL h^{-1} ·kg)	V_{SS} (mL/kg)	C_{MAX} (ng/mL)
Camel A	258.9	0.30	2.46	772.4	1,068.7	443.9
Camel B	195.3	0.29	1.48	1,024.0	700.0	414.2
Camel C	196.4	0.34	2.29	1,018.5	932.0	351.1
Mean	216.9	0.31	2.08	938.3	900.2	403.1
SD	36.4	0.03	0.52	143.7	186.4	47.4
Median	196.4	0.3	2.29	1,018.5	931.9	414.2
Range	195.3–358.9	0.29–0.34	1.48–2.46	772.4–1,024.0	700.0–1,068.7	351.1–443.9

$T_{½\alpha}$ and $T_{½\beta}$, half-lives of distribution and elimination phase, respectively; $AUC_{0-\infty}$, area under the curve from time 0 to infinity; Cl, plasma clearance; V_{SS}, volume of distribution at steady state; $C_{MAX,}$ maximum plasma concentration.

over three days). Under our experimental conditions, the method was linear over the concentration range of 0.5–1,000 ng/mL (the calibration levels for BSA were 0.1, 0.5, 10.0, 25.0, 50.0, 100, 250, 500, and 1,000 ng/mL). Extraction recovery for BSA and the internal standard ranged from 90.2–97.5%. The matrix effect was less than 12% for both BSA and the internal standard. The lowest concentration on the calibration curve that could be measured consistently with acceptable accuracy (80–120%) and precision (±20%) was defined as the lower limit of quantification (LOQ). The lowest concentration that could be detected at a signal-to-noise ratio of ≥3 was defined as the LOD. The LOQ was 0.5 ng/mL and the LOD was 0.1 ng/mL. The accuracy and precision of calibrators and QCs were less than 15%. Buscopan was well tolerated by camels, and no adverse effects were observed during the study. Table 1 displays the estimated pharmacokinetic parameters of BSA after intravenous injection (mean, SD, median, and range). Figure 2 shows the concentration-time profile of BSA in plasma. BSA was detectable in plasma for 8 h.

BSA was quickly cleared from plasma with a terminal elimination half-life of 2.29 h (median) and a clearance of 938.3 mL/kg (mean). BSA could not be quantified in plasma after 8 h of administration. To the best of the author's knowledge, this is the first report describing the PK of BSA in camels, and thus there are no reports for comparison. However, in horses, BSA was reported to have a quick terminal elimination half-life of 0.45 ± 0.27 h (mean ± SD) following a similar intravenous dose used in the current study.[9] Roelvink evaluated the analgesic effect of BSA alone (0.2 mg/kg body weight) and in combination with dipyrone in ponies.[14] A short half-life in ponies is further implied by the fact that BSA alone had an analgesic effect within 30 s of injection and persisted for 20 m. However, Moris *et al*. observed a half-life of 2.0 h (geometric mean) and a median of 1.9 h following a single oral 10 mg dosage to six greyhounds utilizing a non-compartmental PK analysis. Their findings are fairly comparable to our reported values in camels.[10]

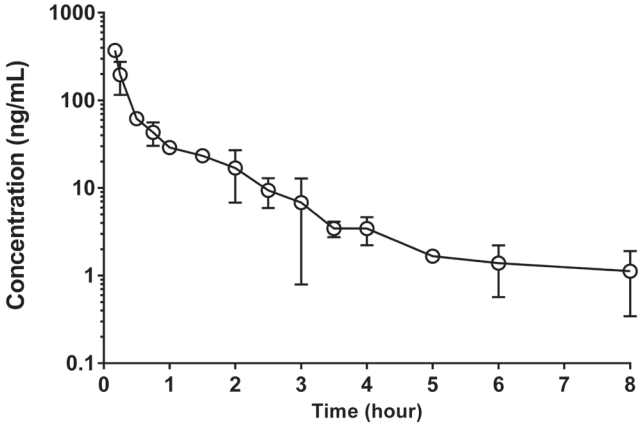


Fig. 2. Butylscopolamine plasma concentrations-time profile of three camels after an intravenous dose of 0.2 mg/kg body weight. Values are presented as means ± standard deviations.

One of the goals of the current study is to guide withdrawal periods after receiving therapeutic doses of BSA. However, the analytical skills of racing chemists have significantly increased due to the development of high-sensitivity drug testing tools and procedures, as well as the growing detection capabilities of analytical chemists. Chemists can often detect prohibited substances in the low parts per billion concentration range using today's analytical techniques. All drugs are retained in the animal's body for extended periods, and the animal does not fully eliminate them until long after the pharmacological effects have subsided. As a result, minute drug levels can be found on the day of the race due to significant advancements in analytical technology. Therefore, to maintain fair competition without compromising quality veterinary care, a screening limit should be estimated based on no pharmacological effect or an irrelevant plasma and/or urine concentration.[15,16]

The experimental determination of a pharmacological no-effect concentration necessitates multiple time-consuming and expensive PK/PD studies.[15] However, Toutain and Lassourd,[17] recently proposed a model for predicting irrelevant amounts of veterinary medicines in biofluids using a few PK factors. In their model, the effective plasma concentration (EPC) of the drug is calculated as follows:

$$EPC = \frac{\text{dose per dosing interval}}{\text{plasma clearance per dosinginterval}}$$

Then, by using a safety factor (SF), the EPC is converted to an irrelevant plasma concentration (IPC). EPC/SF = IPC. Toutain and Lassourd proposed an SF of 500, which is a decision made by a regulatory body. Using these formulae and the most recent PK data, we rounded the obtained IPC of 17.7 ng/mL to 20 ng/mL. It follows that two hours after intravenous BSA treatment, the plasma concentration will be irrelevant.

Future directions

More studies involving a larger sample of animals (8–12) are need-

ed to accurately characterize the pharmacokinetic characteristics. These factors could be used to predict the irrelevant plasma concentration and establish a precise withdrawal time.

Conclusions

BSA would be challenging to detect in plasma at the usual dose of 0.2 mg/kg body weight 24 h before camel racing since it has a short plasma half-life and is mostly eliminated from plasma within 8–12 h of intravenous administration.

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Conflict of interest

None.

Author contributions

Study concept and design (MSN, IAW), acquisition of the data (SW), assay performance and data analysis (SW, NA), drafting of the manuscript (IAW), critical revision of the manuscript (MSN), and supervision (MSN, IAW).

Ethical statement

This study was carried out in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The study protocol was approved by the UAE Ministry of Agriculture's Veterinary Department. The camels were housed in open pens and were given high-quality hay and Lucerne (alfalfa) once per day, along with unlimited access to water. Camel handling, including husbandry, care, and experimentation, was performed by qualified veterinarians.

Data sharing statement

No additional data are available.

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