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Plasma Concentration of Butorphanol in Northern Royal Albatross Undergoing Fracture Repair

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Received: 28 February, 2018; Accepted: 13 March, 2018; Published: 16 March, 2018

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Abstract

Aims: The objective of this study was to determine the plasma concentration of butorphanol injected intravenously at 4mg/kg dose in Northern Royal Albatross and compare the pharmacokinetic parameters with that of broiler chickens.

Methods: The plasma concentration of butorphanol was analysed by High Performance Liquid Chromatography. The pharmacokinetic parameters were calculated by non-compartmental approach using standard equations in spreadsheet.

Results: The half-life, volume of distribution, clearance, mean residence time were 94.4 minutes, 860.5 ml/kg, 6.31 ml/kg/min, and 146.4 minutes, respectively. The levels remained above the minimum effective concentration for mammals for about 4 hours.

Conclusion: Though we have data from only one albatross for butorphanol kinetics, it confirms the chicken data: butorphanol does not last as long in birds as in mammals. This shows that dose regimes for mammals are unsuitable for injured wild birds, but we can use chickens as a model for other wild bird species. The levels remained above the minimum effective concentration for mammals

Clinical Relevance: Butorphanol can provide good post operative analgesia in wild birds. The broiler chickens may be used as a model of drug research for wild birds, but further work is required to establish this fact.

Introduction

Avian veterinarians always face problems while deciding the dosing regimen of drugs to be used for treatment of various conditions in birds. Reason being the scarcity of information on pharmacology of even the most commonly used drugs in birds. Class Aves, contains 9702 species and such myriad number makes it impossible to conduct pharmacokinetics in each and every wild species. There is no established model of drug research for avian species. This fact also stands true for pharmacology of analgesic drugs in birds. Butorphanol is the recommended analgesic drug for birds. Birds have higher number of kappa receptors and butorphanol being a kappa agonist is the analgesic of choice in case of birds. Butorphanol improved the welfare and increased the walking ability of lame turkeys [1,2]. Analgesic efficacy of butorphanol was also demonstrated by isolfurane sparing effect. Butorphanol when injected intramuscularly at 1 mg/kg dose reduced the effective dose for isoflurane in Cockatoos. At this dose rate, butorphanol also increased the threshold for electrical stimulus in African grey parrots [3,4]. *Sladky et al. 2006*, found that analgesic effects of butorphanol did not last long after intramuscular injection at 5 mg/kg [5]. They used liposome encapsulated Butorphanol to increase the duration of analgesia. The analgesic efficacy of liposome encapsulated butorphanol was also demonstrated in Conures and Hispaniolan Parrots [6]. Other methods such as slow release butorphanol formulations and mini osmotic pumps have been used to increase the duration of action of butorphanol in birds. Butorphanol is also a safe drug to use for perioperative analgesia [7,8,9]. Thus, butorphanol is commonly used for pre and post operative analgesia in birds.

Case History

A Northern Royal Albatross, 8 months old, was admitted to the wild life ward of Massey University Teaching Hospital with the history of sore left leg. The effected leg was radiographed under isoflurane anaesthesia. Radiographs showed a long oblique femur fracture with mild displacement. The fracture was fixed by placing an intra-medullary pin and external fixator. The surgery was performed under isoflurane anaesthesia. Butorphanol injection 10mg/mL (Lloyd Laboratories, New Zealand) was injected intravenously at 4-mg/kg dose rate. Intravenous fluid line was set up in the left wing vein for fluids given at 10 mg/kg/hr. Blood samples were taken at 0, 0.25, 0.5, 1, 1.5, 2 and 4 hours. The vials were kept chilled immediately after collection and were centrifuged at 3000 rpm for 10 minutes. Plasma was pipetted out and kept at -70^{0}C until day of analysis. The recovery from the surgery was smooth. The procedure from start to finish took 1.5 hours. Augmentin 50mg/kg was given intravenously during the surgery.

Biochemistry

Biochemical analysis of blood was unremarkable with elevated Creatinine Kinase (CK) which was expected due to muscle trauma. Rest of the biochemical profile was normal with no elevation in liver enzymes and normal salts and proteins.

Sample Analysis

The plasma samples were analysed by high performance liquid chromatography described elsewhere [10]. Briefly, The High Performance Liquid Chromatography (HPLC) system

consisted of LC-20AD pumps, SIL-20AC HT auto-injector, Diode array detector SPD- M20A, CTO-20A column oven, DGU-20A3 Degasser (Shimadzu Japan). The chromatographs were analysed in LC solutions. The analytical column used was Phenomenex C18 (2) (150 X 4.6 mm I.d, 5µm particle size). The mobile phase consisted of 0.1M phosphate buffer pH 4.8: Acetonitrile (80:20) with flow rate of 1.0 ml/min. The separation was achieved under isocratic conditions at 30^0C. The injection volume was 50µl and the Diode Array Detector (DAD) was set at 202 nm wavelength.

Sample Preparation

The plasma samples were prepared by the solid phase extraction procedure using Phenomenex Strata X Reversed Phase Solid Phase Extraction (SPE) cartridges. The standard solution used to spike the plasma samples was prepared in the Milli-q water. 300µL of plasma was spiked with 300µL of the standard solution and 300µL of concentrated hydrochloric acid was added and vortex mixed for 1 minute. Then this solution was centrifuged at 3000 rpm for 10 minutes. The supernatant was separated and loaded into the SPE cartridge preconditioned with 1 volume of methanol followed by 1 volume of water. The first wash used 3 ml of water and dried for 2 minutes followed by a second wash with 2 mL of 40 % methanol and again the cartridge was dried for 2 minutes. The elution was made with 100% methanol. The sample was dried under gentle stream of air at 20°C and was reconstituted with 200µL of mobile phase. The injection volume was 50µl and each sample was injected three times in the HPLC system.

Data Analysis

All the chromatograms were analysed for peak height, area, width and the concentration for the unknowns using the software LC solutions (Shimadzu). The standard calibration curve was also processed in the same software.

Pharmacokinetic Analysis

Pharmacokinetic parameters were calculated using standard equations in a spreadsheet (Excel, Microsoft). These included half life of the terminal phase (T1/2 ƛz), area under the curve extrapolated from time zero to infinity (AUC 0-∞), area under the moment curve extrapolated from time zero to infinity (AUMC 0-∞), volume of distribution (Vd), clearance (Cl) and Mean Residence Time (MRT).

Results

The semi log plot of concentration time curve for butorphanol after intravenous administration at 4 mg/kg in albatross is shown in figure 1. The pharmacokinetic parameters thus calculated are given in table 1. The terminal half-life (minutes), volume of distribution (mL/kg) and clearance (mL/min/kg) were 94.4, 860.5 and 6.3, respectively.

Discussion

Butorphanol is recommended for providing analgesia in avian species. Despite of that, not much information is available on its pharmacokinetics in different birds. An injured

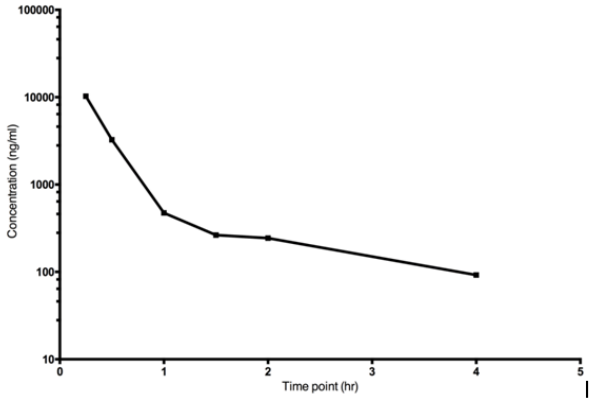

Figure 1: Semi-log plot of concentration time curve for Butorphanol after intravenous administration at 4 mg/kg in Northern Royal Albatross

Table 1: Pharamcokinetic parameters of for butorphanol after 4mg/kg intravenous dose rate in Northern Royal Albatross (n=1). The pharmacokinetic parameters were calculated using Non-Compartmental approach.

Parameter	Butorphanol
$AUC_{(0-\infty)}$ ng.min/ml	641091.7
AUMC (0-∞) ng.min^2/ml	14954263.7
Vd ml/kg	860.5
Cl ml/min/kg	6.316
$T_{1/2\lambda}$ min	94.4
MRT_{λ} min	146.4
C (max) ng/ml	4738.4

$AUC_{(0-\infty)}$ Area under the concentration time curve from time zero to infinity
$AUMC_{(0-\infty)}$ Area under Moment curve from time zero to infinity
Vd Volume of distribution at steady state
$T_{1/2\lambda}$ min Elimination half life
MRT_{λ} min Mean resident time
C (max) ng/ml Maximum concentration (extrapolated)

Albatross was admitted in wild life ward and provided a good opportunity to analyse the plasma concentration of butorphanol and to ascertain the time for how long the minimum effective concentrations in plasma are maintained. The minimum effective plasma concentration of butorphanol that should be maintained for analgesia is 50 to 80 ng/mL [11]. In Albatross, after 4 mg/kg IV. dose rate, the levels of butorphanol were higher than the minimum effective concentration for 4 hours. No behavioral analysis were conducted on the albatross, thus these assumptions about the analgesia were based on the pharmacodynamics study in chickens. It was assumed that these levels would also provide good analgesia in albatross. Butorphanol provided analgesia parrots after 1 and 2 mg/kg intramuscular injection, but it did not last long [4,5].

Butorphanol was cleared faster in this albatross as compare to hawks and owls but much slower as compared to chickens

[10,12]. The total body clearance means the amount of drug cleared per unit time based on the total dose from renal, hepatic and pulmonary system. As there was no remarkable change in the kidney and liver function as per the biochemistry profile, there was no effect on clearane of the drug. Faster clearance in chickens could be due to smaller body weight and higher metabolic rate as compared to hawks, owls and albatross. The volume of distribution was much less in albatross as compared to other avian species. Volume of distribution describes the distribution of a drug between its central compartment and rest of the body. A higher volume of distribution means higher distribution of drug to various compartments. A lower volume of distribution as compared to other avian species could be due to the state of the animal. This albatross was given intravenous fluid therapy and was in a state of hypovolaemic shock which would decrease the tissue blood flow and thus reduce the volume of distribution.. In this study, the number of subjects was only 1 and that too was an injured albatross, suffering from pain. The distribution and metabolism of drugs vary with change in physiological state of an animal.

This study was not intended to do pharmacokinetics. The number of subjects in this study was only one, but it presents valuable information about butorphanol dosing regimens, which may be used for further used of butorphanol perioperatively in other injured Albatross or other wild avian species of similar body weight. Also, there is a need to develop slow release formulations of butorphanol, which can provide analgesia for a much longer duration than the standard commercially available formulation.

References

1. Alfred Mansour, Henry Khachaturian, Michael E Lewis, Huda Akil, Stanley J Watson. Anatomy of CNS opioid receptors. Trends Neurosci. 1988;11(7):310–314.
2. T Buchwalder, B Huber-Eicher. Effect of the analgesic butorphanol on activity behaviour in turkeys (Meleagris gallopavo). Res in Vet Sci. 2005;79(3):239–44.
3. Thomas G Curro. Anesthesia of pet birds. Seminars in Avian and Exotic Pet Medicine. 1998;7(1):10–21.
4. Paul-Murphy J, Brunson D, Miletic V. Analgesic effects of butorphanol and buprenorphine in conscious African grey parrots (Am J Vet Res. 1999; 60(10):1218-1221.
5. Sladky KK, Krugner-Higby L, Meek-Walker E, Heath TD, Paul-Murphy J. Serum concentrations and analgesic effects of liposome-encapsulated and standard butorphanol tartrate in parrots. Am J Vet Res. 2006;67(5):775–781.
6. Paul-Murphy J R, Krugner-Higby L A, Tourdot R L, Sladky K K, Klauer J M, Keuler N S, et al. Evaluation of liposome-encapsulated butorphanol tartrate for alleviation of experimentally induced arthritic pain in green-cheeked conures (Pyrrhura molinae). Am J Vet Res. 2009;70(10):1211–1219.
7. Laniesse D, Guzman D S-M, Knych H K, Smith D A, Mosley C, Paul-Murphy J R, et al. Pharmacokinetics of butorphanol tartrate in a long-acting poloxamer 407 gel formulation administered to Hispaniolan Amazon parrots (Amazona ventralis). Am J Vet Res. 2017;78(6):688–694.
8. Clancy M M, KuKanich B, John M Sykes. Pharmacokinetics of butorphanol delivered with an osmotic pump during a seven-day period in common peafowl (Pavo cristatus). Am J Vet Res. 2015;76(12):1070–1076.
9. Eric Klaphake, Juergen Schumacher, Cheryl Greenacre, Michael P Jones, Nancy Zagaya. Comparative Anesthetic and Cardiopulmonary Effects of Pre- Versus Postoperative Butorphanol Administration in Hispaniolan Amazon Parrots **(***Amazona ventralis***)** Anesthetized With Sevoflurane J Avian Med Surg. 2006;20(1):2-7.
10. P M Singh, C Johnson, B Gartrell, S Mitchinson, P Chambers. Pharmacokinetics of butorphanol in broiler chickens. Vet Rec. 2011;168:588–588. doi: 10.1136/vr.d1191
11. Singh PM, Johnson CB, Gartrell B, Mitchinson S, Jacob A, Chambers P. Analgesic effects of morphine and butorphanol in broiler chickens. Vet Anaes and Analg. 2017;44(3):538-545.
12. Riggs SM, Hawkins MG, Craigmill AL, Kass PH, Stanley SD, Taylor IT. Pharmacokinetics of butorphanol tartrate in red-tailed hawks (Buteo jamaicensis) and great horned owls (Bubo virginianus). Am J Vet Res. 2008;69(5):596–603.