Plasma Concentration of Butorphanol in Northern Royal Albatross Undergoing Fracture Repair

Preet Singh1*, Brett Gartrell1, Craig Johnson1 and Paul Chambers1

1Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Tennant Drive, Palmerston North, New Zealand

Abstract

**Aims:** The objective of this study was to determine the plasma concentration of butorphanol injected intravenously at 4 mg/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 isoflurane 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°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...
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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 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].

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 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.

Table 1: Pharmacokinetic 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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Butorphanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (0-∞) ng.min/ml</td>
<td>641091.7</td>
</tr>
<tr>
<td>AUMC (0-∞) ng.min²/ml</td>
<td>14954263.7</td>
</tr>
<tr>
<td>Vd ml/kg</td>
<td>860.5</td>
</tr>
<tr>
<td>Cl ml/min/kg</td>
<td>6.316</td>
</tr>
<tr>
<td>T (\frac{1}{2}) min</td>
<td>94.4</td>
</tr>
<tr>
<td>MRT, min</td>
<td>146.4</td>
</tr>
<tr>
<td>C (max) ng/ml</td>
<td>4738.4</td>
</tr>
</tbody>
</table>

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

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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 clearance 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