



NOTE

Wildlife Science

Long-term deep sedation using Zoletil and haloperidol for the treatment of streptococcal pneumonia in an orangutan (*Pongo pygmaeus*)

Paolo MARTELLI^{1)*} and Serena OH²⁾¹⁾Ocean Park Corporation Hong Kong, Wong Chuk Hang Road, Aberdeen, Hong Kong²⁾Wildlife Asia Veterinary Services, 10 Anson Road, #27-15 International Plaza, 079903 Singapore*J. Vet. Med. Sci.*

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ABSTRACT. A 13-year-old Bornean orangutan diagnosed with life threatening *Streptococcus pyogenes* broncho-pneumonia was kept in a state of deep sedation for 20 days via continuous intra-venous (IV) infusion of zolazepam -tiletamine and IV haloperidol to allow consistent IV administration of ceftazidime and gatifloxacin. The use of long-term deep sedation allowed carrying out a particularly demanding treatment not generally associated with zoological patients. The treatment was ultimately successful.

KEY WORDS: haloperidol, long-term sedation, orangutan, pneumonia, zolazepam-tiletamine

Conducting a thorough physical examinations and diagnostic workups on fully conscious orangutans is a challenging task. Common diseases, such as respiratory infections tend to be primarily treated symptomatically with courses of antibiotics based on past institutional experience. However, occasionally, respiratory infections will progress to more serious conditions that warrant detailed workups and invasive treatments [2, 7, 9, 11, 15, 16, 19].

Placement of indwelling catheters for efficient long term intravenous (IV) access are rarely tolerated even by the more amenable individuals, further limiting treatment options in high dependency patients.

Although general anesthesia is commonly performed in zoo animals to conduct physical examinations, diagnostic workups or to carry out medical or surgical interventions; repeated daily anesthesia over an extended period is seldom considered due to the psychological and physiological stress implications as well as the inherent risks posed.

We report the case of a captive born, 13 year-old female Bornean orangutan (*Pongo pygmaeus*), housed in a local zoo that was initially presented with reduced appetite, mild lethargy and bilateral runny mucopurulent nasal discharge. Diagnostic access to the conscious animal was limited to a cursory chest auscultation revealing mild rales. Temperature, full blood profile and radiographs were not taken. Initial treatment consisted of a course of oral trimethoprim-sulfonamide for 7 days (Co-Trimoxazole Paediatric Suspension, Drug houses of Australia Pte, Ltd., Singapore) that did not improve her condition. The antibiotics were then changed to a week of amoxicillin-clavulanic acid (Augmentin ES suspension, GlaxoSmithKline, Singapore) followed by another five days of doxycycline (Vibravet, Pfizer Australia Pty Ltd., Adelaide, Australia). However, the condition deteriorated over the course of these treatments. Respiration became labored, she developed a weak and painful cough with thicker mucopurulent discharge from both nostrils and there was significant weight loss. Airsacculitis, which is common in orangutans, was not present [2, 10].

A thorough physical examination and diagnostic work up under general anesthesia was deemed necessary. The orangutan was anesthetized with 2.5 mg/kg of zolazepam + tiletamine 1:1 (Zoletil®, Virbac Laboratories, Carros, France) delivered intramuscularly (IM) by blow dart.

Physical examination revealed that the animal was emaciated, had normal rectal temperature, mildly cyanotic mucosae and its right axillary lymph node was hard and enlarged. The upper quadrant of the left lung field was silent on auscultation and poorly resonant on percussion. The entire right lung field was not resonant. Moist rales could be heard in the remainder of the right and left lung fields. Intra-dermal tuberculin skin test was done by injecting 0.1 ml of Purified Protein Derivative tuberculin in the right upper eyelid. Blood was taken for complete blood count (CBC) and biochemistry.

Chest radiographs showed diffuse radio-opacity of the entire right lung (Fig. 1) with poorly demarcated borders cranially and denser well demarcated shadowing caudally, pointing to consolidation and pneumonia. The right lung had collapsed to a large degree, the left lung was overinflated and the heart was displaced to the right. The cardiac silhouette was barely visible through

*Correspondence to: Martelli, P.: paolo.martelli@oceanpark.com.hk

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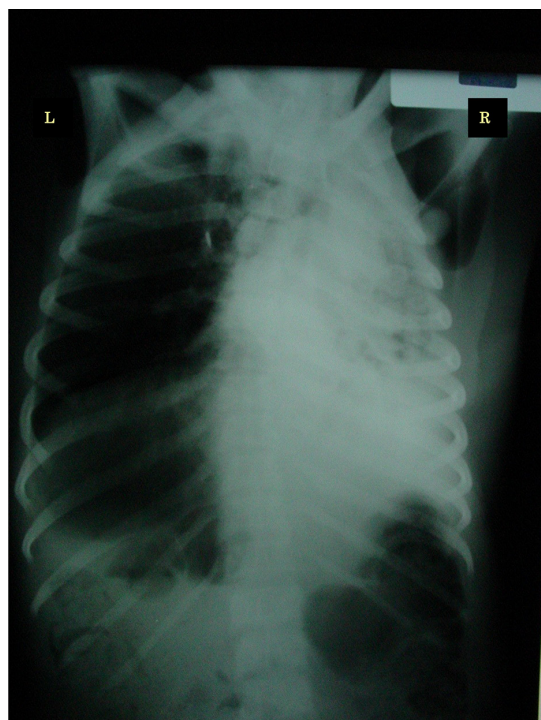


Fig. 1. Chest radiograph prior to treatment. Right lung: marked radio-opacity, poorly demarcated borders cranially and denser shadowing caudally pointing to consolidation and pneumonia.

the opacity of the right lung. Pneumonic changes were also present cranially in the left lung (Fig. 1).

Bronchoscopy was performed as it is easier and less invasive than laparoscopic lung biopsy [18] and allows a detailed evaluation and sampling of the airways for identification of lesions and etiological agents. Bronchoscopy revealed pooling of pus in most airways. Swabs and broncho-alveolar lavages (BAL) of the left, right and right apical airways were carried out during the bronchoscopy. The samples were examined for bacterial and fungal cultures and for cytology, including Diff-Quick, Gram and Acid-Fast stains. Tuberculosis, nocardiosis, melioidosis and fungal infections as well as lung mites must be included in the differential diagnosis of respiratory infections of primates [11, 16, 19].

Intra-dermal tuberculin skin test was negative at 24, 48 and 72 hr. Tracheal, fecal and BAL cultures and cytology did not reveal fungal elements or acid fast bacteria, i.e. *Mycobacterium* spp. and *Nocardia* spp.

Streptococcus pyogenes was cultured from all bronchoscopy swabs and BAL samples. The orangutan was diagnosed with extensive bilateral bacterial acute-on-chronic streptococcal bronchopneumonia, with complete involvement of the right lung and partial involvement of the left lung with a very poor prognosis.

Considering the diagnosis, prognosis and consultations with human pulmonologists it was concluded that for any chance of a successful outcome, the orangutan required continuous intravenous (IV) antibiotics over a long period. Based on the results of bacterial culture and sensitivity as well as recommendations from the specialists the antibiotic treatment of choice was a combination of 1,000 mg ceftazidime (Fortum[®], Glaxo-Wellcome Vidhyasom Ltd., Samut Prakarn, Thailand) three times a day (tid) for 2 to 3 weeks and 400 mg of gatifloxacin (Tequin[®], Bristol-Meyers Squibb

Laboratories, Manati, RQ, USA) once a day (sid), for the same duration. Both antibiotic drugs had to be delivered by slow IV, each over a period of 45 to 60 min. Initial multiple attempts to place long term IV ports failed because upon recovery from anesthesia the orangutan would rip apart the bandages protecting the IV line, including a sturdy custom-made methyl-metacrylate armored bandage. The decision was made to keep the orangutan continuously sedated to carry out the necessary treatments undisturbed.

Zoletil[®] was chosen because of our team's familiarity with this drug in orangutans. 500 mg of Zoletil[®] was mixed into a 250 ml bag of saline and connected in parallel with the hydrating solutions. Daily doses of Zoletil[®] required to maintain the desired state of sedation ranged from 150 to 600 mg/24 hr. Although this dose rate corresponds to 0.2 to 0.8 mg/kg/hr, in reality the rate of administration varied throughout the day with the desired level of sedation. 20 G catheters were placed alternatively in the saphenous and cephalic veins, maintained daily and replaced every 4 to 6 days. At times, multiple catheters were in place, as a port was added if a catheter appeared perfect but the associated vessel started to look imperfect or vice-versa.

Fluid management included rehydrating solutions Ringers and 5% Dextrose given intravenously at a total rate of 2.9 ml/kg/hr. Urine output was not measured precisely as we opted against lasting bladder catheterization to avoid the inevitable ascending cystitis associated with long-term bladder catheters. Urination occurred during sleep or when feeding. On occasion, when a full bladder was palpable, manual transabdominal pressure would easily stimulate voiding.

In addition to fluids and antibiotics, a range of supportive care was needed to manage the impaired nutritional status, the decreased digestive passage, the impaired expectoration and pressure necrosis; all inevitable consequences of the prolonged recumbency and unconscious state. The orangutan spent approximately 23 hr of the day sleeping and was recumbent for 20 full days.

Three attempts at placing a nasogastric tube failed. Voluntary food ingestion was managed successfully through the practice described hereafter. One to three times a day the Zoletil[®] infusion was stopped and an IV bolus of 5 mg of the non-selective dopamine inhibitor butyrophenone neuroleptic haloperidol (Haldol[®], Janssen-Cilag Ltd., Buckinghamshire, UK) was given. This produced a brief state of tranquillity with minimal aggression during which fruits and primate pellets, soaked and softened in fruit juice, were greedily consumed, although fibrous greens were not readily accepted. During these meals the animal was monitored closely and the Zoletil[®] anesthetic drip was resumed as soon as the patient started interacting negatively with the IV line or the caretakers. With this regimen we avoided further loss of body weight during the 20 days of treatment.

Lower intestinal impaction resulting from a lack of activity was managed by ad hoc oral and rectal administration of 10 to 15 ml lactulose (Lactulose Sandoz[®] Salutas Pharma GmbH, Barleben, Germany).

Coupage was performed 1 to 3 times daily to assist in dislodging purulent material in the airways, facilitating its evacuation by the ciliated respiratory epithelium. Furthermore to limit the risk of suffocation by obstruction of the upper airways the animal was

not allowed to lie horizontally, on its sides or back, and instead was kept with the chest slightly upright.

The animal was placed in a cage approximately 1.5 m wide, 1.8 m tall and 0.9 m deep with large double frontal doors for easy access. A thick bedding, daily massages, limb mobilization and frequent positional changes helped to avoid the development of grave pressure sores.

Response to the treatment was best assessed through chest radiographs. On day 3 there were no radiographic changes. On day 6 there was radiographic improvement of both lungs, with the cardiac silhouette becoming discernible in the right thorax. These improvements were also observed on auscultation and percussion. Radiographs on days 11 and 15 showed marked improvements. Most radiographic lesions resolved on day 18, although the heart remained displaced to the right due to the overinflated left lung and the partial collapse of the right upper pulmonary lobe (Fig. 2).

Blood analysis was carried out during the treatment on days 1, 3, 6, 11 and 18 and a month after discharge. A blood sample taken prior to illness was used for comparison. Results are shown in Table 1. A drop in leukocytes on day 11 was of concern as possibly reflecting or leading to ineffectual immunity. A single administration of 150 µg IM of the granulocyte colony-stimulating factor Filgrastim (Neupogen®, offmann-LaRoche Ltd., Basel, Switzerland) was given and the leukocytes reading returned to normal. The progressive decline in total proteins was attributed to a combination of a reduced nutrition and the consumptive effects of fighting the infection. There were no changes in hepatic and renal parameters, suggesting that the prolonged recumbency and the long term use of the sedative and antibiotic drugs were well tolerated by the animal and that fluid management was overall adequate. On day 20 we considered that sepsis had resolved and that the radiographic lesions had improved to the extent possible and were no longer active.

Intravenous antibiotics were discontinued on day 20. The animal was returned to the orangutan house on the same day to allow her to fully wake up in familiar surroundings.

After returning to her quarters the orangutan continued to improve. She resumed feeding and defecating normally and started gaining weight, putting on 5 kg in the first month following her discharge. She did not encounter any difficulties reuniting socially with her peers and overall appeared unaffected by the long separation and prolonged unconscious state.

Computed Tomography (CT) one month after discharge showed areas of lung scarring and areas of bronchiectasis in the right upper quadrant (Fig. 3) and there was no evidence of active pneumonia. Air sacs remained unaffected throughout the illness.

Streptococcus pyogenes is a frequent pathogen of the upper airways, throat and tonsils that can progress to systemic infections including pneumonia [12]. Pneumectomy, a crippling surgery best avoided but sometimes indicated in the treatment of lung diseases, was not required in this case [3, 5, 17].

In the authors' knowledge, no precedents for long term deep sedation could be found in the veterinary literature or from consulting peers. As a result, we were unable to find references on which to base the intended long term sedation. We considered but rejected confinement in a small squeeze cage with a moveable wall which would allow the conscious animal to be repeatedly positioned against the mesh for treatment. We also rejected sequential anesthesia-recoveries repeated at least more than three times daily as being too stressful and psychologically traumatic. Furthermore we had no confidence that without sedation we could locate vessels fit to catheterize three times daily for 2 to 3 weeks. In other words, the alternative options would not have allowed the necessary slow IV administrations of antibiotics and would have caused severe distress, a high risk of injury to animal and staff and an abysmal quality of life, all of which ultimately would work against the treatment. Discussions with respiratory specialists and with human doctors with experience in medically induced (artificial) coma or dealing with dangerous intractable patients persuaded us to attempt the here-reported long term sedation for the purpose of delivering the IV antibiotic therapy required to resolve the life-threatening pneumonia. Furthermore by keeping the animal unconscious, if the treatment had failed, the animal would have succumbed without suffering through the treatment. Zoletil was chosen based on the vast experience and confidence of our team in using this drug with orangutans. To allow the animal brief moments of tranquil consciousness we opted for haloperidol, a drug we had less experience with at that time. In human medicine haloperidol is sometimes used for prolonged periods for mood stabilization [4, 6, 13, 14]. The prolonged usage of haloperidol in humans has low incidence of drug-induced hepatitis and low liver toxicity [13]. Haloperidol is gaining popularity in zoological medicine with many species [6, 8]. It has profound psychomotor effects increasing tractability of game animals [1, 8].

Supportive care during the prolonged sedation significantly contributed to the successful outcome of the case and it included the daily maintenance of the catheters, hydration and nutritional management, coupage, massages to prevent bedsores and periodical bowel and bladder evacuation.

The dedication and the compassionate yet open mind-set of the animal care staff and the zoo management were instrumental in carrying out an undocumented, untested and rather unorthodox treatment in a high profile species on the brink of death.

Building on the success of the case presented above, the veterinary team added prolonged deep sedation and an accompanying supportive care protocol as a tool to treat a variety of other cases in dangerous patients requiring intensive care. Other successful cases treated using similar protocols adapted to individual species and cases includes lower limb septic cellulitis in a baboon and post-operative management care of an extensive surgical site following a bilateral mammary chain ablation in a puma. We believe that medium and long term anesthesia or deep sedation can be recommended in cases where the nature and frequency of the treatment are not compatible with the temperament of the patient or its intolerance to repeated stressful insults.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

Table 1. Blood values before during and after treatment

	ISIS mean ± SD	Pre-illness	Day 1	Day 3	Day 6	Day 11	Day 18	Recovered [^]
PCV %	27–52	40	49	45	29	34	31	41
WBC 10 ⁹ /l	3.9–29	12.5	19.8	18.3	13	4.85	15.5*	12.3
BUN mmol/l	4.6 ± 2	2.3	3.9	2.1	3.2	2.7	1.7	3.2
Creat umol/l	106 ± 80	70	95	70	68	71	72	83
TP g/l	75 ± 7	78	73	76	74	50	55	76
ALT U/l	0–74	16	32	30	5	32	32	35
AST U/l	0–56	9	36	21	9		34	12
ALKP U/l	287 ± 242	312	210	254		178	223	356
Na mmol/l	99–155	140	155	173	168	178	167	152
K mmol/l	2.4–8	4.5	2.6	3.3	3.3	3.8	2.8	4
Ca mmol/l	1.8–2.9		1.81	1.73		1.56	1.78	2.2
Cl mmol/l	92–113	95	125	133	122	131	124	
TBIL mg/dl	12 ± 7	0.4	2	10		0.5		3
GLU mmol/l	5 ± 1.2	5.3	3.8	1.5	7.4	7	2.6	6.1

*: 3 days after 150 mg filgrastim IM. [^]: 1 month after discharge. PCV: packed cell volume, WBC: white blood cell count, BUN: blood urea nitrogen, Creat: creatinine, TP: total protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALKP: alkaline phosphatase, TBIL: total bilirubin, GLU: serum glucose.

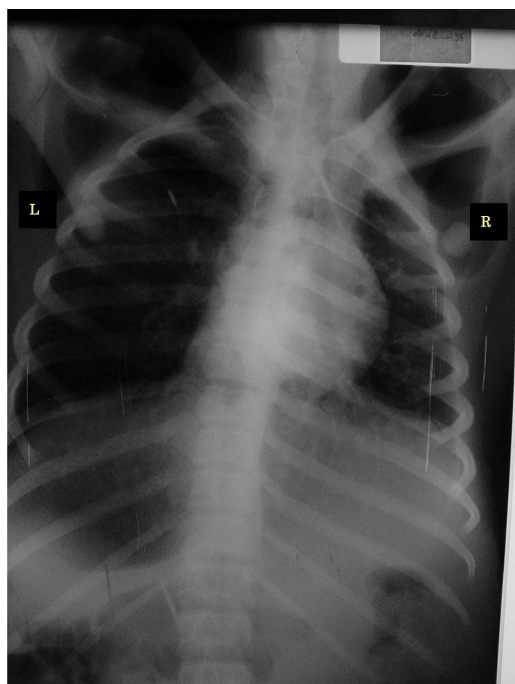


Fig. 2. Day 18 of treatment. Most radiographic lesions have resolved. The heart is displaced to the right due to the overinflated left lung and partial collapse of the right lung.

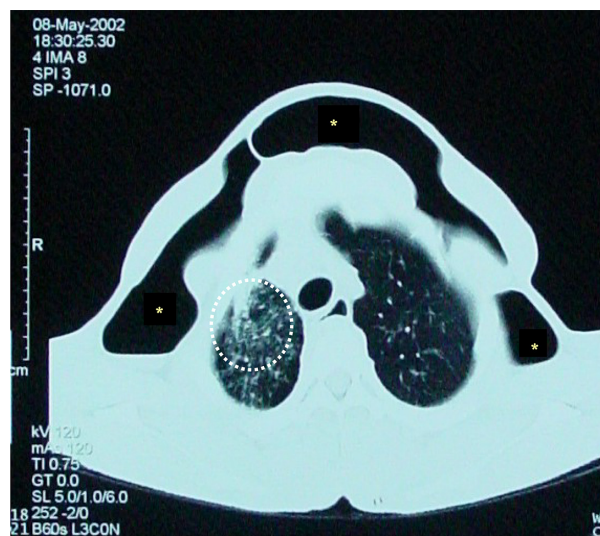


Fig. 3. Computed Tomography one month after discharge. Some areas of pulmonary scarring and bronchiectasis in the right upper quadrant (dotted line circle).

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