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Anaesthesia with medetomidine-ketamine-isoflurane with and without midazolam, in eight captive Chimpanzees (*Pan troglodytes*) premedicated with oral zuclopenthixol

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Summary

In 8 captive adult chimpanzees of various ages premedicated with oral zuclopenthixol anaesthesia was induced intramuscularly with a combination of medetomidine and ketamine (40 or 50 µg/kg and 5 mg/kg, IM, respectively), with and without midazolam (0.05 mg/kg), and maintained with isoflurane in oxygen. At the end of the procedure, sedation was reversed with atipamezole (0.25 mg/kg, IM) and sarmazenil (0.005 mg/kg, IM) when midazolam had been administered. Oral zuclopenthixol resulted in tranquillization of the whole group and only one animal required a second dart injection to achieve adequately deep anaesthesia. Effective and reliable anaesthesia was achieved in all apes; the depth of hypnosis was stable and sudden arousal did not occur. Physiological parameters remained within normal ranges in the majority of the animals; however, manageable anaesthesia-related complications, namely apnoea after darting, hypotension, hypoventilation, hypoxemia and prolonged recovery, occurred in 6 out of 8 animals. The use of monitoring devices was essential to guarantee adequate management of these complications.

Keywords: chimpanzee, ketamine, medetomidine, midazolam, *Pan troglodytes*, zuclopenthixol

Medetomidin-Ketamin-Isofluran Anästhesie mit und ohne Midazolam bei acht Zoo-Schimpansen (*Pan troglodytes*) nach Prämedikation mit oral verabreichtem Zuclopenthixol

Acht adulte Zoo-Schimpansen verschiedenen Alters wurden nach Prämedikation mit oral verabreichtem Zuclopenthixol mit einer Kombination von Medetomidin (40 oder 50 µg/kg, IM) und Ketamin (5 mg/kg, IM), mit und ohne Midazolam, anästhesiert. Die Narkose wurde anschliessend mit Isofluran/Sauerstoff aufrecht erhalten. Am Ende der Anästhesie wurde die Sedation mit Atipamezol (0.25 mg/kg, IM) und, falls Midazolam verwendet worden war, zusätzlich mit Sarmazenil (0.005 mg/kg, IM) antagonisiert. Oral verabreichtes Zuclopenthixol bewirkte eine Beruhigung der ganzen Gruppe und nur ein Tier benötigte eine zweite Injektion mittels Blasrohrpfeil, um eine ausreichende Narkosetiefe zu erreichen. Die Narkosetiefe war stabil und es kam zu keinem plötzlichen Erwachen. Die Mehrheit der Tiere zeigte physiologische Parameter im Referenzbereich, dennoch kam es zu Anästhesie bedingten Komplikationen wie Atemstillstand kurz nach Pfeilinjektion, Hypotension, Hypoventilation Hypoxämie und verzögerten Aufwachphasen bei 6 von 8 Tieren. Die eingesetzten Überwachungsgeräte erwiesen sich als essentiell für ein angemessenes Management der auftretenden Komplikationen.

Schlüsselwörter: Schimpanse, Ketamin, Medetomidin, Midazolam, *Pan troglodytes*, Zuclopenthixol

Introduction

Anaesthesia of great apes is commonly required to perform diagnostic or interventional procedures (April et al., 1982; Adams et al., 2003). The use of various alpha-2 agonists and cyclohexanes combinations has been described in both laboratory and captive or wild primates (Banknieder et al., 1978; April et al., 1982; Lewis et al., 1993; Fahlman et al., 2006; Naples et al., 2010); in particular, the association medetomidine-ketamine resulted in reliable – although short term – sedation in chimpanzees, with minimal cardiovascular effects (Horne et al.,

1997a; Horne et al., 1997b; Adams et al., 2003). Because isolating and darting single individuals without warning the whole group can be challenging, catching and induction are considered the most critical phases of primates' anaesthesia; in order to overcome this problem, the oral administration of anxiolytic drugs prior to darting may offer a valuable help.

Zuclopenthixol is a potent thioxanthene neuroleptic agent with combined dopamine-antagonist activity at the D1 and D2 receptors (stronger at D1 receptors), which also has a moderate affinity for alpha-1 adrenergic receptors, a weak affinity for the muscarinic cholinergic receptors, and no antagonistic activity at serotonin receptor subtypes (Lublin et al., 1991). Several studies performed in both adult humans and children demonstrated that zuclopenthixol is effective for treating several psychotic disorders and can consistently decrease aggressive behaviour, hostility and agitation in this species (Mann et al., 1985; Bhattacharyya et al., 1987; Huttenen et al.; 1995; Grinshpoon et al., 1998; Sabri Ercan et al., 2011). Common adverse effects reported in humans are drowsiness, fatigue, dry mouth and occasionally extrapyramidal effects (Gibson et al., 2009).

Unfortunately, except for a report describing its use in gorillas (Wenger et al., 2012), there is a lack of publications concerning the administration of zuclopenthixol in great apes or other captive and wild animal species. A potential advantage of zuclopenthixol over traditional neuroleptics may be its combined activity on both D1 and D2 receptors, which might lead to decreased incidence of dopaminergic hypersensitivity compared to the pure D2 antagonists (Lublin et al., 1991). Additionally, the availability of an oral formulation makes this drug suitable for being easily administered prior to darting. This paper describes the use of medetomidine and ketamine, with and without midazolam, in captive chimpanzees premedicated with oral zuclopenthixol. The safety, the efficacy and the reliability of this drug combination have not been reported in chimpanzees.

Animals, Material and Methods

Eight adult captive chimpanzees were anaesthetized for transport and diagnostics, including body weight measurement, physical examination, blood sampling, radiographic exam of the thorax, abdomen ultrasonography, and bronchoalveolar lavage. Three days prior to anaesthesia, zuclopenthixol dihydrochloride (Clopixol, Lundbeck AG, Glattbrugg, Switzerland, 0.2 mg/kg; the dose was increased to 0.27 mg/kg on the day of anaesthesia), was administered twice daily orally in raspberry syrup to reduce anxiety associated to darting and transport. The animals appeared healthy at pre-anaesthetic visual examination. Food, but not water was withheld for 12 hours. Chimpanzees were isolated one after the other in a small cage and, there, injected with a dart syringe delivered by a blow pipe. Five apes received a combination of medetomidine (Zalopine, Orion Corporation, Turku, Finland, 50 µg/kg, IM) and ketamine (Narketan, Vétoquinol AG, Ittigen, Switzerland, 5 mg/kg, IM) whereas the other 3 were injected with medetomidine (40 µg/kg, IM), ketamine (5 mg/kg, IM), and midazolam (Dormicurm, La Roche, Basel, Switzerland, 0.05 mg/kg, IM). The doses were calculated on the basis of the estimated weight. Animals were left undisturbed for 10 minutes and, as soon as judged unresponsive to stimulation with a pole they were removed from the enclosure.

In all animals the cephalic vein was catheterized with an 18 gauge over the needle catheter and a balanced electrolyte solution (Ringer Lactat, Baxter AG, Switzerland) was administered at an infusion rate of 10 ml/kg/h). Tracheal intubation was performed in all animals for isoflurane (Isofluran, Baxter AG, Switzerland) in oxygen administration.

Animals were instrumented with a capnograph and pulsoxymeter (Microcap plus, Oridion, Needham, USA), an electrocardiograph (Schiller AT-4; Medical Device Depot, Maryland, USA) and a Doppler ultrasonic flow detector (Doppler Flow Detector, Model 811-B, Parks Medical Electronics, Oregon, USA) over the dorsal metatarsal artery. The following variables were recorded every 5 minutes: end tidal carbon dioxide concentrations ($ET'CO_2$), respiratory rate (f_R), arterial oxygen saturation (SpO_2) heart rate (HR), mucous membrane colour, quality of the pulse and capillary refill time (CRT); systolic arterial pressure (SAP) and rectal temperature (T) were measured and recorded at least once in each animal during anaesthesia. Arterial blood samples were taken, by direct puncture from the dorsal metatarsal artery, after the apes were connected to the breathing system (at least once from each animal), and analysed using a portable blood gas analyzer (i-STAT Analyzer, i-STAT Corporation, Princeton, USA). Measured variables included pH, arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial partial pressure of oxygen (PaO_2), whereas base excess (BE), bicarbonate (HCO_3^-) and arterial hemoglobin oxygen saturation (SaO_2) were calculated from the measured variables. Blood gas analyses were corrected to body temperature. At the end of the procedure, each animal was placed in a transport crate and 0.2 mg/kg atipamezole (Antisedan, Pfizer AG, Switzerland) were administered IM. Animals in which midazolam was part of the anaesthetic protocol also received IM 0.005 mg/kg sarmazenil (Sarmasol, Dr. Graeub AG, Switzerland). The apes were extubated when able to swallow, and observed until they fully recovered from anaesthesia.

Results

Mean error in bodyweight estimation was 6 %. Oral zuclopenthixol provided mild sedation; the chimpanzees still reacted to catching with vocalizations, but isolation

and darting were successfully performed at the first attempt in all the animals but one (Tab. 1, no. 2), which required a second dart (half of the initial doses of both medetomidine and ketamine) to achieve adequate immobilization. The mean (± sd) doses of medetomidine and ketamine were 43.3 (± 6.3) µg/kg and 4.9 (± 0.7) mg/kg, respectively; in the 3 animals which received midazolam, the mean dose (± sd) was 0.04 (± 0.01) mg/kg. One chimpanzee (Tab. 1, no. 6) achieved a deep sedation and became apnoeic within a few minutes from darting. This unexpected complication required immediate removal of the animal from the cage and rapid intubation of the trachea; intermittent positive pressure ventilation was initiated and the animal stabilized.

Physiologic parameters, as well as the blood gas analyses' results, are summarised in Table 2. Rectal temperature and HR stayed within physiological ranges (Sleeman, 2007) during anaesthesia (Tab. 2). However, 3 animals (no. 1, 2 and 8) showed hypotension (SAP < 90 mm Hg) and received one bolus of crystalloids (Lactated Ringer's solution, 10 ml/kg) and one bolus of colloids (Voluven 6 %, Fresenius Kabi, Switzerland; 2 ml/kg) IV; the rate of infusion of Lactated Ringer's solution was increased to 10 ml/kg/h^{-1}. In 4 chimpanzees (no. 1, 4, 6 and 7) the blood gas revealed hypoventilation (PaCO2 > 6 kPa, Tab. 2); 2 of them (no. 1 and no.7) were also hypoxemic (PaO_2 < 13.3 kPa, Tab. 2) and required manually assisted ventilation. In animal no. 7a recruitment manoeuvre was also performed by manually delivering three breaths in order to achieve and hold for 10 seconds a peak inspiratory pressure of 30 cm H_2O.

Arousal from anaesthesia was smooth and uneventful in the majority of the animals. Only 2 animals (no. 6 and no. 8) had a prolonged recovery phase and required further administration of both IM atipamezole and sarmazenil (animal no. 6), or atipamezole only (animal no. 8), at half of the initial doses. In chimpanzee no. 6 sarmazenil administration, 0.0025 mg/kg IM, was repeated twice during recovery phase without producing the desired effects. Rectal temperature and arterial blood pressure were measured every hour and found within normal ranges (SAP > 100 and rectal temperature > 36.5). Crystalloid administration was continued at an infusion rate of 3 ml/kg/h and oxygen supplementation provided with flow by technique until both animals fully recovered from anaesthesia; this occurred after 4 and 11 hours from darting in animals no.8 and no.6, respectively. Neither abdomen ultrasonography nor blood biochemistry revealed abnormalities in these 2 chimpanzees. The day after the procedure both apes showed normal behaviour and anaesthesia did not result in long-term complications.

Discussion

The ideal anaesthetic protocol for potentially dangerous wild or captive animals should guarantee human safety

Table 1: Signalment and anaesthetic induction parameters of 8 adult captive chimpanzees anaesthetized with medetomidine-ketamine or medetomidine-ketamine-midazolam after premedication with oral zuclopenthixol. Parameters' measures are the following: years (age), kg (weight), µg/kg (medetomidine), mg/kg (ketamine), min (time from darting to recumbency and duration of anaesthesia).

Animal	Age (years)	Estimated weight (kg)	Weight (kg)	Ketamine (mg/kg)	Medetomidine (µg/kg)	Midazolam (mg/kg)	Time from darting to recumbency (min)	Duration of anaesthesia (min)
1	6	20	18.4	5.4	48.9	NA	7	85
2	9	40	51.8	3.9	34.7	NA	20	20
3	17	60	69.2	4.3	34.7	0.043	18	25
4	32	45	48	7[a]	55.5[a]	0.047	25	20
5	35	65	60	4.3	48.8	NA	22	30
6	36	70	55	6.4	51	0.064	3	30
7	36	75	78.4	4.8	43.1	NA	15	40
8	49	55	51.8	5.3	47.8	NA	13	50

[a] Total doses administered to this animal, including re-dosing with 50 % of the initial doses of both medetomidine and ketamine, NA: not administered.

by providing effective and reliable immobilization and at the same time be safe for the patients (Popliskis et al., 2008). All animals of this investigation showed reliable sedation and could be safely removed from the cage and manipulated for IV catheter placement and endotracheal intubation without risks for the personnel. However, several anaesthesia-related complications, namely apnoea at induction, hypoventilation, hypoxaemia, hypotension and prolonged recovery, were observed. Although several studies showed that zuclopenthixol has a wide margin of safety in humans and is associated to bearable side effects, only one report investigated the effects of this compound in great apes when co-administered with anaesthetic agents (Wenger et al., 2012). Therefore, the occurrence of potential addictive or synergic effects with other classes of drugs co-administered in this trial cannot be excluded. Nevertheless, there might be other reasons for these anaesthesia-related complications.

In chimpanzee no. 6, the fast onset of the sedative effect and the occurrence of apnoea after darting could have been caused by injectable anaesthetics overdose, due to body weight overestimation by 27 %. As alternative explanations, inadvertent intravenous administration of part of the injected volume and hypersensitivity of this animal to the administered drugs cannot be excluded. However, despite leaving wild primates alone after darting is considered a good practice to decrease the stress and speed the onset of chemical tranquillization (Horne et al., 1997b), a closer observation of the animal immediately after injection might have allowed earlier detection and therefore better management of the complication.

In chimpanzee no. 8, the prolonged recovery could have been caused by the old age and by body weight overestimation by 6 %, which led to slight overdose of the anaesthetic agents.

In chimpanzee no. 1 (Tab. 2), the radiographic exam of the thorax revealed the presence of diffuse consolidated areas in the left lung and mild pleural effusion, which could have provoked the hypoxaemia. Similarly, animal no. 7 was obese and the hypoxaemia could have been caused by hypoventilation and decreased functional residual capacity due to compression of the lungs by the abdominal organs in dorsal recumbency; for this reason, the animal was placed on sitting position and manually assisted ventilation initiated after recruitment manoeuvre.

Field anaesthesia of captive or wild animals often implies a lack of instrumental monitoring, which leads to increased risk of unrecognized anaesthesia-related complications. Invasive monitoring, such as invasive blood pressure measurement and arterial blood gas analysis, are not routinarily performed in captive primates not only because they imply the availability of expensive devices, but also due to the great risk of hazardous zoonotic pathogens transmission to humans (Sleeman, 2007). However, hypoventilation and hypoxaemia were major complications in 2 out of 8 apes despite these animals received 100 % oxygen, were able to breath spontane-

Table 2: Arterial blood gas values and cardiovascular and respiratory parameters from 8 adult captive chimpanzees induced with medetomidine-ketamine or medetomidine-ketamine-midazolam and maintained with isoflurane, after premedication with oral zuclopenthixol. Parameters' measures are the following: mmHg ($ET'CO_2$ and SAP), kPa ($PaCO_2$ and PaO_2), % ($Fi\,O_2$, $Sp\,O_2$, $Sa\,O_2$), Celsius/Fahrenheit (body temperature). HR and f_R are reported as means and standard deviations.

Animal	pH	$Pe'CO_2$ (mmHg)	$PaCO_2$ (kPa)	FiO_2	PaO_2 (kPa)	SpO_2 (%)	SaO_2 (%)	HCO_3^- (mmol/L^{-1})	BE	HR mean (sd) [60–200][a]	f_R mean (sd) [20–60][a]	SAP (mmHg)
1	7.44	36	5.2	1	10.8	95	96	27	2	82 (8)	36 (6)	70
1†	7.40	41	6.2	1	11.2	93	96	38.9	4	ND	ND	75
2	7.43	37	5.3	1	24	95	100	26.3	2	100 (4)	35 (4)	85
3	7.48	37	4.3	1	66.4	96	100	25.5	2	84 (4)	13 (4)	ND
4	7.34	51	8.1	1	65.3	95	100	32.9	ND	64 (5)	25 (2)	110
5	7.49	30	5.4	1	67.3	94	100	31.1	8	66 (6)	11 (2)	110
6	7.34	51	8.1	1	65.3	95	100	32.9	ND	64 (5)	25 (2)	110
6*#	7.5	ND	4.7	0.3‡	21.2	ND	ND	ND	ND	ND	ND	ND
7	7.34	48	7.4	1	12.4	96	93	30.3	5	70 (5)	37 (4)	105
8#	7.57	35	4.8	1	71.7	97	100	33.8	12	75 (4)	13 (1)	70

† Second blood sample collected from this animal during anaesthesia, * second blood sample collected from this animal during recovery phase, # had prolonged recovery, ‡ estimated (oxygen supplementation provided with flow by technique), ND: not determined, [a] physiological ranges for the specie (Sleeman et al., 2007).

ously and even showed SpO_2 values only slightly below the normal range. Likely, unrecognized hypoventilation and related complications do occur during wild animals' field anaesthesia, where instrumental monitoring is often replaced by clinical assessment of cardiovascular and respiratory function only. One limitation of this study, which does not allow for more extensive considerations concerning the effectiveness of zuclopenthizol, is the lack of a control group receiving placebo instead of the oral tranquillizer. Unfortunately, such a study design was not feasible as it would have required a larger number of animals.

In conclusion, oral zuclopenthixol, administered prior to anaesthesia, seemed to facilitate separation and darting by tranquillizing the group and both medetomidine-ketamine and medetomidine-ketamine-midazolam combination, followed by isoflurane, provided effective and reliable anaesthesia for captive chimpanzees. The use of monitoring devices was essential to guarantee adequate management of the anaesthesia-related complications. Despite the risk of zoonotic diseases transmission to humans may be of concern, routine arterial blood gas analysis should be considered as it would greatly decrease the occurrence of unrecognized hypoxaemia.

Anesthésie par médétomidine-kétamine-isoflurane avec ou sans midazolam chez 8 chimpanzés (*Pan troglodytes*) d'un zoo après prémédication orale avec du zuclopenthixol

Huit chimpanzés adultes d'un zoo, d'âges différents, ont été anesthésiés, après prémédication orale au zuclopenthixol, avec une combinaison de médétomidine (40 ou 50 µg/kg, IM) et de kétamine (5 mg/kg, IM), avec ou sans ajout de midazolam. La narcose a ensuite été poursuivie par administration d'isoflurane/oxygène. A la fin de l'anesthésie, la sédation a été antagonisée avec de l'atipamézol (0.25 mg/kg, IM) et, lorsqu'on avait utilisé du midazolam, avec en outre du sarmazenil (0.005 mg/kg, IM). L'administration orale de zuclopenthixol amenait une tranquillisation du groupe entier et seul un animal a nécessité une seconde injection par sarbacane pour atteindre une profondeur de narcose suffisante. La profondeur de narcose était constante et on a constaté aucun réveil soudain. La majorité des animaux présentaient des paramètres physiologiques dans les normes mais il s'est produit diverses complications d'anesthésie, comme arrêt respiratoire peu après la télé-injection, hypotension, hypoventilation, hypoxie et réveil retardé chez 6 des 8 animaux. Les outils de surveillance utilisés s'avèrent essentiels pour une gestion adaptée des complications qui peuvent se produire.

Anestesia con medetomidina-ketamina-isoflurano con e senza midazolam dopo premedicazione con zuclopentizolo orale in 8 scimpanzé allevati in cattività

Otto scimpanzé adulti allevati in cattività e premedicati con zuclopentizolo (soluzione orale), sono stati anestetizzati tramite iniezione intramuscolare di medetomidina e ketamina (40 or 50 µg/kg e 5 mg/kg, rispettivamente), con e senza midazolam (0.05 mg/kg), seguiti dalla somministrazione di isoflurano in ossigeno. Alla fine della procedura, la sedazione è stata antagonizzata con atipamezolo (0.25 mg/kg, IM) o con atipamezole e sarmazenil (0.005 mg/kg, IM), laddove era stato somministrato il midazolam come parte del protocollo anestesiologico. Lo zuclopentizolo orale ha prodotto tranquillizzazione di tutti gli animali e in un solo soggetto è stata necessaria un'ulteriore iniezione al fine di ottenere un livello di anestesia adeguato. In tutti i soggetti è stata ottenuta un'anestesia efficace e sicura; il livello di ipnosi è risultato stabile, senza risvegli improvvisi. I parametri fisiologici sono rimasti entro i normali limiti per la specie; ciononostante, sono state osservate in 6 su 8 animali complicazioni gestibili correlate all'anestesia (apnea subito dopo l'iniezione, ipotensione, ipoventilazione, ipossiemia e risveglio prolungato). L'impiego di sistemi di monitoraggio si è rivelato essenziale al fine di garantire un'adeguata gestione delle complicazioni menzionate.

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