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Authors: WILLIAMS, THOMAS D., WILLIAMS, A. LESLEY, and SINIFF, DONALD B.

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FENTANYL AND AZAPERONE PRODUCED NEUROLEPTANALGESIA IN THE SEA OTTER *(Enhydra lutris)*

THOMAS D. WILLIAMS, Monterey Bay Aquarium, 886 Cannery Row, Monterey, California 93940, USA.
A. LESLEY WILLIAMS, Ocean View Veterinary Hospital, 109 Central Avenue, Pacific Grove, California 93950, USA.
DONALD B. SINIFF, Dept. of Ecology and Behavioral Biology, 318 Church Street S.E., Minneapolis, Minnesota 55455, USA.

Abstract: Fentanyl was used to effectively produce neuroleptanalgesia in sea otters *(Enhydra lutris)* under field conditions when given intramuscularly at dosages of .05 to .11 mg/kg of body weight and in combination with azaperone at dosages of .11 to .45 mg/kg. Fentanyl at a dosage of .05 mg/kg, when combined with azaperone at a dosage of .20 mg/kg met most of the requirements for a safe, short acting, intramuscular immobilizing agent. The effects were readily reversible, there were no serious side effects and a wide safety margin.

INTRODUCTION

Chemical immobilization of the sea otter *(Enhydra lutris)* is essential prior to field investigation requiring manipulation. Previous descriptions of fatalities due to use of sodium pentobarbital [1] and ketamine hydrochloride [2] in the sea otter, emphasize the need for an immobilizing agent with a wide safety margin, rapid reversibility and no serious side-effects.[13,14] CI-744 [3] (tiletamine hydrochloride and zolazepam hydrochloride), etorphine [4] and halothane [5] have all been used successfully in the sea otter but each has limitations for field application.[14] Etorphine, at a dose of 0.75 mg per adult otter met most of the requirements for field use, but chronic convulsions and cyanosis were undesirable side effects.[14] Fentanyl [6] has been tested in sea otters using dosages as high as 0.04 mg/kg with no immobilization.[14] Haigh[6] has reported the successful use of fentanyl in hooded seals *(Cystophora cristata)* at dosages of 0.3 to 0.6 mg/kg, enabling tagging and blood sampling in the field.

Members of the Mustelidae are generally considered good subjects for anesthesia. Fentanyl (0.5 ml/kg) has also produced profound neuroleptanalgesia in ferrets *(Mustela putorius furo)* suggesting its further application in the sea otter.[4]

MATERIALS AND METHODS

Twenty-two sea otters were captured in modified gill nets at Prince William Sound, Alaska, and six sea otters were captured with a diver held net at Monterey Bay, California, during the summer and fall of 1979.

[1] Nembutal, Ceva Laboratories, Inc. Overland Park, Kansas 66212, USA.
[2] Ketaset, Bristol Laboratories, Syracuse, New York 13201, USA.
[3] Telazol, Warner Lambert/Parke-Davis, Detroit, Michigan 48233, USA.
[4] M-99, D-M Pharmaceuticals, Inc. Rockville, Maryland 20850, USA.
[5] Halothane, Halocarbon Laboratories, Inc. Hackensack, New Jersey 07601, USA.
[6] Fentanyl, Pitman-Moore Inc. Washington Crossing, New Jersey 08560, USA.

While the otters remained entangled in the net a rear limb was secured and fentanyl or a combination of fentanyl and azaperone [7] were injected intramuscularly (IM). The dosage of fentanyl ranged from .05 to .11 mg/kg (10 mg/ml) body weight, with or without a concurrently administered dose of .11 to .45 mg/kg (40 mg/ml) azaperone. After immobilization, otters captured in Alaska were weighed, removed from the net and measured, rectal temperatures recorded, respiratory rate determined visually and heart rate established by palpation. Radio-telemetry devices were fitted, otters were given an antagonist and released upon recovery. After immobilization, otters captured in California were weighed, measured, rectal temperatures recorded, respiratory rate determined visually, heart rate established by palpation and blood samples drawn. An antagonist was given and after recovery, otters were confined in a holding pen for three to five days, after which they were released. During confinement, otters were fed squid and abalone.

Neuroleptanalgesia was reversed in 22 cases with naloxone [8] at dosages of .01 to .05 mg/kg and in 6 cases with diprenorphine [9] at dosages of .05 to .11 mg/kg.

Twenty-three of the otters were males, 5 were females, body weights ranged from 15.0 to 38.6 kg. All were adults.

Effectiveness of the dosage was judged by the otters' resistance to handling, amount of voluntary movement, response to external stimuli and reflex response.

RESULTS

The results of the immobilization of 28 sea otters are presented in Table 1. In 10 trials with fentanyl, induction occurred from 3.6 min to 9 min, with an average induction time of 5.5 min. Induction time was not dose related. The time of immobilization varied from 24 min to 37 min, with an average of 30 min and was dose related. In 18 trials using fentanyl in combination with azaperone, induction occurred from 2.75 min to 11.25 min, with an average induction time of 7 min. The time of immobilization ranged from 24 to 73 min with an average of 40 min. The antagonist naloxone hydrochloride in dosages from .01 to .05 mg/kg IM. resulted in recovery from .5 min to 10 min, with an average of 4 min, with the exception of trial 24. In trial 24, when an overdose of fentanyl and azaperone was given, recovery time was 56 min. Diprenorphine was the antagonist used in 6 trials in dosages of .052 to .113 mg/kg IM and resulted in recovery times from 1.75 to 7.5 min with an average of 6.3 min.

With extreme values omitted and a 95% confidence interval, the mean respiratory rate was 14.9 to 17 respirations per min, the mean heart rate was 133.4 to 157.2 beats per min and the mean temperature 36.7 C to 37.4 C.

All otters recovered pre-immobilization motor function and behavior.

DISCUSSION

Neuroleptanalgesia is a useful technique in sea otter immobilization. It produces a state of analgesia and sedation without complete unconsciousness, permitting biological sampling and minor surgery without analgesia.[1,12] Fentanyl is a potent narcotic-analgesic, and its actions are typical of morphine-like drugs.[12] It is faster and shorter acting than other analgesics in clinical use and its potency is approximately 100 times that of morphine.[1,5,9] Studies in

[7] Stresnil, Pitman-Moore, Inc. Washington Crossing, New Jersey 08560, USA.

[8] Narcan, Endo Laboratories, Inc. Garden City, New York 11530, USA.

[9] M50-50, D-M Pharmaceuticals, Inc. Rockville, Maryland 20850, USA.

TABLE 1. Results of 28 trials with fentanyl and azaperone.

Otter No.	Sex	Weight (kg)	Fentanyl mg/kg	Azaperone mg/kg	Induction time (min)	Antagonist* mg/kg	Recovery time (min)	Respiration	Heart Rate	Temp C	Comments
1	M	28.6	.07	—	5	.014 N	1.5	10-14	94-108	38.6	
2	M	29.5	.07	—	5	.014 N	.5	12	104-140	37.2	MCC+
3	M	38.6	.05	—	4:30	.010 N	3.25	16	124	37.2	
4	M	30.9	.06	—	5:30	.026 N	2.0	16-20	140-150	38.7	MCC
5	M	25.0	.08	—	4:45	.032 N	3.5	12	104	37.2	
6	M	29.1	.07	—	5:15	.027 N	2.75	16	140	36.1	
7	M	32.2	.06	—	9:00	.025 N	1.33	16	100	36.7	
8	M	32.7	.06	—	7:30	.061 D	3.5	12	106	38.6	
9	M	38.6	.05	—	3:40	.052 D	1.75	20	100	38.6	
10	M	27.7	.07	—	4:40	.029 N	4.17	16	100	37.5	
11	M	36.3	.06	.11	8:00	.022 N	2.8	12-16	136-152	36.1	
12	M	24.1	.08	.33	10:00	.033 N	5.25	16	144-172	37.2	MCC
13	M	27.7	.07	.29	11:15	.029 N	4.5	16	124-168	36.7	MCC
14	M	28.1	.07	.43	7:00	.028 N	10.0	16	168	35.6	MCC
15	M	32.7	.06	.37	6:20	.061 D	4.5	16-20	132-168	35.1	MCC
16	M	23.2	.09	.26	10:00	.034 N	4.0	20	156-172	36.2	MCC
17	M	25.0	.08	.24	6:00	.080 D	7.5	16	172	37.3	MCC
18	M	29.1	.07	.21	7:45	.027 N	2.75	20	164	37.4	
19	M	26.3	.08	.23	2:45	.030 N	10.0	12	144	36.3	MCC
20	M	29.1	.07	.21	3:45	.027 N	4.9	20	184	37.4	
21	M	22.7	.09	.26	7:00	.090 D	7.0	16	116	36.1	
22	M	34.5	.06	.17	6:40	.012 N	4.75	16	172	36.4	
23	M	27.2	.07	.29	8:00	.029 N	5.5	16	176	38.0	MCC
24	F	17.7	.11	.45	6:00	.023 N .113 D	46.0 9.0	34	200	39.3	Overdose
25	F	20.9	.05	.19	5:00	.038 N	3.0	12	192	36.1	
26	F	15.0	.07	.27	7:00	.053 N	4.0	16	156	37.2	
27	F	20.0	.05	.20	7:00	.040 N	4.0	20	136	37.4	
28	F	16.4	.06	.24	6:00	.048 N	2.0	16	184	36.7	

*Naloxone — N, diprenorphine — D +MCC — Mild clonic contractions

canines have shown that fentanyl has a wide margin of safety and tolerance in animals in a poor physical status.[12] The therapeutic index in mice for fentanyl citrate is 775 and for morphine 31.3.[3] Under field conditions, estimation of the weight of the animal for dose calculation is a major problem.[7] The use of an immobilizing agent such as fentanyl with a wide margin of safety is desirable.

Azaperone is used as a neuroleptic with its action potentiated by the immobilizing compound, fentanyl.[8] The safety margin of fentanyl is higher when given in combination with azaperone because the respiratory depressant action by fentanyl is antagonized by the butyrophenones.[8] Azaperone is virtually nontoxic with the safety margin between effect and lethal dose stated to be in excess of 1000.[8,10] Azaperone does not reduce body temperature at low doses and appears to have no adverse effects on heart rate, cardiac output and aortic blood flow and has a beneficial cardiovascular effect by protecting against shock.[5,8,10]

In this study, fentanyl used alone provided rapid induction, adequate immobilization and no serious side effects. Recovery time was short but upon recovery the otters' behavior seemed to indicate anxiety as they dove in the water for long periods of time upon release.

When fentanyl and azaperone were used in combination, induction time was slightly increased but was well within an acceptable range. Otters receiving a dose of azaperone above .20 mg/kg, regardless of the fentanyl dose, frequently showed clonic contractions and had a prolonged recovery time. The great advantage to the addition of azaperone was that induction and recovery were smooth and otters exhibited less anxiety than when fentanyl was used alone. At the highest dose studied, (.11 mg/kg fentanyl and .45 mg/kg azaperone) respiration rate was significantly increased, heart rate was higher than average and body temperature was elevated. Recovery time was prolonged and an additional dose of antagonist was given. It is possible that the depression was due to the effects of the azaperone, which is not reversed by the antagonist. After recovery this otter appeared normal.

The results of this study indicate that a dosage of .05 mg/kg of fentanyl combined with a dosage of .10 to .20 mg/kg of azaperone provides safe, uncomplicated, easily reversible immobilization in sea otters. A distinct advantage to this drug combination is that the dose can be administered intramuscularly while the otters remain in the water. After injection the otter floats safely on its back with its head out of the water until immobilization occurs. After immobilization, the animal can be handled with no danger to investigators.

Naloxone and diprenorphine, both narcotic antagonists, readily reverse the narcosis produced by fentanyl. The dosage of naloxone used was calculated on the basis that 1 mg was sufficient to antagonize 10 mg of fentanyl.[11] It is known that doubling the dose of naloxone increases the protective effect, therefore suggesting a dosage of at least .01 mg/kg.[2]

Thermoregulation in an immobilized otter can become unbalanced, therefore any immobilized sea otter must have its temperature closely monitored. When temperature is above 38.3 C, it should be reduced with cold water.

All Alaskan otters were followed by radio contact for three weeks after release. California otters were marked with plastic tags which were visually sighted for three weeks. With the exception of numbers 7 and 26, all otters appeared normal. Otters 7 and 26 died in 21 and 14 days, respectively, after handling. Necropsy of otter 7 revealed interstitial emphysema that had been present for 1 to 2 weeks, pulmonary congestion, and severe seminiferous tubular

atrophy and aspermatogenesis. No necropsy was performed on otter 24 because of advanced state of decomposition. Cause of death in both animals was undetermined. It is recognized, however, that the stress of capture and handling can lead to death in sea otters, especially if they are debilitated.

Subsequent to the study reported here, the California Department of Fish and Game have successfully immobilized 24 sea otters and researchers from the University of Minnesota working in Alaska immobilized 35 sea otters with the recommended fentanyl and azaperone combination.

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