Aquatic Mammals 1986, **12.3,** 87–91

Haematological changes in two *Lagenorhynchus obscurus* treated with Ketoconazole

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Summary

Two Cape dusky dolphins, *Lagenorhynchus obscurus* (Gray, 1828), (one male and one female) residing in the same holding pool and both showing signs of candidiasis, were treated with Ketoconazole. This resulted in clinical improvement of both animals and an improved blood picture in the male. However, full blood counts from the female revealed severe pancytopenia on day 37 of treatment. On withdrawal of the drug and after a period of supportive therapy, the haemoglobin level, platelet count and white cell counts (WCC) normalized. As there was no definite relationship between drug therapy and the blood dyscrasia, it was decided to again treat the female with Ketoconazole on recurrence of severe candidiasis. The drug was administered at a much lower dosage (2.6 mg/kg/day) and the blood picture was monitored regularly. There was improvement in the clinical symptoms and an elevation of the peripheral blood leucocyte count. The dose of Ketonocazole was increased to 5.2 mg/kg/day, but within 7 days, at this higher dosage, blood results revealed neutropenia and mild thrombocytopenia. Administration of the drug was immediately discontinued. Recovery of the peripheral blood parameters occurred over the following three months.

Ketoconazole has not been known to cause severe pancytopenia in humans and other species. The authors stress the importance of regular haematological monitoring of cetaceans on long term Ketoconazole therapy. The effect appears to be idiosyncratic rather than dose-related and early recovery occurs if the drug is discontinued before severe cytopenias develop.

Introduction

Blood dyscrasias in cetaceans, following administration of antibiotics, have been reported. Cornell (1978) described five cases of agranulocytic leukopenia in cetaceans treated with sulpha drugs. McBain (1984) described three killer whales which exhibited neutropenia, monocytopenia and thrombocytopenia following prophylactic treatment with Sulphamethoxazole-Trimethoprim drug combination. One whale died, due to internal haemorrhage and the remaining two recovered. In our own experience, as yet unreported, we also had similar problems when three dolphins were treated prophylactically with Sulphamethoxazole-Trimethoprim. One dolphin died of aplastic anaemia, while the bone marrow function of the remaining animals normalized in due course. In another instance a dolphin was treated with a combination of Furazolidene and Sulphonamide. This resulted in a neutrophenia and thrombocytopenia, which proved reversible on withdrawal of the drug. This paper describes haematological changes in two dolphins treated with Ketoconazole. The first, a male *Lagenorhynchus obscurus* was neutropenic at initiation of therapy. His WCC increased on therapy. The second dolphin, a female Cape dusky dolphin had normal haematological parameters prior to therapy on two occasions. There were alterations in haematological parameters on both occasions while on therapy.

Case reports

Case 1—*Lagenorhynchus obscurus* male

This dolphin has resided at the Durban dolphinarium since June 1976 and has worked regularly in shows. During the two hottest months of each year, when pool water temperatures are high, he displayed lethargic and erratic behaviour and a bad colour was present in his mouth. Since July 1976, fungi and yeasts, including *Candida albicans* were regularly cultured on his cough agar plates. Blood counts in the summer of 1983 and 1984 revealed low leucocyte counts of around 3.0×10^9/l. In February 1984 *C. albicans* and *C. tropicalis* were isolated from the dolphin's anus, stomach fluid and blowhole. The dolphin's tongue at this time had a white coating, resembling human oral thrush and dorsally the dolphin's black skin had become interspersed with white patches. On 9 February 1984 a blood count revealed a WCC of 2.1×10^9/l. On the same day oral administration of Ketoconazole was initiated.

Treatment was continued for 77 days, commencing with a daily dosage of 5.5 mg/kg Ketoconazole. On day 6 the daily dosage was increased to 8.2 mg/kg; on day 43 to 11 mg/kg on day 71 it was reduced to 2.8 mg/kg/day.

After nine days of therapy the white coating on the dolphin's tongue was absent, leaving the tongue pink, interspersed with red patches. The red patches appeared to be ulcerated regions, probably now prominent due to the eradication of *C. albicans*. Another interesting change noted was that after approximately two weeks of Ketoconazole therapy normal faeces were regularly observed from the dolphin. Prior to treatment faeces were observed only in the mornings before the first feed. These were always stringy and contained mucus. Cultures from stomach fluid, mouth, blowhole and anus taken on 25/4/84 and 9/5/84 were negative for *Candida* spp. The white blotches on the dolphin's skin disappeared and blood tests taken on day 16 and periodically thereafter, revealed an improved white cell count persistently over 4.0×10^9/l.

Case 2—*Lagenorhynchus obscurus* female.

This dolphin has resided in the Durban dolphinarium since 30 March 1981. She adapted well to captivity and maintained good health until 24/12/82, when she contracted erysipelas. She was treated with penicillin and experienced no further health problems until January/February 1984. She became lethargic and a bad odour was present in her mouth. Grey mucoid faeces were present in the mornings daily before her first feed, but no further defaecation was seen for the remainder of the day. A greyish ulcerating lesion, approximately 7 cm long × 1 cm wide by 1 cm deep, formed just anterior to her dorsal fin, as well as an irregular dark hot patch dorsal to the right pectoral flipper and small white patches interspersed the animal's black dorsal surface. On 30/8/83 and 4/1/84, *C. albicans* was isolated from the blowhole by means of cough plates. on 13/2/84 *C. albicans* and *C. tropicalis* were cultured from a stomach fluid sample.

On 20/2/84 treatment with Ketoconazole was initiated at a daily dosage of 7.7 mg/kg and was continued for 36 days. After approximately two weeks, the skin lesions had completely healed and faeces of normal appearance were observed regularly throughout the day. During the second week, the dolphin was no longer continually lethargic and became very active for extended periods.

On 5/3/84, *Candida parapsilosis* was cultured from a faecal swab and Ketoconazole therapy was continued. From day 12 to day 26 the dolphin consumed her normal food intake, but often displayed difficulty in swallowing. Cultures taken on day 32 from the blowhole, genital area, mouth and anus were negative for *Candida*. However, haematological results from samples taken on day 37 revealed a neutropenia, thrombocytopenia and mild anaemia. Administration of Ketoconazole was discontinued and serial blood samples were taken (Table 1).

In view of the severe pancytopenia associated with a low reticulocyte count, a diagnosis of aplastic anaemia was considered. A bone marrow biopsy was not done as the procedure can be hazardous in cetaceans, especially in the presence of serious neutropenia and thrombocytopenia. In view of the very low absolute neutrophil count of 0.35×10^9/l, a Cephalosporin (Ceporex) was prophylactically administered orally for 18 days at a dosage of 1.5 g eight hourly. On 1/4/84 therapy with Lithium Carbonate (dose 800 mg p.o./day) and Oxymethalone (dose 150 mg p.o./day) was initiated and continued for 18 days. Lithium Carbonate has been shown to increase granulocyte production and has been used in humans with aplastic anaemia with variable response (Levitt 1980; Barret 1977). Androgens may stimulate erythropoiesis (Allen 1968).

Supportive therapy was discontinued on 18/4/84 and at this time the dolphin was still anaemic (Hgb = 14.8 g/d l). The absolute neutrophil count had increased to 0.612×10^9/l and the reticulocyte counts had increased from 0.4% on day 39 to 2.4% on day 54. The platelet count had also returned to normal (221×10^9/l).

Blowhole, stomach fluid and faecal samples cultured periodically during the months from April to November 1984, showed heavy growth of *C. albicans* and *C. kruseii*. During this period the dolphin performed in shows regularly and consumed her normal food intake. However, in December 1984, she developed similar symptoms and signs as previously. The skin lesions on this occasion were limited to white patches on the black dorsal surface. It was decided to administer Ketoconazole again, at a much lower daily dosage and to regularly monitor the blood picture. The Ketoconazole was administered for 16 days at a dosage of 2.6 mg/kg/day (27/11/84–12/12/84) The WCC (Table 1) increased from 3.4×10^9/l to 4.2×10^9/. On 13/12/84 the dosage was changed to 5.2 mg/kg/day. On 19/12/84 a blood sample revealed severe leucopenia with WCC of 1.4×10^9/l of which 20% were neutrophils. There was also a mild decrease in the platelet count to 138×10^9/l. Administration of Ketoconazole was stopped immediately and it was decided not to commence with the supportive therapy previously used. The platelet count soon normalized (Table 2). Subsequent blood tests revealed improved white cell counts but which were still below the mean WCC of 5.6×10^9/l recorded during her first year of captivity.

Discussion

Candida species often cause problems in captive cetaceans (Greenwood & Taylor 1978). Ketoconazole is widely used in dolphinaria to combat fungal

Table 1: Haematological parameters in the female *Lagenorhynchus obscurus* during and following the first course of treatment with Ketoconazole

Date 1984	13/2	5/3	27/3	29/3	30/3	3/4	4/4	9/4	13/4	18/4	24/4	9/5	4/6	7/8	24/9	30/10
Days	7 prior treatment	15	37	39	40	44	45	50	54	59	65	80	106	170	219	254
WCC ($x10^9$/l)	4.2	3.8	1.7	2.7	2.4	2.6	3.1	2.7	3.2	3.4	4.1	3.4	3.3	4.6	5.4	5.1
Neutrophils (%)	32	51	14	13	4	9	6	4	4	18	29	22	29	39	35	34
Neutrophils (Total)	1344	1938	238	351	96	234	186	108	128	612	1189	748	957	1794	1890	1734
Lymphocytes (%)	51	33	83	81	92	90	93	94	93	76	64	62	58	47	53	42
Monocytes (%)	7	7	2	3	3	1	1	2	3	6	3	8	4	1	2	11
Eosinophils (%)	10	8	1	—	—	—	—	—	—	—	3	8	8	10	10	10
Basophils (%)	—	1	—	—	—	—	—	—	—	—	1	—	1	3	—	3
Platelets ($\times 10^9$/l)	250	252	72	52	40	45	49	86	101	221	350	311	202	180	206	229
RBC ($\times 10^9$/l)	6.03	6.01	5.46	5.40	5.34	5.30	5.12	4.76	4.78	4.64	4.55	5.05	5.56	6.14	6.31	6.20
Hgb (g/dl)	19.3	19.5	17.6	17.5	16.6	17.0	16.3	16.0	15.2	14.8	14.8	17.0	19.3	20.3	20.6	19.9
Hct (l/l)	0.539	0.569	0.505	0.504	0.497	0.491	0.478	0.440	0.443	0.427	0.430	0.492	0.543	0.601	0.584	0.569
Reticulocytes (%)				0.4	0.4	0.4		1.8	2.4	1.8						
Ketoconazole therapy	20/2 to 27/3															

Table 2. Haematological parameters in the female *Lagenorhynchus obscurus* during and following the second course of treatment with Ketoconazole

	1984								1985					
Date	27/11	30/11	4/12	7/12	14/12	19/12	21/12	24/12	10/1	30/1	5/3	28/3	6/5	5/11
Days	1	4	8	11	18	23	25	28	45	65	100	123	162	—
WCC ($\times 10^9$/l)	3.4	3.0	3.9	4.2	4.4	1.4	3.4	3.1	2.9	2.7	3.5	4.0	3.5	3.8
Neutrophils (%)	31	60	48	34	41	20	20	27	17	31	21	24	32	45
Neutrophils (Total)	1054	1800	1872	1428	1804	280	680	837	493	837	735	960	1120	—
Lymphoycytes (%)	51	31	44	58	54	71	66	68	78	59	64	55	54	37
Monocytes (%)	9	1	1	3	1	2	5	3	1	6	6	9	2	6
Eosinophils (%)	8	6	6	5	4	7	9	2	6	3	6	11	10	9
Basophils (%)	—	2	1	—	—	—	—	—	1	1	—	—	2	3
Platelets ($\times 10^9$/l)	216	198	201	216	219	138	133	132	239	215	221	177	305	247
RBC ($\times 10^9$/l)	5.83	6.03	6.06	5.95	5.80	6.38	5.71	5.65	5.48	5.73	5.80	5.41	5.66	5.50
Hgb (g/dl)	19.1	19.6	19.9	19.3	19.1	20.5	18.8	18.9	18.0	19.2	19.4	18.5	19.5	18.8
Hct (l/l))	56.1	58.3	58.3	57.3	55.2	60.7	54.1	53.9	52.5	54.2	55.2	52.8	56.6	52.2
Ketoconazole therapy	Commence 27/11 2.6 mg/kg/day		Increase 13/2 5.2 mg/kg/day		Stopped 19/12									

infections. We feel that use of this drug was indicated for its effect against fungal cutaneous lesions and for candidiasis of the mouth and oesophagus. Response to therapy was remarkable in both dolphins.

To the best of our knowledge Ketoconazole has not, so far, been implicated in haematological disorders in cetaceans. In a survey of 1361 human patients treated with Ketoconazole, thrombocytopenia was reported in 0.1% and leucopenia in 0.1% of subjects. These patients were receiving other drugs concomitantly. Therefore a causal relationship with Ketoconazole therapy was not established (Levine 1982).

Case 1 illustrates that some cetaceans can receive large doses of Ketoconazole with no significant toxic effects. This dolphin received up to 11 mg/kg/day. In fact the peripheral WCC actually rose from 3.0×10^9/l to 6.3×10^9/l.

Case 2, the female dolphin, required treatment with Ketoconazole on two occasions. During the first course of treatment she developed severe pancytopenia requiring intensive antibiotic therapy, Lithium Carbonate and androgens. Ketoconazole therapy was begun on the second occasion at a low dose of 2.6 mg/kg/day. There was clinical improvement as well as an increase in the WCC. Within 7 days of increasing the dose to 5.2 mg/kg/day she developed neutropenia and mild thrombocytopenia. Recovery occurred spontaneously on discontinuation of the drug.

The authors conclude that some cetaceans exhibit sensitivity to the drug. This sensitivity may become apparent at higher dosages. As clinical improvement occurred with the use of Ketoconazole at a lower dosage, it is recommended that this dosage be used initially in cetaceans requiring therapy. Drug dosage should be increased gradually if clinically indicated. In such cases, or with prolonged Ketoconazole therapy, we wish to stress the importance of monitoring blood counts regularly.

Acknowledgements

The authors wish to express their gratitude to the staff of the Haematology Laboratory of Addington Hospital for their invaluable assistance; the Director, Prof. A. P. Bowmaker, and staff of SAAMBR for their advice and encouragement; Carolyn Jerman, Dr Graham Thurman and Judith Thompson for editing the manuscript and Lorna Cameron for processing it.

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