VITAMIN B6 (PYRIDOXINE HYDROCHLORIDE) TOXICOSIS IN FALCONS

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Abstract: This manuscript reports three independent accidental cases of Vit B6 toxicosis in gyrfalcons (Falco rusticolus) and peregrine falcons (Falco peregrinus) and a toxicology study that was conducted to characterize the clinical responses of gyrfalcons and gyrfalcon x peregrine falcons to a range of single intramuscular (IM) and oral (PO) doses of Vit B6. Both lethal and not lethal doses were determined. Twelve female gyrfalcons died following IM injection of 1 ml of a vitamin B preparation. Within 30 minutes (min) of injection, the birds passed pistachio-green colored urates, and progressed to vomiting, anorexia, cessation of normal activity, ptosis, collapse and death, occurring 24 to 36 hours post injections. Three individuals vomited frothy, partially digested blood and had clonic spasms and convulsions. Post-mortem and histopathology revealed multifocal severe hepatic necrosis, splenic lymphoid tissue depletion and hemorrhages with arterial necrosis, and acute renal tubular necrosis. Following administration of a different, oral, mineral/vitamin supplement, a total of 21 peregrine falcons (Falco peregrinus) in two separate European facilities died suddenly. Histology of the liver showed diffuse congestion, and multifocal coagulative necrosis with mild infiltration of heterophils. The particular nutritional supplement used by both breeders was analysed and found to contain 5% - 9.7% Vitamin (Vit) B6. Other randomly selected lots of the product contained 0.007% to 0.27% Vit B6. According to the product label, Vit B6 should have been present at 0.004%. To confirm the hypothesis that Vit B6 was responsible for the deaths of the falcons in Abu Dhabi, Vit B6 (British Pharmacopoeia [BP] grade) in powder form was diluted in water for injection and administered IM to four groups of falcons. Groups of four gyrfalcon x peregrine hybrid falcons and/or gyrfalcons were given a single IM dose of 5, 10, 15, or 20 mg/kg of Vit B6, or received an oral dose of 25, 50, or 75 mg of Vit B6. Only birds in the lowest-dose groups survived. The maximum non-lethal single doses of Vit B6 in falcons were 5 mg/kg IM and 25 mg/kg PO.
Key words: Vitamin B6, pyridoxine, toxicosis, gyrfalcon (*Falco rusticolus*), peregrine falcon (*Falco peregrinus*), hybrid falcon.
INTRODUCTION

Vitamin (Vit) B6 (pyridoxine) is a water soluble compound and part of the Vit B complex consisting of Vit B1 (thiamine), Vit B2 (riboflavin), Vit B3 (niacin), Vit B5 (pantothenic acid), Vit B7 (biotin), Vit B9 (folic acid) and Vit B12 (various cobalamin complexes). Vitamin B6 comprises three related pyrimidine vitamers consisting of pyridoxine, pyridoxal and pyridoxamine and their phosphate esters. These compounds are absorbed from the diet and rapidly appear in the liver where they are converted into pyridoxal 5’-phosphate.

The metabolically active form of Vit B6 is pyridoxal 5’-phosphate, a cofactor in many essential enzymes in both birds and in mammals. Pyridoxine is the predominant form of Vit B6 found in foodstuffs derived from plants, and pyridoxine hydrochloride is the form used in vitamin supplements for livestock diets. Vit B6 is required in almost 240 biochemical reactions. Most are related to amino acid biosynthesis and degradation, including gluconeogenesis (the creation of glucose from amino acids). Other B6-dependent reactions are involved in glycogen and fatty acid metabolism. In the domestic fowl (Gallus gallus), Vit B6 is absorbed in the small intestine, mainly from the duodenum, moderately from the jejunum and least from the ileum. According to the European Food Safety Authority (EFSA), pyridoxine hydrochloride is considered to be safe for all animal species at levels used in commercial feed formulations.

Daily requirements appear to be relatively uniform across taxa. The US National Research Council (NRC) has determined that the requirement in dogs for Vit B6 is 1.1 mg/kg diet, the recommended daily intake for humans is approximately 3.0 mg/kg diet, and the Vit B6
requirement in the domestic chicken and the domestic turkey (*Meleagris gallopavo*) ranges from 2.5 to 4.5 mg/kg of diet. In addition to modest variation between species, factors that influence Vit B6 demands include breed differences, environmental temperature, and dietary protein. No information is available on the requirement for Vit B6 in non-domestic species.

In humans, excess dietary Vit B6 supplementation may result in ataxia and sensory neuropathy or motor and sensory neuropathy with demyelination of nervous tissue. There have been at least three reports that high therapeutic doses of pyridoxal 5’-phosphate can cause hepatotoxicity in children. High doses of pyridoxine are known to cause secondary (hepatogenous) photosensitization. A recent report described severe gastrointestinal disorders and light-induced change in skin color in an adult patient following supplementation of 300 mg of Vit B6 daily for over six months.

In experiments with laboratory animals (mammals), pyridoxine toxicity is characterized by necrosis of the dorsal root ganglion (DRG) sensory neurons and degeneration of peripheral and central sensory projections. Large diameter neurons are particularly affected. Morphological and physiological changes in the DRG and the distal myelinated axons of the sciatic nerve in rats following pyridoxine intoxication have been described. In another study, neuropathy was induced in dogs following subcutaneous administration of pyridoxine. The basis for the neurotoxicity of pyridoxine and the reason for its predilection for the DRG are not known. Pyridoxine is rapidly phosphorylated in the liver to pyridoxal 5’-phosphate. It has been postulated that toxicity may be caused by exceeding the ability of the liver to phosphorylate pyridoxine into pyridoxal 5’-phosphate. The high pyridoxine levels in blood could be directly
neurotoxic, or it may compete for binding of pyridoxal 5'-phosphate to cause relative deficiency of the active metabolite.\(^{27}\) The occurrence of neuropathy after prolonged low-dose pyridoxine therapy, as observed in various human studies, suggests direct neurotoxicity rather than competitive inhibition.\(^{8,22}\) The causative agent(s) in the human hepatotoxicity cases is unknown.\(^{30}\)

The tolerable upper intake level of Vit B6 for dogs as suggested by the NRC is approximately 7 mg/kg body weight per day.\(^{19}\) The tolerable upper intake level for humans of Vit B6 established by the EFSA is less than 0.5 mg/kg body weight, possibly reflecting taxonomic differences in sensitivity to high levels of this vitamin.\(^{6}\) No tolerable upper intake has been published for poultry.

Vit B6 is commonly administered to non-domestic avian species in the form of Vit B complex. Either oral or parenteral preparations are often given as supportive therapy in general clinical practice or in rehabilitating sick or injured individuals. Vit B6 is also included in vitamin and mineral preparations widely used in avian medicine for breeding and growing birds, and for raptors undergoing intensive falconry training regimes.

To the knowledge of the authors, there is only one report in the literature of Vit B6 toxicity in avian species resulting from the use of a vitamin supplement.\(^{23}\) In that report, acute toxicity was observed in domestic pigeons (\textit{Columba livia}) following the administration of one tablet PO per pigeon of a human Vit B complex preparation (Befact\textsuperscript{®}, Laboratoires SMB, Brussels, Belgium) containing Vit B1 100 mg, Vit B6 150 mg and Vit B12 15 \(\mu\)g in each tablet. The authors concluded that Vit B6 was responsible for the deaths, after each of the vitamins, or the
combination of the three vitamins, in a range of doses, was administered PO to different groups of pigeons. The lethal dose of B6 was estimated to be 90 to 100 mg PO per pigeon or 200 mg/kg PO. The authors also stated (without showing data) that chickens were unaffected by the dose that was lethal to pigeons.

This paper reports three independent accidental cases of Vit B6 toxicity in gyrfalcons (*Falco rusticolus*) and peregrine falcons (*Falco peregrinus*). Toxicity followed the administration of two preparations: an IM Vit B supplement given to a group of gyrfalcons in the Middle East, and an oral vitamin/mineral product given to groups of peregrine falcons in two European countries. A toxicology study was performed to characterize the clinical responses of gyrfalcon x peregrine hybrid falcons and gyrfalcons to a range of single IM and PO doses of Vit B6; both lethal and non-lethal doses were determined.

**CLINICAL CASES**

**Case No 1**

A group of 12 female gyrfalcons (*Falco rusticolus*), 5 to 6 months old, died unexpectedly in November 2011 following the IM injection of 1 ml of a vitamin B complex preparation (B Complex injection, Troy, Australia) containing 20 mg thiamine (B1), 5 mg riboflavin-6 phosphate (B2), 200 µg hydroxocobalamin (B12), 60 mg nicotinamide (B3), 17 mg d-panthenol (B5) and 20 mg pyridoxine hydrochloride (B6) per 1 ml suspended in water for injection. The incident occurred in Abu Dhabi, United Arab Emirates. The rationale behind the administration of such a large volume of the Vit B complex preparation was to provide approximately 20 mg/kg
of Vit B1 to each falcon. This was in accord with the dose of Vit B complex widely recommended in the avian medicine literature.\textsuperscript{1,2,10,12} The falcons were all clinically normal and in optimum physical condition after undergoing a six week falconry training program. The mean body weight of the falcons was 1300 g. After injection, clinical signs became evident within 30 minutes, starting with the passing of pistachio-green colored urates, regurgitation and vomiting. Symptoms progressed over the next 24 to 36 hours, with decreased and then complete lack of appetite, reduced and then total absence of preening and interactivity, ptosis, collapse and death. Three individuals exhibited vomiting of frothy, partially digested blood, clonic spasms and convulsions prior to death. Gross post-mortem findings were suggestive of an inflammatory process in the liver, spleen and kidneys. Formalin-fixed tissues were submitted to the Central Veterinary Research Laboratory (CVRL) in Dubai, United Arab Emirates and the Diagnostic Pathology Laboratory NOIVBD, in The Netherlands. Swab samples collected from the liver and small intestine of the three individuals showing CNS signs were submitted to the CVRL and an in-house laboratory for microbiological analysis.

Histopathology findings revealed acute changes including widespread hemorrhages in the liver with vacuolization and lytic necrosis of hepatocytes characterized by loss of nuclei, degeneration and necrosis of individual cells; the spleen was hemorrhagic, completely depleted of lymphoid tissue, and necrosis of the arteries was present. Samples from the nervous system were not available for examination.

Anaerobic cultures (on Zeissler agar containing antibiotic supplements, Oxoid, SR93) from intestinal content swabs from the three individuals displaying CNS signs revealed mild to
moderate growth of *Clostridium perfringens*. To detect clostridial toxins an ELISA (Enterotoxaemia ELISA, Cypress Diagnostics, Belgium) was performed using culture supernatants derived after sub-cultivation of suspicious colonies from Zeissler agar with further incubation under anaerobic conditions for 4 hours in Trypticase Glucose Yeast Extract broth (Merck Cat. No. 1.05459). The Cypress ELISA detects alpha (α), beta (β) and epsilon (ε) toxins of *Clostridium perfringens* as well as identifies the bacteria itself. *C. perfringens* type A was identified from all three individuals displaying CNS signs. The Cypress ELISA detects alpha (α), beta (β) and epsilon (ε) toxins of *C. perfringes* as well as identifies the bacteria itself. Only the alpha toxin was detected by ELISA.

Samples were also collected for bacteriological and mycological culture from the bottle of the B-vitamin solution used for injection. Standard microbiology culturing techniques were followed using Blood agar and MacConkey agar plates for bacteriology investigations and Sabouraud’s agar plates for mycology investigations. No growth was observed. Complete toxicological analysis of the content of this bottle was not considered necessary as several other falcons and other avian and mammalian species had been administered lower doses from the same bottle, without subsequent abnormal clinical signs.

**Rationale**

The content of B vitamins in the solution was largely similar to those available in injectable multivitamin preparations widely used in the Middle East. For instance, in one of the most commonly used products (Multivitamin Injection, Norbrook, UK) the content of Vit B1 is 10 mg, Vit B2 is 5 mg, Vit B6 is 3 mg, Vit B12 is 25 µg, Vit B3 is 35 mg and Vit B5 is 25 mg per l.
ml. Vitamins B1 and B12 are available individually in veterinary formulations, and are widely used in supportive therapy strategies in falcon medicine across the Middle East, at much higher doses. Vit B1 from 25 mg up to 50 mg/kg IM, and Vit B12 from 50 µg up to 100 µg/kg IM/kg, are routinely used by the first author and a number of other clinicians working in falcon medicine, without any evident deleterious effect. It was therefore assumed that the levels of Vit B1 and Vit B12 in the preparation could not have caused the deaths of the falcons. Vitamins B2, B3, B5 and B6 are not available individually in veterinary formulations, but they are all integral to multivitamin preparations commonly used in falcon medicine. With the exception of Vit B6, these have been used extensively at similar or slightly higher dose rates. To the knowledge of the authors there are also no reports in the avian medicine literature of toxicity of vitamins B1, B2, B3, B5 or B12 at these doses.

However, Vit B6 was over 6 times higher in the B-complex solution putatively responsible for the death of the 12 falcons than in other routinely used products. Suspicion therefore focused on Vit B6 toxicosis. This theory was reinforced after the authors became aware of a similar case of acute toxicity in domestic pigeons (*Columba livia*).²³

**Case No 2**

In late March 2014, 15 out of a group of 30 peregrine falcons (*Falco peregrinus*) in a private captive breeding facility in The Netherlands died suddenly. The birds were housed as breeding pairs in breeding chambers, in a large shed, along both sides of a corridor. In the same building, approximately 50 birds of other raptor species were also housed, also as breeding pairs. Prior to their deaths, the falcons did not show any clinical symptoms and many of the pairs were sitting
on eggs. The falcons were fed quails (*Coturnix japonica*), day-old chicks and goose breast meat, and, newly, an oral multivitamin/multimineral dietary supplement. Mortality occurred in various ages and both sexes.

Preliminary post-mortem revealed a moderately enlarged, diffusely dark red liver with scattered 10 to 20 pinpoint tan foci suggestive of multifocal acute necrotizing hepatitis and a herpesvirus infection was suspected. Formalin-fixed liver tissues from 2 cases were sent to a pathology laboratory in the Netherlands (Diagnostic Pathology Laboratory NOIVBD, Veldhoven, The Netherlands) for histopathological examination. The liver samples had diffuse-congestion and multifocal coagulative necrosis of individual or small groups of hepatocytes randomly distributed throughout all lobules in the absence of significant inflammation. Portal areas appeared morphologically normal. Samples for polymerase chain reaction (PCR) analyses were sent to a specialist pathology laboratory (Division of Poultry, Exotic and Laboratory Animals, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium). Analysis of the liver using pan-herpes and other virus primers was negative. In addition, analysis of the liver for *Chlamydia psittaci* was also negative.

**Case No 3**

At approximately the same time, 6 peregrine falcons out of 16 birds died at a breeding facility in Denmark. Death in all cases was sudden, without any clinical signs observed. Gross post-mortem findings were similar to those from carcasses of Case No 2. The histological findings included multifocal hepatic necrosis involving all liver lobes. No viral inclusion bodies or
bacteria were seen. Bacteriology, virology or PCR analyses for *Chlamydia psittaci* were not performed. This breeder was using the same nutritional supplement as in Case No 2.

225 Rationale

After excluding a common infectious agent as cause of the sudden mortality in cases No 2 and No 3, suspicion focused on possible toxicity of the common vitamin/mineral preparation used by the two breeders. The nutritional supplement originated from the same lot, and the deaths occurred immediately after it was first administered. Both breeders immediately stopped all supplementation, and deaths ceased. Samples of the nutritional supplement were analysed (below).

Analyses of the vitamin/mineral preparation involved in Cases No 2 and No 3

Analyses of the nutritional supplement used by both breeders were carried out on samples from 1 kg and 10 kg containers at an independent laboratory in The Netherlands (Masterlab Nutreco, Boxmeer, The Netherlands). Preliminary toxicology screening, using gas chromatography–mass spectrometry (GC-MS), included analyses of trace elements in case there was a production error, and of heavy metals to rule out the possibility of raw materials contamination. The supplement was found to contain 176 ppm copper, 803 ppm manganese, 845 ppm zinc, 2.9 ppm selenium, 0.1 ppm arsenic, 0.17 ppm cadmium, 0.23 ppm lead, and <0.01 ppm mercury. These levels were within acceptable limits. Next, vitamin levels were addressed. Measuring vitamins is expensive and tedious, and therefore it was decided to narrow the scope of the analyses and test for Vit B6 only, based on previous reports of Vit B6 toxicosis in pigeons, and suspicion regarding the falcons involved in case No 1.
The nutritional supplement from the lot used by the breeders was found to comprise approximately 5% to 5.2% Vit B6; the highest level was 9.7%. Other randomly selected lots and containers of the same brand of supplement contained 0.007 to 0.27% Vit B6 in 1 kg containers, and 0.008% to 0.0218% Vit B6 in 10 kg containers. According to the supplement’s product label, added Vit B6 (as Pyridoxine HCl 99%, Impextraco, Heist-op-den-Berg, Belgium) should have been only 0.004%. The actual levels in the lot that caused fatal toxicosis were thus more than 1000-fold higher than that specified on the label.

MATERIALS AND METHODS

To confirm the hypothesis that Vit B6 was responsible for the deaths of the falcons in Abu Dhabi, Vit B6 (British Pharmacopoeia [BP] grade) in powder form was diluted in water for injection and administered IM to four groups of falcons. Group No 1 was composed of four male juvenile gyrfalcon x peregrine hybrid (Falco rusticolus x Falco peregrinus) falcons with a mean body weight of 774g. Each bird received 20 mg/kg IM. Group No 2 was composed of four male juvenile gyrfalcon x peregrine hybrid falcons with a mean body weight of 752.5g. Each bird received 15 mg/kg IM. Group No 3 was composed of four female gyrfalcons with a mean body weight of 1036g. Each bird received 10 mg/kg IM. Group No 4 was composed of four female gyr falcons with a mean body weight of 1256g. Each bird received 5 mg/kg IM. Three additional groups were created to assess the effect of Vit B6 administered orally. Group 5 was composed of four male gyrfalcon x peregrine hybrids with a mean body weight of 687.5g. Each bird received 75mg/kg PO. Group No 6 was composed of four female gyrfalcons with a mean body weight of 1133g. Each bird received 50 mg/kg PO. Group No 7 was composed of four female gyr falcons with a mean body weight of 1270g. Each bird received 25 mg/kg PO. Bacteriology swabs from
the liver and small intestine from all deceased falcons were sent to the CVRL for standard aerobic and anaerobic microbiology cultures. ELISA testing was carried to detect clostridial toxins as described previously for Clinical Case No 1.

RESULTS

All falcons in group Nos 1, 2, and 3 which were administered Vit B6 IM, and groups Nos 5 and 6 which were administered Vit B6 PO, died within 24 hours (Table 1). Gross post-mortem findings included moderate to severe congestion of the lungs, enlarged pale liver and acute catarrhal to hemorrhagic enteritis. The most relevant histopathology findings included marked congestion and perivascular hemorrhages of the lungs, individual liver cell degeneration and necrosis with hemorrhages. Histology confirmed acute catarrhal to hemorrhagic enteritis with necrosis of the villi tips. The histopathological findings in these five groups of falcons were similar to those observed in the group of 12 falcons that died previously (Case No 1) and are consistent with severe and acute toxic changes. All falcons in groups No 4 and No 7 did not show any clinical signs and were alive and well two years after the completion of this study (Table 1).

_Clostridium perfringens_ A was isolated from liver and intestinal content from most individuals examined at post-mortem. The isolates were Alpha toxin producers as shown by ELISA testing. As in the previous clinical cases, the presence of _C. perfringens_ was considered secondary to the primary cause of death, but may have accelerated the disease outcome.
DISCUSSION

To the knowledge of the authors these are the first documented cases of Vit B6 toxicosis in gyrfalcons, gyrfalcon x peregrine hybrid falcons and peregrine falcons after the administration of high doses of Vit B6 given by the IM and PO routes.

The 12 gyrfalcons that died in Case 1 received 15 mg/kg vit B6 IM, a dose that was uniformly lethal in the toxicology study presented here (Table 1). In Cases 2 and 3, the supplement powder should have contained 0.004% pyridoxine per the manufacturer, but instead was measured to contain 5% - 9.7% pyridoxine. If the peregrine falcons in those two cases were fed the amount of powder recommended on the label (1 gram per 100 grams food), they should have received approximately 0.035 mg Vit B6/kg body weight per day. Instead, in a single dose, they received ~40 mg/kg of Vit B6 PO at a minimum, and possibly up to twice that amount. As shown in the toxicology trial (Table 1), one dose of 50 mg/kg PO is uniformly lethal.

In the Middle East the PO administration of human Vit B complex preparations in falcons is widespread. Such products are given mainly to newly arrived falcons into the country, reputedly to help the birds recover from the stresses of transport and to adapt to the new environment; or during the training season to improve hunting performance. The most commonly used product is a human Vit B-complex tablet supplement (Neurobion®, Merck, Frankfurter Str. 250 D-64293, Darmstadt, Germany), a therapeutic formulation taken by mouth for peripheral nerve disorders or Vit B-complex deficiencies. Each tablet contains Vit B1 100 mg, Vit B6 200 mg and Vit B12 200 µg. If falcons are dosed PO at the standard 20 mg/kg of Vit B1 with this supplement, they
receive 40 mg/kg of Vit B6, an amount between 25 mg/kg which is non-lethal, and 50 mg/kg which is uniformly lethal.

Over the past 9 years the CVRL in Dubai has performed over 25 post-mortem examinations in falcons after the PO administration of this or similar Vit B-complex products. The histopathological findings have been consistent in all cases, and have included congestion and perivascular hemorrhages of the lungs, individual liver cell degeneration and necrosis with hemorrhages. Similar cases of possible Vit B6 toxicity in falcons have been observed in various countries of the Middle East in the past 25 years (J.S., personal communications with multiple clinicians) after similar products were given either PO or IM. Vit B6 toxicosis may have occurred in not only in falcons, but also possibly in other avian species in the region and possibly worldwide, without clinical diagnosis.

While the numbers of falcons in each of the toxicology trials presented here were relatively small, these studies clearly suggest the highest single non-lethal dose of Vit B6 in falcons are 5 mg/kg IM, and 25 mg/kg PO. Non-lethal levels for sequential or daily supplementation are likely to be considerably lower.¹⁹

It is notable that even among birds, there is a very wide inter-order spectrum of sensitivity to high doses of Vit B6. Domestic chickens are not affected by single oral doses above 200 mg/kg, while pigeons are killed by that level.²³ As the results presented here show, falcons are approximately eight times more sensitive than pigeons. Since pyridoxine is a cofactor in many
enzymes involved in amino acid metabolism, it is possible that high activity of such enzymes in their livers contributes to the sensitivity of these faunivorous birds.\textsuperscript{24}

Additional toxicology trials with larger numbers of falcons per group, or similar trials with other vitamins contained in the multivitamin preparation from Clinical Case No 1, were not feasible because of the high value of the falcons and the reluctance of the authors to carry out further trials using live birds. While the authors regret sacrificing the lives of the falcons used in this study, it was believed necessary in order to methodically generate quantitative and convincing data and thus prevent further loss of lives.

This report highlights the need to re-examine the recommended dose rates of specific vitamins contained in Vit B-complex preparations used in falcons, with particular attention to levels of Vit B6. Given the range of vulnerabilities to Vit B6 toxicosis among avian orders, this issue is applicable to other bird species--and perhaps other classes of animals--as well.

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Table 1. Survival of falcons after various single doses of Vit B6.

<table>
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<th>Route of administration</th>
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<sup>a</sup>Each group consisted of four birds.
Figure legends

Figure 1a. Peregrine falcon (*Falco peregrinus*) liver showing congestion and necrosis. Hematoxylin Eosin (HE) stain. Objective 10x bar 50 µm. 1b. Insert liver showing eosinophilic bodies or “protein globules”. HE objective 40x bar 20 µm.