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# What is an appropriate dose of voriconazole for treatment of aspergillosis in African grey parrots?

## Clinical scenario

An African grey parrot (*Psittacus erithacus*) is presented to your practice with severe dyspnoea, inappetence and loss of body condition. Following a diagnostic workup, aspergillosis of the air-sacs is diagnosed. Itraconazole (Fungitraxx 10 mg/ml oral solution for ornamental birds, Pet Life International Ltd, UK) is licensed for the treatment of aspergillosis in birds, but itraconazole toxicity has been reported in this species. Voriconazole (various manufacturers) is an alternative antifungal agent, not licensed for use in veterinary species, that can be prescribed under the Cascade. You wonder what the most appropriate dose would be to treat this parrot.

## The question

In [an African grey parrot with aspergillosis] is [low dose voriconazole (6mg/kg)] or [high dose voriconazole (10-18mg/kg)] more appropriate [for treatment of aspergillosis]?

## Search parameters

The search terms

Aspergillus OR aspergillosis OR mycoses OR mycosis

AND

African grey parrot' OR 'African gray parrot' OR 'African grey parrots' OR 'African gray parrots' OR 'Timneh grey parrot' OR 'Psittacus erithacus' OR 'Psittacus erithacus timneh' OR 'Psittacus timneh'

AND

Voriconazole

## Search outcome

Two relevant papers found in CAB Abstracts search

One relevant paper found in Medline search

Two relevant papers from both Medline and CAB.

## Search last performed

December 7, 2017

## Summary of evidence

Paper 1: Pharmacokinetics of voriconazole after oral administration of single and multiple doses in African grey parrots (*Psittacus erithacus timneh*) (Flammer et al. 2008).

Patient group: Healthy Timneh African grey parrots (n=20), assigned into one of two groups. Group One received single doses at Day 0 of 6 mg, 12 mg and 18 mg/kg voriconazole orally (n=12), either mixed with water or with a commercial suspending agent. Single doses were repeated with the same individuals 14 or 21 days after each previous dose. Group Two received multiple doses of 18 mg/kg voriconazole (PO q 12h) mixed with a commercial suspending agent for nine days (n=6). A control group (n=2) received tap water (equivalent volume, PO q 12h for nine days).

Study type: Non-randomised, controlled trial

Outcomes: Plasma samples were collected at 30 minutes and one, six, 12 and 24 hours after drug administration for the single dose trials. Pooling of data points produced a mean plasma concentration of voriconazole which was used for pharmacokinetic analysis. For the multi-dose trial, plasma samples were collected twice for measurement of the trough plasma concentration (lowest concentration of voriconazole reached prior to the next dose being administered).

Key results: Increases in the dose of voriconazole resulted in disproportional increases in maximum concentration of the drug in plasma. Plasma half-life of voriconazole was short (1.1 to 1.6 hours). The use of a commercial suspending agent increased both the Area Under Curve (AUC) and maximum concentration of voriconazole compared to mixing the drug with water. Polyuria was more severe in the treatment groups than the control group.

Study Weaknesses: This study used a small sample size of healthy animals and a small control group and was non-randomised. Pharmacokinetics of voriconazole are dose-dependent, therefore it is not possible to accurately extrapolate plasma concentrations of different doses. There may be an induction of metabolism effect of voriconazole administration in African grey parrots, where recurrent administration stimulates the hepatic enzymes that metabolise the drug. The single dose group received subsequent single doses 14 days or 21 days after the first dose, which may have affected drug clearance. The investigators were not blinded to the treatment but acknowledge this in the paper. The single dose trial plasma measurements at 24 hours post-administration were all excluded because of inconsistencies in the data.

FLAMMER, K., NETTIFEE OSBORNE, J.A., WEBB, D.J., FOSTER, L.E., DILLARD, S.L. & DAVIS, J.L. (2008) Pharmacokinetics of voriconazole after oral administration of single and multiple doses in African grey parrots (*Psittacus erithacus timneh*). *American Journal of Veterinary Research* **69**, 114 -121

Paper 2: Evaluation of the influence of formulation, food intake and species on voriconazole plasma concentration in birds (Burhenne & Scope 2012).

Patient group: Clinically healthy, adult Congo African grey parrots (*Psittacus erithacus*). Experiment One: effect of food on voriconazole absorption trial. On Day One, after overnight fasting, parrots (n=12) were orally administered a single dose of 10 mg/kg voriconazole. On Day Five, the same parrots were administered, by gavage, another single dose of 10 mg/kg voriconazole administered in combination with food. Experiment Two: African grey parrots (n=17) were administered a single dose of 10 mg/kg voriconazole suspended in water, orally.

Study type: Non-randomised, non-controlled trial.

Outcomes: Experiment One: Blood was sampled to measure concentration of voriconazole at 30 minutes, 60 minutes, 90 minutes, three, six and 12 hours after drug administration. Experiment Two: Plasma concentration of voriconazole was measured once per bird, 90 minutes after administration.

Key results: Experiment One: Plasma concentrations of voriconazole 90 minutes after administration were not significantly different between fasted ( $1.75 \pm 1.40 \mu\text{g/ml}$ ) and not fasted parrots ( $1.72 \pm 0.36 \mu\text{g/ml}$ ). Experiment Two: mean plasma concentration of voriconazole in African grey parrots 90 minutes after oral administration was  $1.6 \mu\text{g/ml}$ .

Study Weaknesses: This study used a small sample size of healthy animals with no control group and was non-randomised. The authors don't state whether the parrots used in Experiment One are the same animals used in Experiment Two. The authors don't state what medium the voriconazole was suspended in for Experiment One. Both experiments in this study were single dose trials, which may not be representative of the pharmacokinetics of voriconazole after multiple doses.

BURHENNE, J. & SCOPE, A. (2012) Evaluation of the influence of formulation, food intake and species on voriconazole plasma concentration in birds. *Veterinary Medicine Austria* **99**, 157-162

#### Comments

A Minimum Inhibitory Concentration (MIC) of  $0.38 \mu\text{g/ml}$  voriconazole has been reported for *Aspergillus* infections cultured from falcons (Silvanose and others 2006). Both low dose (6 mg/kg) and high dose (10-18 mg/kg) treatments in these studies achieved maximal concentrations exceeding  $0.38 \mu\text{g/ml}$ . Trough plasma concentrations were maintained above MIC for approximately 10 hours in the single dose 10 mg/kg and 12 mg/kg trials and 12 hours for the single dose 18 mg/kg trial. Due to a possible induction of metabolism effect, the multiple dose 18 mg/kg trough plasma concentration was lower than the single dose. Both these studies were carried out on healthy birds over a short time frame. It is possible that the pharmacokinetics of voriconazole will be different in parrots with aspergillosis, as well as with extended treatments. One of the studies was carried out on Timneh African grey parrots and the other on Congo African grey parrots. The Timneh African grey parrot was previously considered a conspecific to the Congo African grey parrot but is now considered a separate species (*Psittacus timneh*). Further work is needed to more accurately identify the doses of voriconazole needed to treat African grey parrots with aspergillus infections.

#### Bottom line

10 -18 mg/kg twice daily is a reasonable dose for administration of voriconazole to African grey parrots infected with aspergillosis. Using a commercial suspending agent, rather than just mixing in water, may greatly increase the bioavailability of the drug. More research is needed to determine the optimum duration of treatment. It is not necessary to give the drug with or without food.

Authors of this CAT

Luke O'Connor, Emma Place – University of Bristol

Tariq Abou-Zahr - Great Western Exotics, Vets Now Referrals

Silvanose CD, Bailey TA, Di Somma A. Susceptibility of fungi isolated from the respiratory tract of falcons to amphotericin B, itraconazole and voriconazole. *Vet Rec* 2006;159:282–284.