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Evaluation of the influence of formulation, food intake and species on voriconazole plasma concentration in birds

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Summary

Voriconazole is currently recommended as first choice treatment for aspergillosis in birds. An evaluation of the influence of food intake was performed with twelve African grey parrots. The birds received 10 mg/kg voriconazole orally in the morning after overnight fasting. Five days later, the same birds were treated with 10 mg/kg voriconazole in combination with 10 ml food. Blood was sampled from 0 to 12 hours after drug application. Further, a comparison of the commercially available suspension of voriconazole with suspended tablets was performed with two groups of pigeons. Blood was taken 90 minutes after drug administration. Compared species were African grey parrots (n=17), Amazon parrots (n=10), Macaws (n=4), racing pigeons (n=10), common kestrels (n=10) and common buzzards (n=10); all birds received 10 mg/kg voriconazole orally; blood was taken after 90 minutes.

There was no significant difference between the mean plasma concentrations of voriconazole in fasted African grey parrots and when the drug was given together with food, also not between the mean plasma concentrations of voriconazole from suspended tablets and commercially available suspension in racing pigeons. But there were distinct differences in plasma concentrations between species after 90 minutes.

The enteral absorption of voriconazole does not seem to be influenced by food intake in African grey parrots. The formulation had no influence on the plasma concentrations in racing pigeons. As anticipated, there are obviously marked individual and species-dependent differences in the pharmacokinetics of voriconazole in birds.

Schlüsselwörter: Antimykotika, Aspergillose, Vorikonazol, enterale Absorption.

Zusammenfassung

Evaluierung des Einflusses von Darreichungsform, Futteraufnahme und Spezies auf den Plasmaspiegel von Vorikonazol bei Vögeln

Einleitung

Voriconazol wird derzeit als erstes Mittel der Wahl zur Aspergillosetherapie beim Vogel empfohlen.

Material und Methode

Der Einfluss der Futteraufnahme auf den Plasmaspiegel von Voriconazol wurde bei Afrikanischen Graupapageien untersucht. Die über Nacht nüchtern gehaltenen Vögel erhielten 10 mg/kg Voriconazol, fünf Tage später erhielten dieselben Vögel ohne vorherigen Futterentzug 10 mg/kg Voriconazol gemeinsam mit Handaufzuchtfutter. Die Blutabnahmen erfolgten nach null bis zwölf Stunden. Der Vergleich der kommerziell erhältlichen Suspension von Voriconazol mit suspendierten Tabletten erfolgte mit zwei Gruppen von Brieftauben. Die Blutabnahme erfolgte nach 90 Minuten. Für den Vergleich verschiedener Vogelspezies wurden untersucht: Afrikanische Graupapageien (n=17), Amazonen (n=10), Aras (n=4), Brieftauben (n=10), Turmfalken (n=10), und Mäusebussarde (n=10). Die Blutabnahme erfolgte jeweils nach 90 Minuten.

Ergebnisse

Es bestand kein signifikanter Unterschied in den Plasmakonzentrationen von Voriconazol bei nüchternen Graupapageien und jenen, die das Medikament gemeinsam mit Futter erhielten, auch nicht zwischen den Plasmakonzentrationen nach Verabreichung der kommerziell erhältlichen Suspension und suspendierter Tabletten. Hingegen konnten nach 90 Minuten erhebliche Unterschiede zwischen den untersuchten Spezies festgestellt werden.

Schlussfolgerungen

Die enterale Absorption von Voriconazol scheint bei Graupapageien durch die Futteraufnahme nicht beeinflusst zu werden. Die Darreichungsform hatte bei Brieftauben keinen Einfluss auf die Plasmakonzentrationen. Wie erwartet konnten erhebliche Spezies-spezifische Unterschiede in den Plasmakonzentrationen von Voriconazol bei Vögeln gezeigt werden.

Introduction

Fungal infections are frequently diagnosed in birds; and aspergillosis in particular is a serious health problem in various bird species, especially in those kept in captivity. Aspergillosis-associated species are most commonly *Aspergillus fumigatus*, followed by *A. flavus* and *A. niger,* which primarily affect the respiratory tract (TELL, 2005). Various antimycotics have been used for the treatment of aspergillosis in birds. For some years itraconazole has been recommended as a first-choice treatment because of its broad spectrum (LUMEIJ et al., 1995; OROSZ et al., 1995; FISCHER and HATT, 2003). There are, however, safety concerns for its use in African grey parrots, because it may cause severe side effects, including symptoms of the central nervous system, vomiting, and even death (VANDERMAST et al., 1990; QUESENBERRY et al., 1991; OROSZ et al., 1995). Especially in this species, and in any case of antifungal drug resistance, it is recommended to revert to other drugs. Within the last years, voriconazole (Vfend®, Pfizer) developed to the drug of first choice for the treatment of aspergillosis in birds. Voriconazole is a highly potent triazole antifungal agent and a chemical derivative of fluconazole. It is available as a lyophilized powder for intravenous infusion, as film-coated tablets for oral administration, and as a powder for oral suspension. The primary mode of action is the inhibition of fungal cytochrome P450-mediated 14-alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. Voriconazole shows high *in vitro* activity against a wide variety of fungal pathogens, including *Aspergillus, Candida*, and *Cryptococcus* spp., and its efficacy in the treatment of invasive aspergillosis has been shown in large clinical trials in humans (ABRAHAM et al., 1999; ESPINEL-INGROFF et al., 2001; DENNING et al., 2002; HERBRECHT et al., 2002; WALSH et al., 2002; MUIJSERS et al., 2003). It has been shown that voriconazole is also effective in the treatment of aspergillosis in birds (DI SOMNA et al., 2007; BERNAERT et al., 2009b; TELL et al., 2010). In the past years some studies on voriconazole pharmacokinetics in birds have been published (SCHMIDT et al., 2007; GUZMAN et al., 2010; KLINE et al., 2011). SILVANOSE et al. (2006) surveyed on the susceptibility of fungi isolated from falcons. In their study, voriconazole had the lowest median minimal inhibitory concentration (MIC) against all strains of *Aspergillus* species, as well as greater potency and a broader spectrum than other tested antimycotics.

For reasons of practicability, dosage recommendations of voriconazole are mostly based on plasma concentrations. However, because fungal infections are typically located in tissues, a better prognostic marker of therapeutic outcome may be the evaluation of tissue concentrations of the drug (OROSZ et al., 1995). A previous study in chickens focusing on voriconazole plasma pharmacokinetics showed a low and variable oral bioavailability (BURHENNE et al., 2008). The absolute oral bioavailability was only about 20 %. In contrast with the need to optimize bioavailability of some azoles (e.g. itraconazole), where the pH in the gastrointestinal tract must be low, it is known that pH does not affect the absorption of voriconazole (OROSZ et al., 1995). But when voriconazole is administered together with a high fat meal in humans, bioavailability is reduced by about one-third (FOOD AND DRUG ADMINISTRATION, 2001). Published data on pharmacokinetics of voriconazole in falcons, African grey parrots, and Amazon parrots differ considerably. SCHMIDT et al. (2007) measured plasma concentrations of voriconazole in falcons and reported good results in the treatment of falcons using a dose of 12.5 mg/kg; no side effects have been reported. FLAMMER et al. (2008) published data on pharmacokinetics of voriconazole in African grey parrots recommending 12–18 mg/kg BID. BEERNAERT et al. (2009b) recommend a treatment protocol for racing pigeons of 10 mg/kg BID. KINE et al. (2011) found out that for mallard ducks a dosing interval of at least every 8–12 hours at a dose of 20 mg/kg is required. All authors state the necessity of further studies in this field, because further differences between bird species can be anticipated.

The aims of the present study were to evaluate factors that influence enteral absorption, like food intake; to investigate a possible influence of the formulation (commercially available suspension versus suspended tablets) on plasma concentrations; and to rate species-specific differences in plasma concentrations using the same dosage.

Material and methods

This study was conducted according to the guidelines of the Austrian law for animal testing, authorized under permissions no. GZ 68.205/13-BrGT/2005 and GZ 68.205/15-BrGT/2006. Voriconazole (Vfend®) tablets and powder were kindly supplied by Pfizer Pharmaceuticals (Vienna, Austria). The analytical reference compounds voriconazole (UK-109,496) and the internal standard (UK-115,794) were supplied by Pfizer Pharmaceuticals (New York, USA).

Evaluation of the influence of food intake on absorption in African grey parrots (*Psittacus erithacus erithacus*)

The evaluation of the influence of food intake was performed with twelve adult clinically healthy African grey parrots. On day 1 the birds received 10 mg/kg voriconazole orally (suspended tablets) in the morning after overnight fasting. Five days later the same birds were treated with 10 mg/kg voriconazole without previous food restriction. To assure drug administration in combination with food, voriconazole was given together with 10 ml hand feeding formula containing 12 % fat and 19 % protein (Nutri Bird A19, No. BE 6236, Versele Laga, Belgium) by gavage. Because the maximal blood sampling volume should not exceed 1 % of the body weight (FUDGE, 2000), blood was sampled in a staged scheme from 0 to 12 hours. Drug-free control blood samples had been taken two days before the study started. Three groups of four parrots each were formed. Blood was sampled after 0.5 and 1 hour (group 1), 1.5 and 3 hours (group 2) and 6 and 12 hours (group 3). Blood (1 ml/sampling) was taken from the right jugular vein or from the V. basilica using heparinized syringes. Samples were centrifuged at 1,500 g for 10 min. The plasma was frozen within one hour after sampling and kept at -20 °C until analysis.

Comparison of commercially available voriconazole powder for suspension with suspended tablets in racing pigeons (*Columba livia domestica*)

The comparison of the commercially available voriconazole powder for suspension with suspended tablets was performed in pigeons because the number of parrots that could be used for the studies was limited. The oral voriconazole suspension was reconstituted according to the manufacturer's instructions. The addition of 45 ml water yields a suspension of 40 mg/ml voriconazole. For oral administration, 5 ml of this stock suspension was diluted with 15 ml water to reach a concentration of 10 mg/ml voriconazole in suspension.

Vfend® tablets were first crushed and then suspended in water (50 mg/5 ml water) also resulting in a 10 mg/ml concentration. The tablet suspension tends to settle quickly; therefore the suspension has to be shaken thoroughly immediately prior to administration. Two groups of pigeons consisting of five birds each received 10 mg/kg voriconazole orally. One group was treated with voriconazole suspension made from the commercially available lyophilized powder for solution; the other group received the suspended tablets. Blood (1 ml/sampling) was taken after 90 min from the V. basilica using heparinized syringes. Processing and storage of the samples was according to the method described above.

Comparison of plasma concentrations in different species after oral administration

For comparison of different species, sample groups of following birds were examined: African grey parrots (*Psittacus erithacus erithacus*) (n=17), Amazon parrots (*Amazona* spp.) (n=10), Macaws (*Ara* spp.) (n=4), racing pigeons (*Columba livia domestica*) (n=10), common kestrels (*Falco tinnunculus*) (n=10), and common buzzards (*Buteo buteo*) (n=10). All birds included in this study part were clinically healthy and in good body condition. The birds received 10 mg/kg voriconazole orally. For drug administration, Vfend® tablets were suspended in water (50 mg/5 ml water); the suspension was shaken thoroughly before administration and 1 ml/kg bodyweight was given directly into the beak with a syringe (the powder for oral suspension was not yet available in Austria at the time of this part of the study). Blood (0.5 ml) was taken from the right jugular vein or from the V. basilica 90 min after drug administration using heparinized syringes. The decision to take blood after 90 minutes was based on the fact that Tmax in birds ranged between 1 and 2.15 hours (BURHENNE et al., 2008; FLAMMER et al., 2008; KLINE et al., 2011). The samples were processed and stored according to the procedure described above.

Analytical procedure

Solid phase extraction technology was used for the extraction of voriconazole from plasma samples. The extracts were analyzed using high pressure liquid chromatography. The analytical methods applied were published by BURHENNE et al. (2008). All reagents and solvents used for the chromatographic, spectroscopic, and sample procedures were of analytical or higher quality and were purchased from E. Merck (Darmstadt, Germany).

Calculations

For standard calculations, KyPlot 2.0 and Microsoft Excel 2003 were used. Data are given as mean values ± standard deviation (SD). Statistical evaluation was

performed using GraphPad Prism 5.01 (one-way analysis of variance (ANOVA) with Bonferroni's multiple comparison test) and GraphPad InStat 2.1 (unpaired, two-sided t-test).

Results

Evaluation of the influence of food intake on absorption in African grey parrots

Ninety minutes after oral application there was no significant difference between mean plasma concentrations in African grey parrots that received voriconazole after one night fasting and those who received the drug together with food (p=0.97, unpaired, two-sided t-test). The mean voriconazole plasma concentrations (±SD) after 90 min were 1.75±1.40 µg/ml (fasted) and 1.72±0.36 µg/ml (not fasted). The plasma concentration time curves fasted and not fasted show similar profiles (Fig. 1).

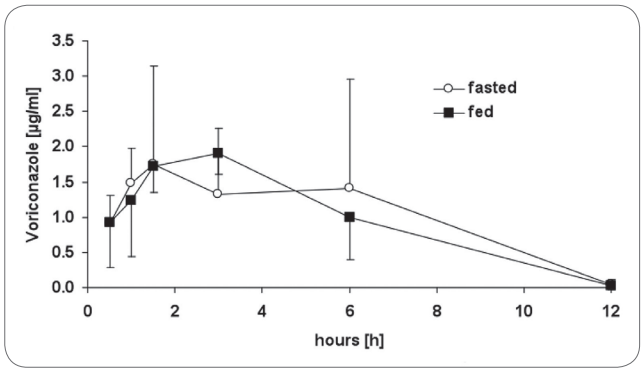

Fig. 1: Mean plasma concentrations of voriconazole in African grey parrots with and without food intake

Comparison of commercially available voriconazole powder for suspension with suspended tablets in racing pigeons

Ninety minutes after oral application there was no significant difference between the mean plasma concentrations of voriconazole from suspended tablets and commercially available powder suspension in pigeons (p=0.60, unpaired, two-sided t-test). The mean voriconazole plasma concentrations ± SD after 90 min of application were 5.5±1.4 µg/ml (suspended tablet) and 5.1±1.1 µg/ml (suspended powder).

Comparison of plasma concentrations in different species after oral administration

Mean plasma concentrations of voriconazole 90 min after oral administration ranged from 0.6 µg/ml (macaw, n=4), 0.8 µg/ml (amazons, n=10), 1.6 µg/ml (African grey parrots, n=17), 4.4 µg/ml (falcons and buzzards, n=10 each) and up to 5.5 µg/ml (pigeons, n=10) (Tab. 1). In pigeons, falcons, and buzzards, voriconazole plasma concentrations were significantly higher compared to either African grey parrots, amazons, Macaws, or chickens (ANOVA, p<0.0001).

Discussion

In contrast with humans, the enteral absorption of voriconazole does not seem to be influenced by food intake in the species studied. No significant differences between voriconazole plasma concentrations in African grey parrots which were fasted and in those that received the drug in combination with *ad libitum* and forced feeding could be found. This result is useful for clinical applications because it is not necessary to consider whether the bird has eaten before the treatment. It would be undesirable to restrict food in birds with pre-existing health problems. However this result contrasts with SCHMIDT et al. (2007), who reported reduced mean plasma concentrations between 21 and 26 % in falcons when voriconazole was given in the meat, possibly reflecting another between-species difference (granivorous/carnivorous).

In pigeons, voriconazole tablets suspended in water yielded plasma concentrations comparable to those recorded for the suspension made from commercially available powder for suspension. Interestingly, FLAMMER et al. (2008) reported that plasma con-

Tab. 1: Species dependent plasma concentrations of voriconazole 90 minutes after oral application

Species	n	Mean [µg/ml]	SD [µg/ml]	CV [%]	Min [µg/ml]	Max [µg/ml]
African grey parrot	17	1.6	1.0	58.9	0.2	3.3
Amazon	10	0.8	1.2	143.4	<0.050	4.0
Macaw	4	0.6	0.3	53.5	0.1	0.8
Pigeon	10	4.5	1.5	33.5	2.0	7.6
Falcon	10	4.4	1.8	39.9	3.5	6.1
Buzzard	10	4.4	1.5	34.0	2.6	6.9
Chicken	8	0.9	0.8	90.8	0.2	2.5

SD = standard deviation, CV = coefficient of variation

centrations in birds treated with voriconazole in a pharmacist-compounded suspension agent were 1.5 and 1.6 times higher than those achieved after treatment with voriconazole mixed with water. A commercially available suspension is to be preferred because it is stable and therefore more appropriate for use in oral treatment. It has to be mentioned that the commercial oral suspension is not available everywhere and in some countries it is much more expensive than compounded suspensions from tablets. If the suspension is not available on the domestic market, it may be substituted by a tablet suspension, optimally using a commercial suspending agent (e.g. Ora-Plus®, Paddock Laboratories Inc., MN) as used by FLAMMER et al. (2008) to avoid sedimentation. According to the manufacturer, the oral suspension is stable for 14 days and should not be refrigerated after preparation, whereas the powder has to be cooled. FLAMMER et al. (2008) reported the stability of the refrigerated suspension as 17 days, however it is recommended to discard aqueous drug suspensions after 14 days to avoid microbial growth.

As anticipated, significant differences in voriconazole plasma concentrations between the examined species were evident. Administration of 10 mg/kg orally resulted in the highest plasma concentrations after 90 min in pigeons (4.5 µg/ml), as well as in common kestrels and common buzzards (4.4 µg/ml), while plasma levels of voriconazole in African grey parrots (1.6 µg/ml) and Amazons (0.8 µg/ml) were considerably lower. The number of examined Macaws was low (n=4), and so the results in this species might not be conclusive, but plasma concentrations were lower (0.6 µg/ml) than in other examined Psittacine species. Comparison with data from chickens (BURHENNE et al., 2008) show that the same dosage (10 mg/kg) yielded considerably lower concentrations (0.9 µg/ml) than in most of the other examined species. Plasma concentrations in falcons, buzzards and pigeons were more than four times higher than those in chickens. These results obviously illustrate that studies on the plasma concentration of voriconazole in one species may not be directly transferrable to others. Plasma concentrations in African grey parrots in the present study are comparable with those reported by FLAMMER et al., (2008) using a slightly higher dosage of 12.5 mg/kg of crushed tablets in water. In our study, plasma concentrations of voriconazole in common kestrels 90 min after administration were considerably higher (4.4 µg/ml) than reported by SCHMIDT et al. (2007). The authors reported plasma concentrations of 1.9–2.4 µg/ml in falcons one hour after administration, even though they used a higher dosage of 12.5 mg/kg. Possible explanations include assuming that Tmax in falcons might be closer to 90 minutes. Another possible reason for the differences might be assumed in the species differences between the two studies; SCHMIDT et al., (2007) examined a mixed group of six Saker falcons, gyrfalcons and hybrids. These two differences may represent the cause for the discrepancies between the studies rather than the small differences in the dosage.

One reason for distinctions between bird species could be supposed in differences in enteral motility and absorption and/or presystemic metabolization (BEERNAERT et al., 2009b). Other possible reasons could be delayed absorption or differences in elimination. In all examined species the individual variability of plasma concentrations was as high as it has been reported in humans (0.5–6.0 µg/ml), which could also explain disagreements between the studies (FOOD AND DRUG ADMINISTRATION, 2001). In humans it has been shown that there is a genetic polymorphism in the cytochrome P450 which results in poor and extensive metabolizers (GOLDSTEIN and DE MORAIS, 1994; HYLAND et al., 2003).

Conclusion

In opposite to a study with falcons (SCHMIDT et al., 2007), food administration did not influence plasma voriconazole concentrations in African grey parrots 90 min after administration. In pigeons there was no significant difference in plasma concentrations achieved by the commercial or compounded formulation at 90 min after application. The differences in plasma voriconazole concentrations seen in various species at 90 minutes after application confirm the suspicion that relevant species differences in voriconazole metabolism have to be expected. However, clear individual and species-dependent differences in the pharmacokinetics of voriconazole in birds have to be considered and should be evaluated further.

References

ABRAHAM, O.C., MANAVATHU, E.K., CUTRIGHT, J.L., CHANDRASEKAR, P.H. (1999): In vitro susceptibilities of Aspergillus species to voriconazole, itraconazole and amphotericin B. Mycology **33**, 7–11.

BEERNAERT, L.A., PASMANS, F., VAN WAEYENBERGHE, L., DORRESTEIN, G.M., VERSTAPPEN, F., VERCAMMEN, F., HAESENBROUCK, F., MARTEL, A. (2009a): Avian *Aspergillus fumigatus* strains resistant to both itraconazole and voriconazole. Antimicrob Agents Ch **53**, 2199–2201.

BEERNAERT, L.A., PASMANS, F., BAERT, K., VAN WAEYENBERGE, L., CHIERS, K., HAESENBROUCK, F., MARTEL, A. (2009b): Designing a treatment protocol with voriconazole to eliminate *Aspergillus fumigatus* from experimentally inoculated pigeons. Vet Microbiol **139**, 393–397.

BURHENNE, J., HAEFELI, W.E., HESS, M., SCOPE, A. (2008): Pharmacokinetics, tissue concentrations, and safety of the antifungal agent voriconazole in chickens. J Avian Med Surg **22**, 199–207.

DENNING, D.W., RIBAUD, P., MILPIED, N., CAILLOT, D., HERBRECHT, R., THIEL, E., HAAS, A., RUHNKE, M., LODE, H. (2002): Efficacy and safety of voriconazole in the treatment of active aspergillosis. Clin Infect Dis **34**, 563–571.

DI SOMMA, A., BAILEY, T., SILVANOSE, C., GARCIA-MARTINEZ, C. (2007): The use of voriconazole for the treatment of aspergillosis in falcons (*Falco* species). J Avian Med Surg **21**, 307–316.

ESPINEL-INGROFF, A., BOYLE, K., SHEENAN, D.J. (2001): In vitro antifungal activities of voriconazole and reference agents as determined by NCCLS methods: Review of the literature. Mycopathologia **150**, 101–115.

FISCHER, I., HATT, J.M. (2003): Antifungal therapy in birds: A review and critical discussion of new trends. Proc Annu Conf Euro Coll Avian Med Surg (ECAMS), p. 21–22.

FLAMMER, K. (2006): Antifungal Drug update. Proc Annu Conf Assoc Avian Vet, p. 3–6.

FLAMMER, K., NETTIFEE, J.A., OSBORNE B.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*). J Am Vet Med Assoc **69**, 114–121.

FOOD AND DRUG ADMINISTRATION (FDA) (2001): Background document for the antiviral drug products: Voriconazole tablets, voriconazole injection. Pfizer Global Research & Development. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_02_FDA-voriconazole.pdf Accessed 2011-07-15

FUDGE, A. (2000): Avian blood sampling and artefact considerations. In: FUDGE, A. (ed): Laboratory Medicine Avian and Exotic Pets. WB. Saunders, Philadelphia, p. 3.

GOLDSTEIN, J.A., DE MORAIS, S.M. (1994): Biochemistry and molecular biology of the human CYP2C subfamily. Pharmacogenetics **4**, 285–299.

GUZMAN, D.S., FLAMMER, K., PAPICH, M.G., GROOTERS, A.M., SHAW, S., APPLEGATE, J., TULLY Jr., T.N. (2010): Pharmacokinetics of voriconazole after oral administration of single and multiple doses in hispaniolian amazon parrots (*Amazona ventralis*). Am J Vet Res **71**, 460–467.

HERBRECHT, R., DENNING, D.W., PATTERSON, T.F.; BENNETT, J.E., GREENE, R.E., OESTMANN, J.W., KERN, W.V., MARR, K.A., RIBAUD, P., LORTHOLARY, O., SYLVESTER, R., RUBIN, R.H., WINGARD, J.R., STARK, P., DURAND, C., CAILLOT, D., THIEL, E., CHANDRASEKAR, P.H., HODGES, M.R., SCHLAMM, H.T., TROKE, P.F., DE PAUW, B. (2002): Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. New Engl J Med **347**, 408–415.

HYLAND, R., JONES, B.C., SMITH, D.A. (2003): Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metab Dispos **31**, 540–547.

KLINE, Y., CLEMONS, K.V., WOODS, L., STEVENS, D.A., TELL, L.A. (2011): Pharmacokinetics of voriconazole in adult mallard ducks (*Anas platyrhynchos*). Med Mycol **49**, 200–512.

LUMEIJ, J.T., GORGEVSKA, D., WOESTENBORGHS, R. (1995): Plasma and tissue concentrations of itraconazole in racing pigeons (*Columba livia domestica*). J Avian Med Surg **5**, 32–35.

MUIJSERS, R.B., GOA, K.L., SCOTT, L.J. (2003): Voriconazole: in the treatment of invasive aspergillosis. Drugs **62**, 2655–2664.

OROSZ, S.E., SCHROEDER, E.C., COX, S.K., DOSS, S., FRAZIER, D.L. (1995): The effect of formulation on the systemic availability of itraconazole in pigeons. J Avian Med Surg **4**, 255–262.

SCHMIDT, V., DEMIRAJ, F., DI SOMNA, A, BAILEY, T., UNGEMACH, F.R., KRAUTWALD-JUNGHANNS, M.E. (2007): Plasma concentrations of voriconazole in falcons. Vet Rec **161**, 265–268.

SILVANOSE, C.D., BAILEY, T.A., DI SOMMA, A. (2006): Susceptibility of fungi isolated from the respiratory tract of falcons to amphotericin B, itraconazole and voriconazole. Vet Rec **159**, 282–284.

TELL, L.A. (2005): Aspergillosis in mammals and birds: impact on veterinary medicine. Med Mycol **43** (Suppl. 1), 71–73.

TELL, L.A., CLEMONS, K.V., KLINE, Y., WOODS, L., KASS, P.H., MARTINEZ, M., STEVENS, D.A. (2010): Efficacy of voriconazole in Japanese quail (*Coturnix japonica*) experimentally infected with *Aspergillus fumigatus*. Med Mycol **48**, 234–244.

QUESENBERRY, K., BAUCK, L., SPEER, B, FLAMMER, K., IRMIGER, R., HILLYER, E. (1991): Roundtable discussion: Clinical therapy. J Avian Med Surg **5**, 186–191.

VANDERMAST, H, DORRESTEIN, G.M., WESTERHOF, J. (1990): A fatal treatment of sinusitis in an African grey parrot. J Assoc Avian Vet **4**, 189.

WALSH, T.J., LUTSAR, I., DRISCOLL, T., DUPONT, B., RODEN, M., GHAHRAMANI, P., HODGES, M., GROLL, A.H., PERFECT, J.R. (2002): Voriconazole in the treatment of aspergillosis, scedosporidiosis and other invasive fungal infections in children. Pediatr Inf Dis J **21**, 240–248.

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