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Comparison of Voriconazole (UK-109,496) and Itraconazole in Prevention and Treatment of *Aspergillus fumigatus* Endocarditis in Guinea Pigs

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Left-sided *Aspergillus fumigatus* endocarditis was established in the guinea pig heart by catheterization and inoculation with conidia via a tributary of the femoral vein. This animal model was used to compare the efficacy of the triazole antifungal agents voriconazole (UK-109,496) and itraconazole. In the prophylaxis experiments, voriconazole at a dosage of 10 mg/kg of body weight given intraperitoneally twice daily prevented *A. fumigatus* endocarditis in all but 1 animal (11 of 12 animals were cured). Itraconazole did not prevent *Aspergillus* endocarditis when it was given at the same dosage and by the same route (0 of 12 animals were cured). In the treatment experiments with 10 animals per group, voriconazole at 10, 7.5, and 5 mg/kg given orally twice daily for 7 days produced cure rates of 100, 70, and 0%, respectively. In contrast, itraconazole at 10 mg/kg given orally twice daily did not cure *A. fumigatus* endocarditis in the guinea pig. It is concluded that voriconazole is highly efficacious in the prevention and treatment of *Aspergillus* endocarditis in the guinea pig and is superior to itraconazole in these respects.

Aspergillus endocarditis is a condition whose incidence appears to be rising in both adults and children (3, 16). It can occur without previous valve surgery, but it is more common if a cardiac prosthesis is in situ. The usual causative organism is *A. fumigatus*, and vegetations on the valves detected by echocardiography, evidence of thrombotic spread, or failure to respond to antibacterial antibiotics are important diagnostic signs and symptoms (4, 16). Treatment of *Aspergillus* endocarditis is usually with amphotericin B and valvular surgery to remove the vegetations, but the prognosis is still poor (4). Indeed, the infection is usually fatal because the diagnosis is often not made until postmortem (16). There is a dearth of information on the efficacy of itraconazole against *Aspergillus* endocarditis, and in the only published report to date, it was inactive against the disease when assessed at autopsy (5). This was probably due to the fact that serum itraconazole levels were below the MIC for the infecting *Aspergillus* strain. In fact, it is well documented that itraconazole shows variable oral bioavailability, particularly in immunocompromised patients, resulting in suboptimal levels of drug in blood and tissue (1, 9).

Voriconazole is a new, highly potent, broad-spectrum triazole antifungal agent with a fungicidal mode of action against *Aspergillus* spp. (10). In addition, it achieves prolonged systemic exposures in vivo following administration by the oral (p.o.) and intravenous routes (12, 14). Consistent with this, voriconazole has been shown to be curative in a rabbit model of systemic aspergillosis (8) and guinea pig models of systemic and pulmonary aspergillosis (11), irrespective of the immune status of the animals. The aim of this study was to compare the efficacies of voriconazole and itraconazole in the prevention and treatment of *A. fumigatus* endocarditis. The guinea pig was chosen for evaluating voriconazole against *Aspergillus* endocarditis because the drug achieves prolonged systemic exposures in this species that are comparable to those observed in humans (12, 14).

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MATERIALS AND METHODS

Antifungal susceptibility in vitro. *A. fumigatus* H0.6.12 (Pfizer Central Research, Sandwich, United Kingdom) was maintained as frozen stock cultures in liquid nitrogen, and subcultures on Sabouraud's dextrose agar (SDA) slants were made as needed. For each experiment, the organisms were grown on fresh SDA slants at 56°C for 48 h. Conidia were harvested by centrifugation at 2,000 × *g* for 10 min, washed twice in sterile saline, and quantitated by counting with a hemocytometer. The in vitro antifungal susceptibilities of voriconazole and itraconazole against *A. fumigatus* H0.6.12 were determined by agar dilution in high-resolution medium (HR medium; Oxoid, Basingstoke, United Kingdom) mixed with L13 agar no. 3 (Oxoid) buffered with potassium phosphate (pH 7.5). Both compounds were prepared as stock solutions (10× final concentrations) in dimethylformamide (DMF) and double diluted in 15 ml of HR agar to produce a final concentration range of 100 to 0.001 μg/ml. Drug-free agar plates contained 1% (vol/vol) DMF, which did not adversely affect fungal growth. Both control and test agar plates were inoculated with 1 μl of sterile saline containing 10^3 conidia by using a multipoint inoculator and were incubated at 37°C for 48 h. The MIC was determined visually and was defined as the lowest drug concentration at which there was no growth. The in vitro fungicidal activities of voriconazole and itraconazole were determined by the broth macrodilution method in liquid HR medium, essentially as described above. The minimal fungicidal concentration was defined as the lowest drug concentration at which no viable *Aspergillus* organisms could be recovered by subculturing in fresh medium. Voriconazole was synthesized at Pfizer Central Research, and itraconazole was extracted from commercial (itraconazole) Sporonox capsules.

Establishment of endocarditis in the guinea pig. Male Dunkin-Hartley guinea pigs (weight, approximately 500 g; Interfauna, Cambridge, United Kingdom) were used throughout this study. The animals were given 0.3 mg of oxytetracycline per ml in their drinking water for 14 days to ensure that no enteropathogens were present; tetracycline was discontinued 4 days prior to the study. Five animals were anesthetized with 0.5 ml of fentanyl citrate and fluanisone (Hypnorm) (Janssen, Oxford, United Kingdom) per kg of body weight and 2.5 mg of diazepam (Valium; Roche, Welwyn Garden City, United Kingdom) per kg administered intramuscularly in the hind leg. The left side of the heart was then catheterized by the technique described by Longman and Martin (13). Briefly, this consisted of introducing a catheter into the internal carotid artery in the neck and passing it through the left auricle and just through the mitral valve; this prevents full closure of the mitral valve. The position of the catheter was checked by passing contrast medium (meglumine ioxaglate [Hexabrix]; May and Baker, Dorset, United Kingdom) down the catheter and visualizing its position with an image intensifier (Siemens Cerumobile, Bensheim, Germany). The catheter was tied into position, and the wound was closed. Three days later the animals were reanesthetized with ketamine hydrochloride (100 mg/kg of body weight; Parke-

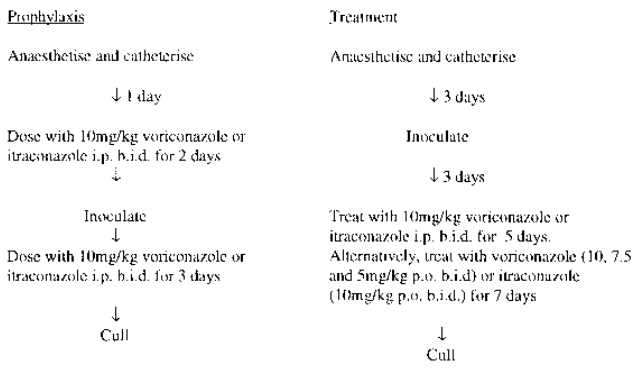

FIG. 1. Summary of prophylaxis and treatment experiments.

Davis, Gwent, United Kingdom). The medial aspect of the thigh was anesthetized locally with 2% (wt/vol) lignocaine hydrochloride (Astra, Kings Langley, United Kingdom). The femoral vein was then exposed and the animal was inoculated in the vein with approximately 10^4 conidia of *A. fumigatus*. The wound was closed and the animals were left for a further 3 days before they were killed by administering an overdose of fentanyl citrate and fluanisone. The hearts of the killed animals were exposed, the great vessels were clamped off and cut, and the heart was removed from the thorax. A longitudinal incision was made through the left atrium and ventricle, and the mitral valve was exposed. Any clot was carefully washed away, and the inferior part of the valve was swabbed with small plain cotton wool swabs (Medical Wire Co., Corsham, United Kingdom). The swabs were inoculated onto Sabouraud's agar, and the agar plates were incubated aerobically at 30°C for 7 days. Growth of *A. fumigatus* on Sabouraud's agar was taken as the presence of endocarditis.

The mitral valve was incised from the heart and immersed in neutral buffered fomalin. The animals' abdomen was opened, and the liver and kidneys were examined macroscopically for any signs of pathology. Samples of macroscopically observed pathological changes in these organs were also placed in formalin and processed for histology. Representative sections were stained with hematoxylin and eosin and also with methenamine-silver to detect the presence of fungal elements. The sections were examined microscopically for the presence of acute inflammation and the presence of fungal elements.

Preparation of inocula. The inocula for the animals were prepared by growing *A. fumigatus* H0.6.12 on SDA slants, as described above. Conidia were harvested as described earlier, and the final suspension in sterile saline was adjusted to contain approximately 10^4 conidia/ml.

Prophylaxis and treatment experiments. The plan for assessing the efficacies of voriconazole and itraconazole in preventing and treating *A. fumigatus* infections is presented in Fig. 1. The details of the catheterization, inoculation, and assessment of endocarditis were described above. In the prophylaxis experiments, both agents were administered at 10 mg/kg intraperitoneally (i.p.). At the end of the experiment the mitral valves, kidneys, and livers were examined macroscopically and microscopically as described above.

Dose-ranging experiments. In the dose-ranging experiments, 40 male guinea pigs were divided into four groups of 10 animals each prior to induction of *Aspergillus* endocarditis by the techniques described above. Three days after inoculation (6 days postcatheterization) the animals received either voriconazole (5, 7.5, and 10 mg/kg) or itraconazole (10 mg/kg) p.o. twice daily (b.i.d.) for 7 days; the animals were dosed at 9 a.m. and 4 p.m. On the last day of the experiment the animals were dosed at 9.00 a.m. and were culled by the administration of an overdose of anesthetic 2 to 3 h later. The inferior vena cava was exposed, and approximately 10 ml of blood was collected for assessment of serum voriconazole and itraconazole levels. The hearts of the animals were examined for *Aspergillus* endocarditis as described above. The mitral valves, livers, and kidneys of the animals were examined macroscopically and microscopically as described above.

Preparation of azoles for p.o. and i.p. administration. Itraconazole and voriconazole for i.p. injection were dissolved in hydroxypropyl-β-cyclodextrin (CD; American Maize Products Company, Hammond, Iowa). The CD was dissolved slowly by sonication in sterile distilled water to a concentration of 250 mg/ml. Itraconazole was added to a final concentration of 30 mg/ml and voriconazole was added to a final concentration of 15 mg/ml. For oral dosing, both itraconazole and voriconazole were dissolved in polyethylene glycol 200 (PEG; Fisons, Loughborough, United Kingdom) to final concentrations of 10 mg/ml. Itraconazole was prepared by heating the PEG to 80°C and adding the itraconazole with sonication until it was dissolved. Voriconazole was prepared in a similar fashion, except no heating of the PEG was required.

Estimation of concentrations of itraconazole and voriconazole in serum. The concentration of voriconazole in serum was estimated by a plate inhibition assay. HR agar (Oxoid) was prepared in 25-cm-square bioassay petri dishes, and 1.7 ml of a suspension of *Candida kefyr* NCPF 3234 was inoculated onto the plates. The inocula contained approximately 2×10^5 cells/ml. The *C. kefyr* inoculum was prepared from a culture grown for 24 h at 28°C in Sabouraud's dextrose medium and was adjusted to 2×10^5 cells/ml by counting in a hemocytometer. Circular wells 5 mm in diameter were cut aseptically into the agar in a six-by-six pattern. A stock solution of 1,000 μg of voriconazole per ml was prepared by dissolving 3 mg in 2.7 ml of DMF. By using a positive-displacement Gilson M250 pipette (Anachem, Luton, United Kingdom), 0.9 ml of human plasma was placed in a sterile tube and 100 μl of the stock solution of voriconazole was added. Serial dilutions of this solution were prepared in fresh plasma until standard solutions of voriconazole were obtained at concentrations in the range of from 100 to 0.049 μg/ml. The agar wells were loaded in triplicate, using a Latin-square design, with the prepared voriconazole standards, the plasma, which was used as a diluent, and the guinea pig serum. The concentrations of plasma-diluted standards of voriconazole used were between 0.19 and 3.12 μg/ml. The plates were incubated at 28°C for 18 h, and the zones of inhibition were measured. A standard curve of the concentration of the antifungal agent against the inhibition zone size was constructed, and the concentration of voriconazole in the guinea pig serum was calculated by interpolation. The assay is reliable and reproducible, with day-to-day analyses varying by <10%. The concentrations of itraconazole in serum were determined by high-pressure liquid chromatography by a previously published method (17).

RESULTS

Azole susceptibilities of *A. fumigatus*. When tested in vitro in HR medium, voriconazole and itraconazole were equipotent against *A. fumigatus* H0.6.12, with an MIC and a minimal fungicidal concentration of 0.39 and 0.78 μg/ml, respectively.

Establishment of *Aspergillus* endocarditis in the guinea pig. *A. fumigatus* was recovered from the mitral valves of all the guinea pigs which were catheterized and inoculated with this organism, consistent with the establishment of *Aspergillus* endocarditis. Furthermore, the animals had lost 10 to 20% of their body weight during the infection, and their mitral valves showed acute inflammation, which is also characteristic of *Aspergillus* endocarditis. Therefore, the procedure described above was considered to be suitable for establishing *Aspergillus* endocarditis in the guinea pig and was used in all subsequent prophylaxis and treatment experiments.

Prophylaxis and treatment experiments. A summary of the results of the prophylaxis experiments is presented in Table 1. All 12 animals treated prophylactically with voriconazole at 10 mg/kg i.p. b.i.d survived the course of the experiment (3 days postinoculation); only one colony of *A. fumigatus* was recovered from one guinea pig in this group. Acute inflammatory cells were detected in the hearts from two animals, but no fungal elements were seen. Furthermore, no inflammation or pathology was observed in the guinea pig livers or kidneys. By contrast, only three animals survived the prophylactic treatment with itraconazole at 10 mg/kg i.p. b.i.d.; one animal developed respiratory distress and two animals developed left-sided hemiparesis. The remaining nine animals lost 25% of their body weight and were culled before the end of the experiment. Consistent with these findings, *A. fumigatus* was recovered from the hearts of all of the animals treated prophylactically with itraconazole; their mitral valves, livers, and kidneys were acutely inflamed, and fungal elements were present.

All the animals in the treatment group dosed via the i.p. route lost weight. No fungal colonies were isolated from the hearts of the animals treated with voriconazole when the animals were culled, and there was no evidence of inflammation or fungal elements in their livers and kidneys. Seven animals were culled after 4 days of treatment with voriconazole due to excessive weight loss. In contrast, all the animals treated with itraconazole lost weight, and none survived beyond 4 days of treatment; all had inflammation of the endocardium, and *A. fumigatus* was recovered from their hearts.

Dose-ranging experiments. A summary of the results of the dose-ranging treatment studies is presented in Table 1. All of

TABLE 1. Summary of activities of voriconazole and itraconazole against *Aspergillus* endocarditis in immune-normal guinea pigs

Expt	Compound	Dose (mg/kg)	Route/no. of days	No. of animals	No. of survivors/total no. of animals (%)	No. of cures/total no. of animals (%)
Prophylaxis	Voriconazole	10	i.p./5	12	12/12 (100)	11/12 (92)
Prophylaxis	Itraconazole	10	i.p./5	12	3/12 (25)	0/12 (0)
Treatment	Voriconazole	10	i.p./5	12	5/12 (42)	12/12 (100)
Treatment	Itraconazole	10	i.p./5	12	0/12 (0)	0/12 (0)
Treatment	Voriconazole	10	p.o./7	10	10/10 (100)	10/10 (100)
Treatment	Voriconazole	7.5	p.o./7	10	10/10 (100)	7/10 (70)
Treatment	Voriconazole	5	p.o./7	10	10/10 (100)	0/10 (0)
Treatment	Itraconazole	10	p.o./7	10	0/10 (0)	0/10 (0)

the animals treated with voriconazole at 10, 7.5, and 5 mg/kg p.o. b.i.d. survived *Aspergillus* endocarditis. There were dose-dependent changes in the weights of the animals, with the animals in the group receiving 10 mg/kg increasing in weight, the animals in the group receiving 7.5 mg/kg either increasing or maintaining their weight, and the animals in the group receiving 5 mg/kg either maintaining or losing a small amount of weight (up to 10%; data not shown). Consistent with these results, there was a dose-dependent increase in the recovery of *Aspergillus* from the animals' hearts. Thus, animals in the 10-mg/kg group were completely cured of their *Aspergillus* endocarditis (100% cure rate), whereas for those in the 7.5- and 5-mg/kg groups, the cure rates were 70 and 0%, respectively. The mean concentrations of voriconazole in the sera of the animals in the groups receiving 10, 7.5, and 5 mg/kg were 3.27, 1.13, and 0.66 μg/ml, respectively.

In marked contrast to the animals treated with voriconazole, none of the animals treated with itraconazole at 10 mg/kg p.o. b.i.d. survived more than 3 days, with the majority of them losing up to 25% of their body weight. Ten animals developed severe ataxia or left-sided hemiparesis, and two animals showed severe respiratory distress. Furthermore, all of the mitral valves were acutely inflamed, and fungal spores and hyphae were recovered from them. Areas of acute inflammation were also found in the medullas of the kidneys and within the lobes of the liver. The mean concentration of itraconazole in serum was 0.35 μg/ml.

DISCUSSION

Rabbits were the previous animal models used to study *Aspergillus* endocarditis (2, 13). Although voriconazole is effective against systemic aspergillosis in immunocompromised rabbits, it is not as active as would be predicted from its potency in vitro (8). This probably reflects the rapid metabolism of voriconazole in this species, and the same is also true in mice and rats (12). However, pharmacokinetic studies have shown that metabolism is much less pronounced in the guinea pig, in common with the situation in dogs and humans, and consistent with this, voriconazole is highly efficacious in guinea pig models of systemic and pulmonary aspergillosis (11, 12). Consequently, a model of *Aspergillus* endocarditis was developed in the guinea pig, drawing on the principles and techniques that have been established in the rabbit (2, 13). One practical difficulty is that the mitral valve in the guinea pig is small and difficult to sample. In this study, a simple swabbing technique was found to be a reproducible and reliable method for the assessment of infection. Infection was established in the heart 3 days postinoculation and 6 days postcatheterization. No attempt was made to determine the progress of infection in untreated animals after 3 days postinoculation because they were starting to lose weight rapidly and to be unwell and it was necessary to humanely kill them. In this respect, *A. fumigatus* endocarditis in the guinea pig is similar in severity to that in the rabbit (13) and to bacterial endocarditis in rabbits and rats (4).

In the prophylaxis studies with voriconazole, a dosage of 10 mg/kg i.p. b.i.d. given prior to and just after inoculation prevented *A. fumigatus* endocarditis in all but one animal. The reason that this animal remained infected is not clear, but it would be reasonable to expect complete protection if the animal were on extended prophylaxis. By contrast, itraconazole at 10 mg/kg p.o. i.p. failed to prevent *A. fumigatus* endocarditis in the guinea pig, although it has been reported to be partially protective in the rabbit (13). A more extensive series of experiments with higher doses would be necessary to evaluate the prophylactic potential of itraconazole in this model.

In common with the prophylaxis experiments, voriconazole was more active than itraconazole against established *Aspergillus* endocarditis, when assessed by the numbers of animals surviving, body weights, and cure rates. There was, however, a clear difference between animals that were treated p.o. and those that were treated by i.p. injection, with the latter losing weight rapidly. The animals that were treated with voriconazole i.p. fared much better than those receiving itraconazole, but there was considerable weight loss in animals treated with both antifungal agents. Therefore, the weight loss was due most likely to the i.p. administration of the antifungal agents. Voriconazole was also superior to itraconazole against established endocarditis when it was administered by the p.o. route. Thus, at the top dose of 10 mg/kg p.o. b.i.d., voriconazole produced 100% survivors and cures, whereas itraconazole failed to prolong survival, treat the infection, or prevent weight loss. Voriconazole is also more active than itraconazole against immune-normal and immunocompromised guinea pig models of systemic and pulmonary aspergillosis (11). Although both compounds have similar potencies against *Aspergillus* in vitro, voriconazole achieves higher and more prolonged concentrations in serum than does itraconazole, which is reflected in the superior efficacy of voriconazole over that of itraconazole against aspergillosis in guinea pigs. Furthermore, the concentration of voriconazole in serum (3.27 μg/ml) that was achieved in the present study after the administration of a dosage of 10 mg/kg p.o. b.i.d. is comparable to that observed in patients receiving 200 mg p.o. b.i.d. for the treatment of acute and chronic invasive aspergillosis (6, 7, 15). In conclusion, voriconazole is highly efficacious in the prevention and treatment of *Aspergillus* endocarditis in guinea pigs and is superior to itraconazole in these respects. Accordingly, voriconazole has the potential to prevent and treat *Aspergillus* endocarditis in humans, and clinical studies are warranted.

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