Comparison of the Efficacy of Posaconazole Delayed Release Tablets and Suspension in Pediatric Hematology/Oncology Patients

Erika N. Wass, PharmD; Elvin A. Hernandez, DrPH, MPH; and Caroline M. Sierra, PharmD

OBJECTIVES Posaconazole is effective in preventing invasive fungal infections in neutropenic pediatric patients. The oral suspension has challenges in administration and absorption that are theorized to be minimized with delayed release tablets. However, this has not been validated in the pediatric population. This study was conducted to compare the efficacy and safety of posaconazole suspension and delayed release tablets in pediatric hematology/oncology patients.

METHODS A retrospective chart review in pediatric hematology/oncology patients was conducted from February 2013 to February 2017. Data collected include patient demographic data; posaconazole formulation, dose, and serum concentrations; and adverse events.

RESULTS Sixty-five patients with 353 serum posaconazole concentrations were included; 51.6% of concentrations drawn while patients were receiving posaconazole suspension were therapeutic, whereas 62.5% of concentrations drawn while patients were receiving posaconazole delayed release tablets were therapeutic ($p = 0.035$). Serum concentrations drawn while taking acid suppression (histamine receptor antagonists or proton pump inhibitors) and posaconazole suspension were less likely to be therapeutic ($p < 0.0001$) compared with those taken while receiving delayed release tablets. Adverse event profiles were similar between both formulations.

CONCLUSIONS Delayed release tablets proved more effective in achieving therapeutic serum posaconazole concentrations than posaconazole suspension, with minimal difference in adverse events, in pediatric hematology/oncology patients.

ABBREVIATIONS AST, aspartate aminotransferase; ALT, alanine aminotransferase; CT, computed tomography; QTc, corrected QT interval

KEYWORDS antifungal; dosage formulation; immunosuppression; neoplasms; pediatrics; prophylaxis

J Pediatr Pharmacol Ther 2020;25(1):47–52

DOI: 10.5863/1551-6776-25.1.47

Introduction

Posaconazole is an azole antifungal with activity against *Aspergillus* spp and *Candida* spp that is effective at preventing invasive fungal infections in neutropenic pediatric patients.^{1–4} Pediatric patients commonly receive the oral suspension formulation until they are able to swallow solid dosage forms. However, there are many challenges with the suspension formulation, limiting its use. Posaconazole suspension demonstrates variable absorption and bioavailability, which requires divided dosing 3 to 4 times daily.^{4–7} Bioavailability of posaconazole suspension is dependent upon gastric acidity, gut motility, and coadministration with food.^{4–7} Coadministration with medications that reduce gastric acid production or increase gut motility has been shown to result in subtherapeutic serum concentrations, further limiting its use.^{4–7}

It has been postulated that posaconazole delayed release tablets are preferred to the oral suspension

because they have increased bioavailability and are less affected by the timing of administration and its relationship to food.^{6,7} These properties can be especially valuable for pediatric patients, but there are no published comparisons that have studied the therapeutic serum concentrations or clinical outcomes of the 2 dosage forms. Another advantage of the delayed release tablets is that they are dosed once daily, as compared with 3 times daily for the suspension.⁴

Posaconazole has been successfully used to prevent invasive fungal infections in adults. The National Comprehensive Cancer Network Guidelines for Prevention and Treatment of Cancer-Related Infections recommend using posaconazole to prevent fungal infections in patients with acute myeloid leukemia, myelodysplastic syndrome, allogeneic hematopoietic stem cell transplantation, and those with significant graft versus host disease, although this is not specific to pediatric patients.⁸ Liebenstein et al⁹ report that adults receiving the delayed release tablet of posaconazole achieved

higher drug serum concentrations at first measurement. Patients receiving the delayed release tablet were also significantly more likely to have a serum posaconazole concentration >700 ng/mL compared with the suspension. The Science et al¹⁰ publication from 2014, which has been endorsed by the Children's Oncology Group, recommends use of posaconazole in patients at least 13 years old: 1) with acute myeloid leukemia or myelodysplastic syndrome in centers where there is a high local incidence of mold infections; or 2) undergoing allo-hematopoietic stem cell transplant with acute or chronic graft versus host disease. However, this has not been extended to the general pediatric oncology population, nor has it been extended to children younger than 13 years of age.

Some studies showed higher serum posaconazole concentrations in patients receiving delayed release tablets, and 1 study showed an average subtherapeutic drug concentration in patients receiving the suspension.^{11–13} These studies did not show an increase in adverse events with the delayed release tablet compared with the suspension. One study found that elevated serum posaconazole concentrations are associated with grade 3 or 4 liver toxicity,¹⁴ which brings the safety of achieving high serum posaconazole concentrations into question. However, posaconazole concentrations that correlated with liver toxicity in this study were >1830 ng/mL, and other studies contradicted the findings of this study.^{15,16}

Although a small study in pediatric patients did show that posaconazole tablets were as effective as the suspension in preventing invasive fungal infections in patients receiving hematopoietic stem cell transplantation,¹⁷ this has not been validated in general pediatric oncology patients. A pharmacokinetic study of posaconazole suspension conducted in children with hematologic malignancy found that a dose of 100 mg 3 times daily resulted in a mean trough concentration of 850 ng/mL.¹⁸ A single-center study conducted in pediatric patients found that a median posaconazole suspension dose of 20 mg/kg/day achieved a posaconazole concentration of 700 ng/mL or greater.¹⁹ However, there are no studies comparing the suspension and delayed release tablets in pediatric patients.

The primary objective of this study is to compare the efficacy of the posaconazole suspension and delayed release tablets at attaining desired serum drug concentrations. The secondary objectives are to evaluate the impact of acid suppression on achieving therapeutic concentrations, to describe the rates of fungal infections in patients treated with each formulation, and to compare the rate of adverse events between posaconazole suspension and delayed release tablets.

Materials and Methods

Institutional review board approval was obtained for a retrospective, single-center analysis conducted in pe-

diatric patients at risk for invasive fungal infection who were receiving posaconazole for antifungal prophylaxis. Written informed consent was not required by the institutional review board. Inclusion criteria were patients who were 18 years of age or younger who had a serum posaconazole concentration drawn at Loma Linda University Children's Hospital between February 1, 2013, and February 1, 2017. Posaconazole concentrations were excluded from analysis if the patient was receiving concomitant antifungals when their posaconazole concentrations were drawn. Posaconazole concentrations were not included in analysis if they were measured after a treatment failure with posaconazole, or if they were drawn within 72 hours of posaconazole initiation. Treatment failure was defined by switching to another antifungal agent due to infection or patient intolerance of medication as documented in the medical records.

The medical records of these patients were reviewed, and the dates of birth and death, if applicable, were recorded. The patients' gender, weight, height, diagnosis, and primary medical service responsible for their care were also recorded. Posaconazole dose, frequency, formulation, start and end dates, and serum concentrations were also recorded. Posaconazole concentrations were considered therapeutic if they were ≥ 700 ng/mL. Data on concomitant acid suppression medication and antiemetics were noted, as well as addition of antifungal medications, agent(s) used, and date of antifungal initiation. Microbiology results for fungal cultures were collected. Data on liver function test results, QT and corrected QT (QTc) intervals, and adverse events (rash, nausea, vomiting) were also included.

Serum posaconazole concentrations were evaluated with each value being considered a unique event. Statistical analysis consisted of a univariable analysis for describing the demographic variables and corresponding data. Bivariate analysis of categorical variables was conducted with χ^2 and Fisher exact tests for differences between categories. Independent samples *t*-tests were used for continuous data. Multivariate analysis was conducted using logistic regression for predictive modeling of achieving therapeutic serum posaconazole concentrations regressed on various independent variables. For all statistical tests, the level of significance was set at $\alpha = 0.05$.

Results

A total of 605 serum posaconazole concentrations from 100 unique patients were collected. Of these, 252 concentrations from 35 patients were excluded. One hundred fifty-five concentrations were drawn while the patient was receiving concomitant antifungals, 79 were excluded due to insufficient data found in the medical records regarding posaconazole dosing, 7 because posaconazole was not being administered to the patient when the concentration was drawn, and 11 due to data collection error. After these exclusions,

Table 1. Demographic Information

Parameter	Value (n = 65)
Male (%)	32 (49)
Mean age at posaconazole concentration, yr	8.6
Mean weight at posaconazole concentration, kg	35.6
Patients on blood and marrow transplant service, n (%)	17 (26)
Patients on hematology/oncology service, n (%)	45 (74)
Underlying medical condition, n (%)	
Acute lymphoblastic leukemia	24 (37)
Acute myeloid leukemia	24 (37)
Solid organ tumor	10 (15)
Non malignant	4 (6)
Neuroblastoma	3 (5)

353 serum posaconazole concentrations drawn in 65 unique patients were available for analysis. Of these, 217 (61%) were drawn when the patient was taking posaconazole suspension. Demographic information for these patients can be found in Table 1.

Overall, 197 (56%) of these serum concentrations were therapeutic. Of the concentrations drawn while patients were taking posaconazole suspension, 112 (52%) concentrations were therapeutic of which 13 (12%) were concurrent with acid suppression. There were 105 concentrations that were subtherapeutic, of which 49 (47%) were concurrent with acid suppression. Conversely, 136 posaconazole concentrations were drawn while patients were taking delayed release posaconazole tablets, of which 85 (63%) were therapeutic and 51 (38%) were subtherapeutic. A χ^2 test showed a statistically significant difference between these values ($\chi^2 = 4.461$, $p = 0.035$). Patients receiving posaconazole suspension had a mean posaconazole concentration of 863 ng/mL, as compared with those receiving the delayed release tablets, who had a mean posaconazole concentration of 1044 ng/mL. An analysis of variance shows a statistically significant difference in mean serum concentrations between formulations ($F = 5.143$, $p < 0.024$), though both formulations resulted in a therapeutic mean posaconazole concentration.

Of the 65 unique patients in this study, 27 (42%) started additional antifungals during their course of posaconazole therapy (Table 2). Of these 27 patients, 21 were receiving suspension and 6 were receiving delayed release tablets at the time of additional antifungal initiation. The most recent serum posaconazole concentration for these patients was therapeutic in 10 of 21 (48%) patients receiving suspension and 1 of 6 (17%) patients receiving the delayed release tablets. This difference between posaconazole formulations in rates of additional antifungal initiation was not statistically significant ($p = 0.161$). Most patients were started on a single alternative antifungal therapy, but 3 patients (11%) were started on both micafungin and amphotericin B at the same time. Only 1 patient had a positive fungal microbiology result and grew *Rhodotorula mucilagi-*

nosa. The patient was taking the delayed release tablet, and the most recent serum posaconazole concentration drawn prior to the sputum culture that grew this organism was 696 ng/mL. This patient had a diagnosis of acute lymphoblastic leukemia and was deceased 16 days after the culture was drawn.

Multivariate regression showed that serum concentrations drawn in patients receiving concomitant posaconazole suspension and acid suppression were less likely to be therapeutic compared with those drawn in patients taking delayed release tablets ($\chi^2 = 13.070$, $p < 0.0001$). An analysis of variance revealed that patients taking acid suppression medications were statistically significantly more likely to have lower posaconazole concentrations compared with those who were not receiving acid suppression ($F = 18.940$, $p < 0.0001$). The most commonly used acid suppression medication was famotidine (111, 83%), followed by pantoprazole (19, 14%), lansoprazole (3, 2%), and esomeprazole (1, 1%). The majority of patients in this study were receiving antiemetics, most commonly ondansetron. Detailed information about posaconazole dosing can be found in Table 3.

Frequency of nausea, vomiting, and rash is documented in Table 4. All of these adverse reactions were attributed to the chemotherapy the patient was receiving, as documented in the medical charts. Rates of nausea and vomiting were similar between patients taking the suspension and the tablets ($p = 0.375$ and $p = 0.469$, respectively). Both formulations had similar increases in transaminases from baseline, though the differences between formulations were not significant (Table 5). Change in QTc from baseline after initiation

Table 2. Antifungal Therapies

Therapy Initiated	Frequency
Liposomal amphotericin b	17
Micafungin	9
Fluconazole	3
Voriconazole	1

Table 3. Posaconazole Dosing and Patient Information

	Therapeutic	Non-Therapeutic
Suspension (n = 217)		
Number of concentrations	112	105
Mean number of days on dose prior to concentrations	27	28
Age, mean $\pm$ SD	7.03 $\pm$ 4.3	5.4 $\pm$ 4.39
Weight, kg, mean $\pm$ SD	28.7 $\pm$ 17.86	20.98 $\pm$ 15.24
Dose, mg/kg/day, mean $\pm$ SD	13.26 $\pm$ 7.77	17.24 $\pm$ 13.85
Dose, mg/m ² /day, mean $\pm$ SD	333.8 $\pm$ 180.81	390 $\pm$ 326.77
Concurrent acid suppression, n	13	49
Delayed release tablets (n = 136)		
Number of levels	85	51
Number of days on dose prior to level, mean	39	21
Age, mean $\pm$ SD	11.9 $\pm$ 2.91	12.9 $\pm$ 3.95
Weight in kg, mean $\pm$ SD	54.25 $\pm$ 22.3	52 $\pm$ 19.91
Dose in mg/kg/day, mean $\pm$ SD	4.13 $\pm$ 2.95	4.4 $\pm$ 3.41
Dose in mg/m ² /day, mean $\pm$ SD	141.2 $\pm$ 81.15	139 $\pm$ 82.42
Concurrent acid suppression, n	36	34

of posaconazole was only measured in 15 patients (23%); a minimal change from baseline was noted in these patients.

Discussion

The results of this study show that a statistically significantly higher number of serum posaconazole concentrations was therapeutic by utilizing the delayed release tablets as compared with the suspension. Sixty-three percent of patients taking the tablets had posaconazole concentrations > 700 ng/mL, whereas only 52% of patients taking suspension had therapeutic concentrations. Despite having a lower average total daily weight-based dose, patients taking delayed release tablets were more frequently therapeutic and were less likely to require additional antifungal agents. The mean total daily weight-based dose for patients who had therapeutic concentrations and were taking posaconazole tablets was lower than that of those taking the suspension, supporting the increased bioavailability of the tablets over the suspension.^{6,7}

The average age of patients receiving the delayed release tablets is higher than that of the patients receiving

the suspension. This is not surprising because older patients are generally better able to swallow tablets than younger children, making this formulation more appropriate for them. Similarly, delayed release tablets do not allow for tailored weight-based dosing, which is essential in younger and smaller patients. Patients who were subtherapeutic on either formulation also had a higher total daily weight-based dose than therapeutic patients, which begs the question as to if some patients have other underlying factors contributing to their lower serum posaconazole concentrations. Possible factors contributing to this difference include patient adherence to medication, differences in drug absorption, or genetic factors. Liebenstein et al⁹ did show improved adherence when utilizing delayed release tablets in comparison with suspension. This may be due to increased likelihood of adherence with once-daily dosing as compared with 3 times daily administration.

Cost is another potential issue driving decision making in this patient population. The average wholesale price for a 30-day supply of the 200-mg delayed release tablet at the time of publication is approximately equal to a comparable dose utilizing the suspension. Therefore, the cost of either medication should not be

Table 4. Adverse Events

Reaction	Patients Reporting, Total n (%)	Patients Taking Delayed Release Tablets Reporting, n (%)	Patients Taking Suspension Reporting, n (%)
Nausea	20 (31)	12 (45)	8 (21)
Vomiting	17 (26)	9 (33)	8 (21)
Rash	3 (5)	0	3 (8)

Table 5. Transaminase Values

	AST	ALT
Percent change from baseline on suspension, mean $\pm$ SD	145 $\pm$ 163	220 $\pm$ 281
Percent change from baseline on tablet, mean $\pm$ SD	121 $\pm$ 113	196 $\pm$ 298
p value	0.133	0.464

ALT, alanine aminotransferase; AST, aspartate aminotransferase

a major factor in determining which formulation is appropriate for a patient.

At the study institution, micafungin and voriconazole are only orderable by infectious disease specialists, whereas amphotericin b is orderable by any provider. For indications other than acute myeloid leukemia and hematopoietic stem cell transplant, posaconazole must also be ordered by infectious disease specialists. This may explain why more patients received amphotericin b as compared with micafungin or voriconazole. Although a high frequency of patients switched to other antifungal agents was seen, it is important to note that only one of these patients had a documented fungal infection.

Patients receiving posaconazole suspension and acid suppression concomitantly were significantly more likely to have subtherapeutic posaconazole concentrations compared with those receiving delayed release tablets and acid suppression concomitantly. This supports previously published data by Vehreschild et al²⁰ stating that coadministration of posaconazole suspension with proton pump inhibitors decreases the patient's exposure to posaconazole.^{5,20} Although the aforementioned study only showed the effect of proton pump inhibitors, this study showed this effect in the study population, in which the large majority of the patients were receiving histamine receptor antagonists rather than proton pump inhibitors. The results of this study support that acid suppression in general, rather than just use of proton pump inhibitors, decreases the patient's exposure to posaconazole. The results of this study also support the postulated advantage of utilizing delayed release tablets over the suspension, as drug exposure may be less affected by acid suppression when utilizing delayed release tablets.

Assessment of QTc in patients receiving posaconazole is infrequently completed in patients receiving posaconazole. Given the small sample in which QTc was monitored, it is difficult to make conclusions about the effect of posaconazole formulation on QTc prolongation. Of those patients in which QTc was measured, adverse events were not frequently reported and were consistently attributed to chemotherapy or other drug therapy. However, the possibility that this was due to administration of posaconazole cannot be ruled out.

Hepatic function was consistently monitored in the patient population. This study supports data showing that posaconazole increases liver function enzymes. However, this study found that patients receiving the

delayed release tablet showed no difference in increase in liver function enzymes compared with those patients receiving the suspension. In sum, there was no difference in adverse events or liver function enzyme increase between patients receiving posaconazole suspension and the delayed release tablets.

There are several limitations to this study. First, it is a single-center retrospective study. Second, the doses included in this study were those documented by clinic staff, and any deviations from these as directed by the provider may not have been included. Similarly, although all serum posaconazole concentrations drawn are drawn as troughs, it was not possible to determine if the patients were adherent to refraining from taking the medication prior to the concentrations being drawn. This study also did not examine all concurrent QT prolonging agents the patient was receiving. Third, this study is limited by incomplete documentation because it was a retrospective study, and compliance data were not consistently obtained as most patients were treated both inpatient and outpatient. Fourth, posaconazole delayed release tablets were not available until November 2013, so not all patients in this study had the delayed release tablets available as a therapeutic option, and many patients are unable to swallow tablets due to their age. Lastly, this study was unable to thoroughly evaluate the rates of fungal infection in this patient population because patients may have been switched to an alternative antifungal without positive fungal culture results, computerized tomography (CT) findings, or other conclusive data.

In conclusion, these data show that patients receiving posaconazole delayed release tablets were more likely to achieve therapeutic serum posaconazole concentrations as compared with those receiving posaconazole suspensions. The impact of concomitant acid suppression appears to be more marked in those patients receiving the posaconazole suspension. Adverse events and hepatic function were similar in patients receiving both formulations. Although not all pediatric patients are candidates for receiving delayed release tablets, this study supports the use of delayed release tablets over the suspension as shown by increased frequency of therapeutic serum posaconazole concentrations and decreased impact of acid suppression on therapeutic serum concentrations without increasing adverse events. Further prospective study on this topic is warranted to validate these results.

ARTICLE INFORMATION

Affiliations Loma Linda University Medical Center (ENW), Loma Linda, CA; Marshall B. Ketchum College of Pharmacy (EAH), Fullerton, CA; Loma Linda University School of Pharmacy (CMS), Loma Linda, CA

Correspondence Caroline M. Sierra, PharmD; csierra@llu.edu

Disclosure Drs Hernandez and Sierra declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. Dr Wass received consulting fees from Coherus Biosciences. The authors had full access to all data and take responsibility for the integrity and accuracy of the data analysis.

Acknowledgments The authors acknowledge Derek Steele-Wass for his assistance in editing the manuscript.

Accepted April 18, 2019

Copyright Published by the Pediatric Pharmacy Association. All rights reserved.

For permissions, email: mhelms@pediatricpharmacy.org

REFERENCES

- Döring M, Müller C, Johann PD, et al. Analysis of posaconazole as oral antifungal prophylaxis in pediatric patients under 12 years of age following allogeneic stem cell transplantation. *BMC Infect Dis*. 2012;12:263.
- Döring M, Blume O, Haufe S, et al. Comparison of itraconazole, voriconazole, and posaconazole as oral antifungal prophylaxis in pediatric patients following allogeneic hematopoietic stem cell transplantation. *Eur J Clin Microbiol Infect Dis*. 2014;33(4):629–638.
- Döring M, Eikemeier M, Cabanillas Stanchi KM, et al. Antifungal prophylaxis with posaconazole vs. fluconazole or itraconazole in pediatric patients with neutropenia. *Eur J Clin Microbiol Infect Dis*. 2015;34(6):1189–1200.
- Posaconazole [package insert]. Ontario, Canada: Pathocon, Inc; 2006.
- Dekkers BGJ, Bakker M, van der Elst KCM, et al. Therapeutic drug monitoring of posaconazole: an update. *Curr Fungal Infect Rep*. 2016;10(2):51–61.
- Soysal A. Prevention of invasive fungal infections in immunocompromised patients: the role of delayed-release posaconazole. *Infect Drug Resist*. 2015;8:321–331.
- Kersemaekers WM, Dogterom P, Xu J, et al. Effect of a high-fat meal on the pharmacokinetics of 300-milligram posaconazole in a solid oral tablet formulation. *Antimicrob Agents Chemother*. 2015;59(6):3385–3389.
- NCCN Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections. Version 1.2019. October 25, 2018.
- Liebenstein TK, Widmer KM, Fallon MJ. Retrospective analysis of goal drug level attainment of posaconazole for invasive fungal infection prophylaxis in patients with acute myeloid leukemia pre- and post-switch to tablet formulation. *J Oncol Pharm Pract*. 2018;24(8):599–603.
- Science M, Robinson PD, MacDonald T, et al. Guideline for primary antifungal prophylaxis for pediatric patients with cancer or hematopoietic stem cell transplant recipients. *Pediatr Blood Cancer*. 2014;61(3):393–400.
- Belling M, Kanate AS, Shillingburg A, et al. Evaluation of serum posaconazole concentrations in patients with hematological malignancies receiving posaconazole suspension compared to the delayed-release tablet formulation. *Leuk Res Treatment*. 2017;2017:3460892.
- Cumpston A, Caddell R, Shillingburg A, et al. Superior serum concentrations with posaconazole delayed-release tablets compared to suspension formulation in hematological malignancies. *Antimicrob Agents Chemother*. 2015;59(8):4424–4428.
- Welch S, Pallotta A, Weber C, et al. Comparison of serum concentrations between different dosing strategies of posaconazole delayed-release tablet at a large academic medical centre. *Mycoses*. 2017;60(4):241–243.
- Tverdek FP, Heo ST, Aitken SL, et al. Real-life assessment of the safety and effectiveness of the new tablet and intravenous formulations of posaconazole in the prophylaxis of invasive fungal infections via analysis of 343 courses. *Antimicrob Agents Chemother*. 2017;61(8):e00188-17.
- Pettit NN, Miceli MH, Rivera CG, et al. Multicentre study of posaconazole delayed-release tablet serum level and association with hepatotoxicity and QTc prolongation. *J Antimicrob Agents Chemother*. 2017;72(8):2355–2358.
- Pham AN, Bubalo JS, Lewis JS 2nd. Posaconazole tablet formulation at 400 milligrams daily achieves desired minimum serum concentrations in adult patients with a hematologic malignancy or stem cell transplant. *Antimicrob Agents Chemother*. 2016;60(11):6945–6947.
- Döring M, Cabanillas Stanchi KM, Queudeville M, et al. Efficacy, safety and feasibility of antifungal prophylaxis with posaconazole tablet in paediatric patients after haematopoietic stem cell transplantation. *J Cancer Res Clin Oncol*. 2017;143(7):1281–1292.
- Vanstraelen K, Colita A, Bica AM, et al. Pharmacokinetics of posaconazole oral suspension in children dosed according to body surface area. *Pediatr Infect Dis J*. 2016;35(2):183–188.
- Bernardo VA, Cross SJ, Crews KR, et al. Posaconazole therapeutic drug monitoring in pediatric patients and young adults with cancer. *Ann Pharmacother*. 2013;47(7–8):976–983.
- Vehreschild JJ, Müller C, Farowski F, et al. Factors influencing the pharmacokinetics of prophylactic posaconazole oral suspension in patients with acute myeloid leukemia or myelodysplastic syndrome. *Eur J Clin Pharmacol*. 2012;68(6):987–995.