Interaction voriconazole and flucloxacillin, leading to decreased voriconazole blood levels

Introduction

Voriconazole (Vfend®), is a broad-spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above for *treatment of invasive aspergillosis*, *treatment of candidaemia in non-neutropenic patients, treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei) and treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.* Voriconazole should be administered primarily to patients with progressive, possibly life-threatening infections [1]. Voriconazole was granted marketing approval in 2002 [1].

Flucloxacillin (Floxapen®) is a semi-synthetic penicillin used for Gram-positive infections including those caused by S. aureus. Flucloxacillin was granted marketing approval in 1971 [2].

Reports

In 2017, the Netherlands Pharmacovigilance Centre Lareb received 11 reports of a possible interaction between voriconazole and flucloxacillin, leading to decreased voriconazole blood levels. All cases were based on a Dutch article by Muilwijk et al. [3] and sent through the Marketing Authorization Holder (MAH). The authors observed sub therapeutic plasma voriconazole concentrations, defined as 1 mg/liter (local practice at the time of presentation), during flucloxacillin treatment in 11 of these 20 patients. The median voriconazole trough concentration in these 11 patients during flucloxacillin treatment was 0.20 (interquartile range [IQR], 0.1 to 0.8, *n* 32) mg/, while the median voriconazole trough concentration in the other 9 patients was 1.45 (IQR, 1.0 to 4.9, *n* 15) mg/liter. Of the 11 patients with sub therapeutic trough concentrations, multiple voriconazole dose increases only led to a Signi ficant rise in plasm a drug concentrations in 2 patients; both reached toxic concentrations (11.5 and 7.1 mg/liter) after receiving extremely high doses (48 mg/kg/ day and 1,600 mg/day, respectively). The effect of flucloxacillin on plasma voriconazole concentrations was independent of the flucloxacillin dose administered. Of nine patients who started voriconazole before flucloxacillin, four showed a significant decrease in voriconazole concentrations directly at the first measurement after initiation of flucloxacillin therapy (median of 2 [IQR, 0.25 to 5.25] days). Of 11 patients who started flucloxacillin before voriconazole or started both at the same time, 7 showed subtherapeutic voriconazole concentrations. After discontinuation of flucloxacillin, the voriconazole concentrations increased substantially within a week in four of six patients. During voriconazole treatment, no drugs known to be CYP2C9, CYP2C19, or CYP3A4 inducers were used. The concentrations of other known CYP3A4 substrates (such as cyclosporine and tacrolimus) in plasma were not affected during flucloxacillin therapy [3].

Table 1. Reports of interactions between voriconazole and flucloxacillin

Patient	Sex	Age years	Source	Suspect drug dose indication for use	Concomitant medication	Suspected adverse drug reaction
1.	**NL-VIL-SR199, F, 12, Other health professional**			flucloxacilline injectie/infuus 12000mg per 1.0 Days for Staphylococcus aureus infection,voriconazol infuus 12mg/kg per 1.0 Days for Pulmonary aspergillosis,voriconazol infuus 12mg/kg per 1.0 Days for Pulmonary aspergillosis		1: Drug interaction,2: Drug level decreased
2.	**NL-VIL-SR200, F, 17, Other health professional**			flucloxacilline injectie/infuus 10400mg per 1.0 Days for Empiric treatment,voriconazol infuus for Pulmonary aspergillosis,voriconazol infuus for Pulmonary aspergillosis		1: Drug interaction,2: Drug level decreased
3.	**NL-VIL-SR201, M, 24, Other health professional**			flucloxacilline injectie/infuus 12000mg per 1.0 Days for Empiric treatment,voriconazol infuus for Empiric treatment		1: Drug interaction,2: Drug level decreased
4.	**NL-VIL-SR202, M, 25, Other health professional**			flucloxacilline injectie/infuus 4000mg per 1.0 Days for Empiric treatment,voriconazol infuus for Aspergillosis		1: Drug interaction,2: Drug level decreased

5.	**NL-VIL-SR203, M, 38, Other health professional**	flucloxacilline injectie/infuus for Staphylococcus aureus infection,voriconazol infuus for Pulmonary aspergillosis,voriconazol infuus for Pulmonary aspergillosis	1: Drug interaction,2: Drug level decreased
6.	**NL-VIL-SR204, M, 42, Other health professional**	flucloxacilline injectie/infuus 12000mg per 1.0 Days for Staphylococcus aureus infection,voriconazol infuus for Osteomyelitis,voriconazol infuus for Osteomyelitis	1: Drug interaction,2: Drug level decreased
7.	**NL-VIL-SR205, M, 55, Other health professional**	flucloxacilline injectie/infuus 6000mg per 1.0 Days for Staphylococcus aureus infection,voriconazol infuus for Pulmonary aspergillosis,voriconazol infuus for Pulmonary aspergillosis	1: Drug interaction,2: Drug level decreased
8.	**NL-VIL-SR206, F, 56, Other health professional**	flucloxacilline injectie/infuus 6000mg per 1.0 Days for Staphylococcus aureus infection,voriconazol infuus for Aspergilloma,voriconazol infuus for Aspergilloma	1: Drug interaction,2: Drug level decreased
9.	**NL-VIL-SR207, F, 65, Other health professional**	flucloxacilline injectie/infuus 12000mg per 1.0 Days for Staphylococcus aureus infection,voriconazol infuus for Cerebral aspergillosis,voriconazol infuus for Cerebral aspergillosis	1: Drug interaction,2: Drug level decreased
10.	**NL-VIL-SR208, M, 70, Other health professional**	flucloxacilline injectie/infuus 12000mg per 1.0 Days for Staphylococcus aureus infection,voriconazol infuus for Pulmonary aspergillosis,voriconazol infuus for Pulmonary aspergillosis	1: Drug interaction,2: Drug level decreased
11.	**NL-VIL-SR209, M, 71, Other health professional**	flucloxacilline injectie/infuus for Staphylococcus aureus infection,voriconazol infuus for Pulmonary aspergillosis,voriconazol infuus for Pulmonary aspergillosis	1: Drug interaction,2: Drug level decreased

The article by Muijlwijk et al [3]. Contains a table with more information on the cases, which is not present in the reports through the MAH.

TABLE 1 Patient characteristics

Gender[a]	Age (yr)	Underlying disease[b]	Voriconazole indication	Voriconazole administration route(s)[c]	Flucloxacillin indication	Flucloxacillin dose (mg/day)	Voriconazole started before flucloxacillin	Decrease in plasma voriconazole concn
M	3	ALL	Pulmonary aspergillosis	i.v., p.o.	Empirical therapy	770[d]	Yes	No
F	12	ALL	Pulmonary and cerebral aspergillosis	i.v., p.o.	*S. aureus* infection	12,000[e]	No	Yes
F	17	CF	Pulmonary aspergillosis	i.v.	Empirical therapy	10,400[f]	No	Yes
M	22	CGD	Pulmonary and cerebral aspergillosis	p.o.	*S. aureus* infection	12,000	No	No
F	23	Hyper-IgE syndrome	Empirical therapy	p.o.	Empirical therapy	6,000	Yes	No
M	24	CGD	Empirical therapy	p.o.	Empirical therapy	12,000	No	Yes
M	25	CF, lung transplantation	Invasive aspergillosis	i.v.	Empirical therapy	4,000	Yes	Yes
M	34	CGD	Empirical therapy	p.o.	Empirical therapy	12,000	No	No
M	38	Hodgkin lymphoma	Probable pulmonary aspergillosis	i.v., p.o.	*S. aureus* infection	6,000–8,000	No	Yes
M	42	COPD, heart transplantation	*Cryptococcus* osteomyelitis	p.o.	*S. aureus* infection	12,000	Yes	Yes
M	43	CGD	Possible pulmonary aspergillosis	p.o.	Prophylaxis	1,000	No	No
F	45	CMV infection	Candidemia, ocular *Candida glabrata* infection	p.o.	Empirical therapy	6,000	Yes	No
F	54	Influenza	Pulmonary aspergillosis	p.o.	Empirical therapy	4,000	Yes	No
M	55	AML	Possible pulmonary aspergillosis	i.v., p.o.	*S. aureus* infection	6,000	No	Yes
F	56	Destroyed lung, COPD	Aspergilloma	p.o.	*S. aureus* infection	6,000	Yes	Yes
F	65	None	Pulmonary and cerebral aspergillosis	i.v.	*S. aureus* infection	12,000	Yes	Yes
M	67	AML	Probable pulmonary aspergillosis	i.v., p.o.	*S. aureus* infection	6,000–12,000	No	No
F	68	AML	Prophylaxis	p.o.	Unknown	6,000	Yes	No
M	70	Influenza	Possible pulmonary aspergillosis	i.v.	*S. aureus* infection	12,000	No	Yes
M	71	ITP, DMII	Possible pulmonary aspergillosis	p.o.	*S. aureus* infection	6,000–12,000	No	Yes

[a]M, male; F, female.
[b]ALL, acute lymphatic leukemia; CGD, chronic granulomatous disease; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CMV, cytomegalovirus; AML, acute myeloid leukemia; ITP, idiopathic thrombocytopenic purpura; DMII, diabetes mellitus type II.
[c]i.v., intravenous; p.o., *per os*.
[d]Equivalent to 50 mg/kg/day.
[e]Equivalent to 226 mg/kg/day.
[f]Equivalent to 208 mg/kg/day.

Other Sources of information

SmPC

The SmPC of flucloxacillin in section '4.5. Interactions with other medicinal products and other forms of interaction 'mentions: Floxapen should not be administered simultaneously with bacteriostatic agents

such as tetracyclines, macrolides and chloramphenicol. Concomitant use with aminoglycosides is possible (synergistic action) [2].

For voriconazole, the following is mentioned: Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes. Unless otherwise specified, drug interaction studies have been performed in healthy adult male subjects using multiple dosing to steady state with oral voriconazole at 200 mg twice daily (BID). These results are relevant to other populations and routes of administration.

In the SmPC a large interaction table is shown, however an interaction with flucloxacillin is not explicitly mentioned [1].

Literature

In addition to the case series by Muilwijk et al. [3], another article by Kennedy et al. [4] a patient with a disseminated Scedosporium apiospermum infection who was treated with voriconazole, but was unable to achieve therapeutic levels, with a resultant clinical relapse while on flucloxacillin for a Staphylococcus aureus bloodstream infection. The patient's infection involved the skin, lungs and brain, and occurred against a background of recently commenced low-dose prednisolone for polymyalgia rheumatica. Skin biopsies isolated S. apiospermum, and the patient was started on voriconazole and terbinafine. Other medications included docusate with sennosides, magnesium and potassium supplements. After 8 days, the terbinafine was ceased due to liver derangement, which subsequently improved. Therapeutic voriconazole levels (1–5.5 mg/L) were achieved, with clinical improvement of the skin lesions. On Day 33 of treatment, the patient developed an MSSA bloodstream infection and was started on 2 g of flucloxacillin intravenously four times a day. No other changes were made to the patient's medications. The subsequent voriconazole levels fell to <1 mg/L and remained subtherapeutic despite intravenous or increasingly higher oral dosing, until the flucloxacillin was ceased.

Other databases

For the WHO database [5], a query was performed by the UMC on request on 13-12-2018, to detect cases with a possible interaction between voriconazole and flucloxacillin.
In addition to the Dutch cases, the following cases were identified:

Case 14176129, report date 20150811, United Kingdom, Serious Other, M, 48 y, Suspects Rifampicin, Voriconazole, concomitants Amphotericin b, Anidulafungin, Clindamycin, Flucloxacillin, Gentamicin, Piperacillin;Tazobactam. Indications Staphylococcal infection, Invasive bronchopulmonary aspergillosis, Serratia infection. Reported ADRs: Deterioration of liver function, Interaction between rifampicin and voriconazole, Decreased voriconazole plasma concentration. Rifampicin drug withdrawn. Voriconazole dose increased. Rechallenge performed, effect unknown.

Case 17115175, report date 20160711, Australia, non-serious, patient age and gender unknown, Interacting Voriconazole, Flucloxacillin (dose 2 gram), Terbinafine, concomitant Prednisolone, DOCUSATE-SENNOSIDE, Magnesium, Potassium. Reported ADRs: Drug level below therapeutic, Drug ineffective, Drug interaction, Liver disorder. Dechallenge info + outcome unknown.

Case 17660021, Reportdate 20160810, Australia, non-serious, M 80, Interacting Flucloxacillin (2g), Voriconazole. Concomitant Prednisolone, Terbinafine. Reported ADRs Drug interaction, Scedosporium infection, Antibiotic level below therapeutic. Dechallenge info + outcome unknown. This could be a possible duplicate with case 17115175.

Prescription data

Prescription data are shown in table 6, but of limited value since we do not know how many patients use the combination of both drugs in the Netherlands.

Table 2. Number of patients using voriconazole in the Netherlands [6].

Drug	2013	2014	2015	2016	2017
Voriconazole	959	1.051	997	990	1,014
Flucloxacillin	279,950	290,260	287,690	306,540	307,860

Mechanism

Voriconazole inhibits fungal cytochrome P450, impairing the synthesis of ergosterol, but is also metabolized by hepatic cytochrome P450 enzymes CYP2C19, CYP3A4 and CYP2C9, with 0.2% being excreted unchanged in the urine. Its bioavailability is estimated to be 0.90% in healthy adults. Monitoring of drug levels is recommended due to a low therapeutic index, a significant interindividual variation in the expression and function of CYP2C19 and CYP3A4, and the highly variable non-linear kinetics of voriconazole.
At high and/or multiple doses, flucloxacillin activates the pregnane X receptor (PXR) nuclear hormone receptor, with the potential to induce the expression of both CYP3A4 and CYP2C8/9 in a genotype-dependent manner. Kennedy et al. [4] propose that flucloxacillin-mediated PXR activation was the sub therapeutic voriconazole levels in the patient they describe.

Discussion and Conclusion

Kennedy et al. [4] recommend close surveillance when flucloxacillin is used concurrently with voriconazole based on the case they described. The KNMP already monitors this interaction in their medication monitoring system (see addendum 1) [7] and their interaction working group has published a warning about this interaction in the *Pharmaceutisch Weekblad* [8]. The interaction is currently not monitored by Stichting Health Base, but they plan to do this in the near future (confirmed through personal communication on 08-03-2019). The interaction is not explicitly described in the SmPC of voriconazole or flucloxacillin [1,2]. It should be further discussed of mentioning this interaction in the voriconazole SmPC would be a useful addition.

References

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8. Wensveen B, le Comte M. Flucloxacilline kan voriconazolspiegel verlagen tot subtherapeutisch niveau. Pharm Weekbld 31/32 2018.

This signal has been raised on March 25, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl

Addendum; KNMP interactie info

KNMP

Voriconazol + flucloxacilline 14095

Onderbouwend	Stof	Effect	Code
Muilwijk EW. Antimicrobial Agents and Chemotherapy 2017;61:e00915-7.	voriconazol + flucloxacilline	retrospectieve analyse van 20 patiënten op de combinatie, dit nav 3 patiënten met ondetecteerbare spiegels: - subtherapeutische voriconazolspiegel (<1 mg/l) bij 11 van 20 pat. - Cmin 0.2 mg/l bij deze 11 vs 1.45 mg/l bij de overige 9 pat.; dosisverhoging gaf bij 2 van 11 pat. significante stijging voriconazolspiegel; - 9 pat. gebruikten al voriconazol, bij 4 van 9 was de afname snel (2 dagen) na start flucloxacilline; - 11 pat. gebruikten al flucloxacilline, 7 van 11 hadden subtherapeutische voriconazolspiegel; na staken flucloxacilline stijging voriconazolspiegel binnen 1 week bij de meesten; effect onafhankelijk van de flucloxacillinedosering. Auteurs: combinatie leidt tot een niet te beheersen voriconazolspiegel bij de helft van de patiënten. Onduidelijk of andere penicillines met vergelijkbare structuur eenzelfde effect geven. Speculatie over mechanisme: via pregnaan X receptor (PXR). Dit zou zorgen voor upregulering CYP3A4.	2D
Kennedy B. Antimicrob Chemother 2015 doi:10.1093/jac/dkv069 Advance Access publication 15 March 2015. * Methicilline Sensitieve Staphylococcus aureus	voriconazol + flucloxacilline	↓voriconazolspiegel tot subtherapeutisch (<1 mg/l) na start flucloxacilline vanwege MSSA*-infectie bij patiënt met voorheen therapeutische voriconazol-spiegel (1-5.5 mg/l), nieuwe huidlaesies veroorzaakt door Scedosporium spp; geen effect verhogen voriconazoldosering, pas na staken flucloxacilline weer therapeutische spiegel Speculatie over mechanisme: via pregnaan X recep-tor (PXR). Dit zou zorgen voor upregulering CYP3A4.	1D

Overig	Stof	Effect
Radboud UMC. Casus niet gepubliceerd	voriconazol + flucloxacilline	Cmin voriconazol 3.1 mg/ml (binnen referentiegebied) 3 dagen na start voriconazol + flucloxacilline vanwege pneumonie veroorzaakt door aspergillus fumigatus. Dosering voriconazol gehandhaafd en ECMO (Extra Corporele Membraan Oxygenatie) gestart. Bij 2e spiegelmeting na 15 dagen voriconazol Cmin 0.1 mg/ml. Flucloxacilline was 7 dagen eerder gestopt.
Fungal Pharmacology http://www.fungalpharmacology.org/tool geraadpleegd 17-5-2018	voriconazol	Monitor for signs and symptoms of breakthrough infection when flucloxacillin is initiated/dose increased and assess voriconazole plasma concentrations to ensure antifungal efficacy.

Opmerkingen

WFG: vermijd combinatie, dit op basis van de volgende overwegingen (vermelden bij advies):
- effect treedt (zeer) snel in en verhogen van de voriconazoldosering heeft in de meeste gevallen onvoldoende effect.
- bij ernstig zieke patiënten kan de instelling op voriconazol te veel tijd kosten waardoor te laat een therapeutische spiegel wordt bereikt.
- het is niet duidelijk bij welke patiënten het effect gaat optreden, mogelijk speelt PXR-polymorfisme een rol.

SPC VFend, Floxapen: noemen de interactie niet.
Stockley: niet vermeld.

GIC: andere penicillines niet gekoppeld, het is onduidelijk of andere penicillines met een vergelijkbare structuur eenzelfde effect geven. Geen literatuur gevonden.

1. 14095 VORICONAZOL + FLUCLOXACILLINE

Apothekertekst

Therapiefalen kan optreden door een verminderde werking van voriconazol. De voriconazolspiegel daalt tot subtherapeutisch niveau door flucloxacilline.

1. vermijd de combinatie

Het effect treedt (zeer) snel in en verhogen van de voriconazoldosering heeft in de meeste gevallen onvoldoende effect.
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Balietekst

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Voorschrijvertekst

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Ziekenhuistekst

Therapiefalen kan optreden door een verminderde werking van voriconazol. De voriconazolspiegel daalt tot subtherapeutisch niveau door flucloxacilline.

1. vermijd de combinatie

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Bij ernstig zieke patiënten kan de instelling op voriconazol te veel tijd kosten waardoor te laat een therapeutische spiegel wordt bereikt.

Het is niet duidelijk bij welke patiënten het effect gaat optreden, mogelijk speelt PXR-polymorfisme een rol.

Achtergrondinformatie

Mechanisme:
Niet geheel duidelijk. Voriconazol is substraat voor CYP2C19 (hoofdroute), CYP2C9 en CYP3A4. Flucloxacilline activeert de nucleaire pregnaan X receptor (PXR). Dit eiwit induceert de expressie van CYP3A4 en CYP2C9. Mogelijk wordt het metabolisme van voriconazol via deze CYP-enzymen geïnduceerd.

Klinische gevolgen:
Subtherapeutische voriconazolspiegel is gemeld bij 11 van 20 patiënten die tevens flucloxacilline gebruikten. Bij patiënten op voriconazol daalde de voriconazolspiegel gemiddeld 2 dagen na start flucloxacilline.
Er is een casus van nieuwe huidlaesies en subtherapeutische voriconazolspiegel bij een patiënt met Scedosporium-infectie na toevoegen flucloxacilline. Verhogen van de voriconazoldosering had geen effect, pas na staken flucloxacilline werd weer een therapeutische voriconazolspiegel bereikt.

Literatuur

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