Drug-drug interaction: decreased posaconazole trough concentrations during concomitant flucloxacillin treatment

Wortman, J.M.; Leegwater, E.; Lammeren-Venema, D. van; Nieuwkoop, C. van; Sobels, A.; Wilms, E.B.

J Antimicrob Chemother 2023; **78**: 1471–1475
https://doi.org/10.1093/jac/dkad107 Advance Access publication 11 April 2023

Journal of Antimicrobial Chemotherapy

Drug–drug interaction: decreased posaconazole trough concentrations during concomitant flucloxacillin treatment

Julia M. Wortman[1,2]*, Emiel Leegwater [1,2], Daniëlle Van Lammeren-Venema[3], Cees Van Nieuwkoop [4], Annemieke Sobels[1] and Erik B. Wilms [1,2]

[1]*Department of Hospital Pharmacy, Haga Teaching Hospital, Els Borst-Eilersplein 275, 2545 AA The Hague, The Netherlands;* [2]*Laboratory of clinical pharmacy and toxicology, Apotheek Haagse Ziekenhuizen, Charlotte Jacobslaan 70, 2545 AB The Hague, The Netherlands;* [3]*Department of Hematology, Haga Teaching Hospital, Els Borst-Eilersplein 275, 2545 AA The Hague, The Netherlands;* [4]*Department of Internal Medicine, Haga Teaching Hospital, Els Borst-Eilersplein 275, 2545 AA The Hague, The Netherlands*

*Corresponding author. E-mail: j.wortman@hagaziekenhuis.nl

Received 11 November 2022; accepted 22 March 2023

Background and objectives: Posaconazole is used as prophylaxis of invasive fungal disease in immune-compromised haematological patients with prolonged neutropenia after intensive chemotherapy. During routine therapeutic drug monitoring of posaconazole, we repeatedly observed low posaconazole serum concentrations in patients that were concomitantly treated with flucloxacillin. A possible interaction between flucloxacillin and posaconazole was explored in this case series.

Patients and methods: Posaconazole trough serum concentrations during and before/after flucloxacillin treatment were collected from 10 patients.

Results: With a median concentration of 0.5 mg/L (IQR 0.3–0.6), the posaconazole trough serum concentration decreased by 47% during flucloxacillin treatment compared with the concentration before/after flucloxacillin treatment (0.9 mg/L, IQR 0.6–1.3). As a result, the posaconazole target trough concentration of ≥0.7 mg/L was only achieved in five out of nine patients during flucloxacillin treatment.

Conclusions: Careful monitoring of posaconazole serum trough concentrations is recommended when concomitant use of flucloxacillin cannot be avoided.

Introduction

Invasive fungal disease (IFD) is one of the primary causes of morbidity and mortality in immune-compromised haematological patients with prolonged neutropenia after intensive chemotherapy.[1] Therefore, antifungal prophylaxis is warranted. Posaconazole is a triazole antifungal used as prophylaxis for IFD in this patient group. Therapeutic drug monitoring (TDM) of posaconazole is recommended considering the large intra- and inter-individual variability in posaconazole exposure and the relationship between a minimal trough serum concentration of 0.7 mg/L and efficacy.[2,3]

Posaconazole follows linear kinetics in therapeutic doses (single dosing of up to 400 mg and multiple dosing of up to 300 mg). Therefore, dose elevations normally lead to a linear increase of posaconazole trough concentration.[2,4,5] Recently, we observed remarkably low posaconazole serum concentrations in multiple patients during routine TDM. Posaconazole concentrations remained below the target concentration of ≥0.7 mg/L despite dose elevations and switch to IV administration. The cause for these low concentrations could not be ascribed to factors that are known to reduce posaconazole concentrations, such as certain co-medication and mucositis.[2] Notably, these patients were treated with flucloxacillin at the moment the low concentrations were measured. Recently, Verfaillie *et al.*[6] described a similar case in which a decreased posaconazole serum concentration was observed in a patient during flucloxacillin treatment.

To explore the frequency and characteristics of this potential interaction, we performed a retrospective study investigating the effect of flucloxacillin on posaconazole trough concentration in patients with haematological malignancies.

Patients and methods

Patient selection

Patients from the Haga Teaching Hospital, The Netherlands, with at least one posaconazole trough concentration measurement during flucloxacillin treatment or within 7 days after flucloxacillin treatment between January 2017 and August 2022 were selected. Posaconazole concentrations other than trough concentrations were excluded. We obtained a waiver for the Medical Research Involving Human Subjects Act from the

Medical Ethical Review Committee (METC) of Leiden Den Haag Delft (METC-number N22.063). No informed consent from the included patients was needed.

Data collection

Data about sex, age, indication, dose, drug formulation and route of administration of posaconazole and flucloxacillin, posaconazole serum concentrations, occurrence of mucositis and co-medication with inducers of cytochrome P450 (CYP) enzyme CYP3A4, UDP-glucuronosyltransferase (UGT) enzyme UGT1A4 or the transporter P-glycoprotein (P-gp) were collected from the hospital's electronic information system.

Data analysis

To explore the effect of flucloxacillin on posaconazole concentration, the median concentrations were compared between two primary comparison groups consisting of all concentrations measured during flucloxacillin treatment and all concentrations measured before/after flucloxacillin treatment. Concentrations were normalized for the posaconazole dose by dividing the concentration by the dose followed by multiplication with the standard daily dose of 300 mg.

We expected a delay in normalization of posaconazole concentrations after discontinuation of flucloxacillin treatment due to the time needed for posaconazole to reach steady state and the possibility of a prolonged effect of flucloxacillin. Therefore, two secondary comparison groups were formed by placing posaconazole concentrations measured within 1 week after flucloxacillin treatment into the 'during flucloxacillin treatment' group mentioned above. Other analyses included evaluation of the inter-individual difference in effect of flucloxacillin on posaconazole concentrations for patients with at least one concentration measured during and before/after flucloxacillin treatment, and evaluation of the effect of route of administration (oral versus IV) of flucloxacillin on posaconazole concentration.

Results

In total, 11 patients met the inclusion criteria. After data validation, one patient was excluded due to incorrectness of posaconazole trough concentration measurements. In the remaining 10 patients, a total of 47 posaconazole concentrations were available for descriptive analyses (Table 1). For two patients, only concentrations during flucloxacillin treatment were available. Concentration measurements of Patient 10 were not included in the primary comparison groups as for this patient no posaconazole concentrations were measured during flucloxacillin treatment. All patients were treated prophylactically with modified released posaconazole tablets, starting with a loading dose of 300 mg twice daily followed by a maintenance dose of 300 mg once daily. In six patients, posaconazole dose and/or route of administration was adjusted based on measured concentrations. Treatment with flucloxacillin varied in dose and route of administration depending on indication, but the dose remained unchanged for each patient. The occurrence of mucositis was equally distributed between the two primary comparison groups (Table S1, available as Supplementary data at *JAC* Online). Posaconazole concentrations during IV and oral posaconazole treatment were also equally distributed between the two primary groups (Table S2). During posaconazole treatment, none of the patients were treated with inducers or inhibitors of CYP3A4, UGT1A4 or P-gp.

Table 1. Patient characteristics

Patient	Sex	Age (years)	Underlying disease	Posaconazole treatment		Flucloxacillin treatment		Number of posaconazole trough concentration measurements		
				Indication	Total daily dose and route of administration	Indication	Total daily dose and route of administration	Before flucloxacillin treatment	During flucloxacillin treatment	After flucloxacillin treatment
1	Male	33	AML	Prophylaxis	300 mg PO	Cellulitis leg	4000 mg IV	0	1	1
2	Male	66	MDS	Prophylaxis	300–400 mg PO	*S. aureus* wound infection	4000 mg IV	0	2	6
3	Male	61	ALL	Prophylaxis	300–600 mg PO	*S. aureus* bacteraemia	12000 mg IV	0	5	0
4	Female	44	AML	Prophylaxis	300–600 mg PO/IV	*S. aureus* bacteraemia	12000 mg IV	0	5	2
5	Female	34	AML	Prophylaxis	300 mg PO	Furuncle pubic area	4000 mg IV	0	1	3
6	Male	73	AML	Prophylaxis	300 mg PO	*S. aureus* bacteraemia	10000 mg IV	1	1	0
7	Male	45	AML	Prophylaxis	300–600 mg PO	Phlebitis arm	4000 mg PO	0	1	5
8	Female	75	Lymphoblastic lymphoma	Prophylaxis	300 mg PO	Phlebitis arm	4000 mg PO	0	1	0
9	Female	67	AML	Prophylaxis	300–400 mg PO/IV	Phlebitis hand	2000 mg PO	0	1	4
10	Female	47	AML	Prophylaxis	200–400 mg PO	Ecthyma face	4000 mg PO	0	0	7

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; PO, oral administration.

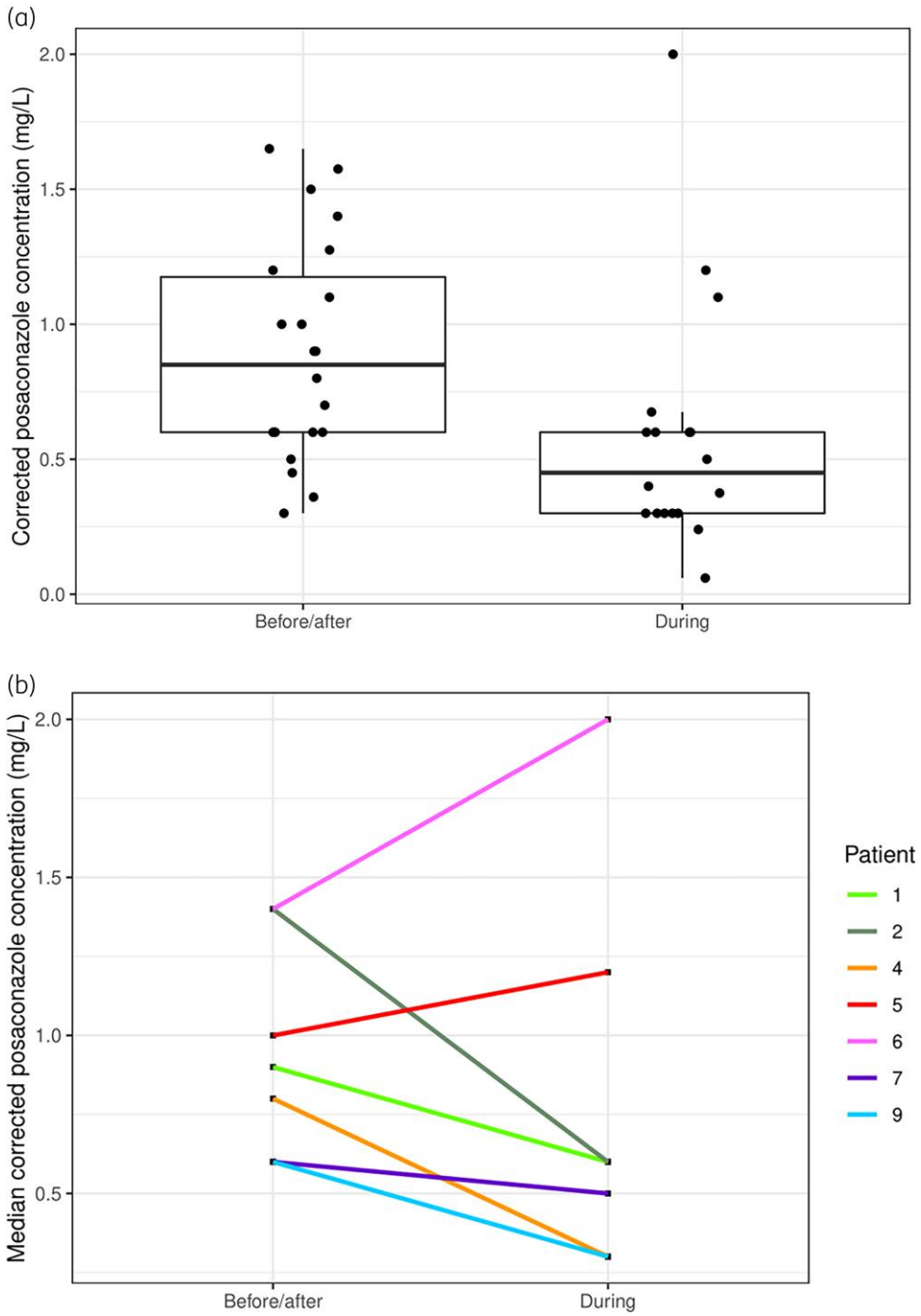

Figure 1. Dose-corrected posaconazole trough concentration before/after versus during flucloxacillin treatment. (a) Boxplots of the two primary comparison groups (dose-corrected posaconazole trough concentrations measured before/after flucloxacillin treatment versus during flucloxacillin treatment). Posaconazole trough concentrations of Patients 1–9 are included in the boxplots. The *y*-axis shows the dose-corrected posaconazole trough concentration in mg/L. The *x*-axis shows the moment of posaconazole concentration measurement in relation to flucloxacillin treatment. (b) Individual median dose-corrected posaconazole trough concentration of the two primary comparison groups (before/after flucloxacillin treatment and during flucloxacillin treatment) for seven patients. On the *y*-axis the median dose-corrected posaconazole trough concentration is shown in mg/L. The *x*-axis shows the moment of posaconazole concentration measurement in relation to flucloxacillin treatment. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Comparison of the posaconazole concentrations in the two primary groups showed that the median dose-corrected posaconazole concentration during concomitant flucloxacillin treatment was 47% lower than before/after flucloxacillin

treatment: 0.5 mg/L (IQR 0.3–0.6) and 0.9 mg/L (IQR 0.6–1.3), respectively (Figure 1a and Table S3). A difference of 62% was observed between the two secondary groups: the median dose-corrected posaconazole concentrations during/within 1 week after concomitant flucloxacillin treatment and before/at least 1 week after flucloxacillin treatment were 0.4 mg/L (IQR 0.3–0.6) and 1.1 mg/L (IQR 0.6–1.3), respectively (Figure S1a and Table S3).

Further exploration of the two primary groups revealed that before/after flucloxacillin treatment target concentrations were achieved in 73% of the measurements. During concomitant flucloxacillin treatment, target concentrations were reached in 28% of the measurements. Similarly, only five out of nine patients eventually reached the target concentration when concomitantly treated with flucloxacillin while all patients reached the target concentration when not concomitantly treated with flucloxacillin (Table S3). Dose adjustments needed to reach the target concentration during flucloxacillin treatment varied among patients; whereas for Patient 2 a dose elevation to 400 mg oral led to a trough concentration ≥0.7 mg/L, Patients 4 and 7 needed dose elevations to 300 mg IV flucloxacillin twice daily.

For seven patients, posaconazole concentrations both during and before/after concomitant flucloxacillin treatment were available. In five patients, the median concentration decreased during flucloxacillin treatment compared with before/after flucloxacillin treatment. In two patients, an increase was observed during flucloxacillin treatment (Figure 1b).

In the secondary comparison group consisting of 23 posaconazole concentrations measured during/within 1 week after concomitant flucloxacillin treatment, none of the seven concentrations reached the target concentration when flucloxacillin was orally administered. When flucloxacillin was administered IV, 6 out of 16 (38%) concentrations reached the target.

Discussion

In this case series we demonstrated a substantial decrease in posaconazole trough concentration during flucloxacillin treatment in haematology patients. As a result, only five out of nine patients reached the posaconazole target trough concentration of ≥0.7 mg/L when concomitantly treated with flucloxacillin, despite increasing the posaconazole dose. This observation is an important warning for the simultaneous use of posaconazole and flucloxacillin in patients that are dependent on adequate IFD prophylaxis or treatment.

To date, the exact mechanism of the observed interaction between posaconazole and flucloxacillin is unknown. One possible explanation is an increased metabolism and/or elimination of posaconazole by flucloxacillin. An *in vitro* study demonstrated that flucloxacillin activates the nuclear hormone pregnane X receptor (PXR).[7] PXR induces the expression of P-gp and several enzymes including CYP and UGT.[8,9] As posaconazole is both inhibitor and substrate for P-gp and for 17% metabolized predominantly by UGT1A4-glucoronidation, activation of PXR by flucloxacillin may be the cause of decreased posaconazole concentration.[10–12] Several studies and case reports have suggested this theory as the mechanism for the interaction between flucloxacillin and various P-gp, CYP and UGT substrates including the other triazole antifungal voriconazole.[7,13–17] Besides for flucloxacillin, similar observations were described for other isoxazolyl penicillins, which implies this interaction may be a class effect.[13,18] An alternative explanation for the interaction is alteration of protein binding of posaconazole by concomitant flucloxacillin use as a result of binding competition, potentially leading to more unbound posaconazole available for metabolism and elimination.[2,19,20] Other possible explanations include decreased absorption and/or increased elimination as a result of altered mRNA stability of P-gp and/or UGT1A4 by flucloxacillin, or presence of diarrhoea as a side effect of flucloxacillin. More research is necessary in order to understand the exact mechanism of the interaction between posaconazole and flucloxacillin and other isoxazolyl penicillins.

Further exploration of the interaction revealed that in the secondary comparison group consisting of posaconazole concentrations measured during/within 1 week after flucloxacillin treatment, none of the concentrations reached the target concentration when flucloxacillin was orally administered. IV administration of flucloxacillin resulted in 38% of the concentrations reaching the target concentration in the same comparison group. This could imply a potential local effect of flucloxacillin on posaconazole absorption. Moreover, in two of the seven patients where posaconazole concentrations before/after and during flucloxacillin treatment were individually evaluated, no decrease in concentration was observed during flucloxacillin treatment. This could be an indication for a potential role of polymorphisms of genes involved in transporters and metabolizing enzymes, which needs further exploration. A similarity in these two patients was that all posaconazole concentrations were above the target trough concentration. Also interesting is that a larger reduction in posaconazole concentration as a result of concomitant flucloxacillin treatment was observed in the secondary comparison groups compared with the primary groups. This observation suggests a prolonged effect of flucloxacillin on posaconazole concentration, which is plausible when UGT and/or P-gp induction is assumed to be the mechanism behind this interaction. The time to maximal effect of induction and de-induction of UGT and P-gp depends on factors including the elimination half-life of flucloxacillin and posaconazole and the time required to upregulate and degrade UGT enzymes and P-gp.[21] This means that the start and termination of the effect of flucloxacillin on posaconazole concentration would be delayed.

This study has some limitations. First, only a limited number of patients were included, making our results susceptible to bias and making it difficult to account for all variables that might influence posaconazole exposure. Second, due to the retrospective character of this study, for none of the patients posaconazole concentrations were available that were measured at pre-set timepoints before, during and after flucloxacillin treatment. Despite these limitations, in this case series a clinically relevant interaction between posaconazole and flucloxacillin is brought to the attention.

In conclusion, we demonstrated that concomitant use of flucloxacillin resulted in low and, most of the time, inadequate posaconazole trough concentrations in haematology patients. Therefore, we recommend avoiding the combination of posaconazole and flucloxacillin when possible or otherwise careful monitoring of posaconazole concentrations and signs of fungal infections (i.e. monitoring of galactomannan concentration) is advised. Further pharmacological research is warranted to

elucidate the mechanism and magnitude of the interaction between posaconazole and isoxazolyl penicillins.

Funding

This study was carried out as part of our routine work.

Transparency declarations

We declare no conflicts of interest.

Supplementary data

Figure S1 and Tables S1 to S3 are available as Supplementary data at *JAC* Online.

References

1 Ruhnke M, Behre G, Buchheidt D *et al*. Diagnosis of invasive fungal diseases in haematology and oncology: 2018 update of the recommendations of the Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO). *Mycoses* 2018; **61**: 796–813. https://doi.org/10.1111/myc.12838

2 Chen L, Krekels EHJ, Verweij PE *et al*. Pharmacokinetics and pharmacodynamics of posaconazole. *Drugs* 2020; **80**: 671–95. https://doi.org/10.1007/s40265-020-01306-y

3 Dolton MJ, Ray JE, Marriott D *et al*. Posaconazole exposure-response relationship: evaluating the utility of therapeutic drug monitoring. *Antimicrob Agents Chemother* 2012; **56**: 2806–13. https://doi.org/10.1128/AAC.05900-11

4 Krishna G, Ma L, Martinho M *et al*. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers. *J Antimicrob Chemother* 2012; **67**: 2725–30. https://doi.org/10.1093/jac/dks268

5 Accord. Posaconazole Accord 100 mg gastro-resistant tablets. https://www.ema.europa.eu/en/documents/product-information/posaconazole-accord-epar-product-information_en.pdf.

6 Verfaillie S, Godinas L, Spriet I *et al*. Interaction between posaconazole and flucloxacillin in a lung transplant patient: decrease in plasma exposure of posaconazole and possible undertreatment of invasive aspergillosis: case report. *BMC Pulm Med* 2022; **22**: 110. https://doi.org/10.1186/s12890-022-01904-4

7 Huwyler J, Wright MB, Gutmann H *et al*. Induction of cytochrome P450 3A4 and P-glycoprotein by the isoxazolyl-penicillin antibiotic flucloxacillin. *Curr Drug Metab* 2006; **7**: 119–26. https://doi.org/10.2174/138920006775541534

8 Gardner-Stephen D, Heydel JM, Goyal A *et al*. Human PXR variants and their differential effects on the regulation of human UDP-glucuronosyltransferase gene expression. *Drug Metab Dispos* 2004; **32**: 340–7. https://doi.org/10.1124/dmd.32.3.340

9 Synold TW, Dussault I, Forman BM. The orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux. *Nat Med* 2001; **7**: 584–90. https://doi.org/10.1038/87912

10 Krieter P, Flannery B, Musick T *et al*. Disposition of posaconazole following single-dose oral administration in healthy subjects. *Antimicrob Agents Chemother* 2004; **48**: 3543–51. https://doi.org/10.1128/AAC.48.9.3543-3551.2004

11 Ghosal A, Hapangama N, Yuan Y *et al*. Identification of human UDP-glucuronosyltransferase enzyme(s) responsible for the glucuronidation of posaconazole (Noxafil). *Drug Metab Dispos* 2004; **32**: 267–71. https://doi.org/10.1124/dmd.32.2.267

12 Lempers VJ, van den Heuvel JJ, Russel FG *et al*. Inhibitory potential of antifungal drugs on ATP-binding cassette transporters P-glycoprotein, MRP1 to MRP5, BCRP, and BSEP. *Antimicrob Agents Chemother* 2016; **60**: 3372–9. https://doi.org/10.1128/AAC.02931-15

13 Chaudhuri A, Wade SL. Flucloxacillin-warfarin interaction: an underappreciated phenomenon. *Intern Med J* 2018; **48**: 860–3. https://doi.org/10.1111/imj.13944

14 Comuth WJ, Comuth JA, Hauer RN *et al*. Interaction of flucloxacillin and quinidine. *Eur J Clin Pharmacol* 2012; **68**: 891–3. https://doi.org/10.1007/s00228-011-1179-0

15 Van Daele R, Wauters J, De Cock P *et al*. Concomitant treatment with voriconazole and flucloxacillin: a combination to avoid. *Antibiotics (Basel)* 2021; **10**: 1112. https://doi.org/10.3390/antibiotics10091112

16 Veenhof H, Schouw HM, Besouw MTP *et al*. Flucloxacillin decreases tacrolimus blood trough levels: a single-center retrospective cohort study. *Eur J Clin Pharmacol* 2020; **76**: 1667–73. https://doi.org/10.1007/s00228-020-02968-z

17 Muilwijk EW, Dekkers BGJ, Henriet SSV *et al*. Flucloxacillin results in suboptimal plasma voriconazole concentrations. *Antimicrob Agents Chemother* 2017; **61**: e00915-17. https://doi.org/10.1128/AAC.00915-17

18 Pottegård A, Henriksen DP, Madsen KG *et al*. Change in international normalized ratio among patients treated with dicloxacillin and vitamin K antagonists. *JAMA* 2015; **314**: 296–7. https://doi.org/10.1001/jama.2015.6669

19 Røder BL, Frimodt-Møller N, Espersen F *et al*. Dicloxacillin and flucloxacillin: pharmacokinetics, protein binding and serum bactericidal titers in healthy subjects after oral administration. *Infection* 1995; **23**: 107–12. https://doi.org/10.1007/BF01833876

20 McElnay JC, D'Arcy PF. Protein binding displacement interactions and their clinical importance. *Drugs* 1983; **25**: 495–513. https://doi.org/10.2165/00003495-198325050-00003

21 Brodie MJ, Mintzer S, Pack AM *et al*. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia* 2013; **54**: 11–27. https://doi.org/10.1111/j.1528-1167.2012.03671.x