**Supplemental Digital Content 1:** **GRADE evidence profiles and summary of findings**

Participants: Adults using voriconazole

Intervention: Voriconazole with therapeutic drug monitoring

Control: Voriconazole without therapeutic drug monitoring

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Treatment response**1 RCT | None | None | None | Seriousa,b | Not detected | None | 30/37 | 20/34 | RR 1.38 [1.00, 1.90] | Moderate |
| **Hepatotoxicity**1 RCT | Seriousc | None | None | Seriousa,b | Not detected | None | 15/55 | 14/53 | RR 1.03 [0.55, 1.93] | Low |
| **Nervous system/psychiatric disorders**1 RCT | Seriousc | None | None | Seriousa,b | Not detected | None | 8/55 | 7/53 | RR 1.10 [0.43, 2.82] | Low |

a Wide confidence; b Insufficient sample size; c Delayed sampling time that failed to prevent adverse events

RCT: Randomized controlled trial; RR: Relative risk

Reference: Chen K, Li G, Zhai S. Efficacy and safety of therapeutic drug monitoring of voriconazole: a systematic review. *Chin J Clin Pharmacol*. 2017;33:80-83.

Participants: Pediatrics using voriconazole

Intervention: Voriconazole with therapeutic drug monitoring

Control: Voriconazole without therapeutic drug monitoring

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Treatment response**1 cohort study | None | None | None | Seriousa,b | Not detected | None | 9/20 | 2/14 | RR 3.15 [0.80, 12.42] | Very low |
| **Hepatotoxicity**1 cohort study | Seriousc | None | None | Seriousa,b | Not detected | None | 13/31 | 7/30 | RR 1.80 [0.83, 3.88] | Very low |
| **Nervous system/psychiatric disorders**1 cohort study | Seriousc | None | None | Seriousa,b | Not detected | None | 4/31 | 1/30 | RR 3.87 [0.46, 32.67] | Very low |
| **Visual disturbance**1 cohort study | Seriousc | None | None | Seriousa,b | Not detected | None | 4/31 | 3/30 | RR 1.29 [0.31, 5.29] | Very low |

a Wide confidence; b Insufficient sample size; c Delayed sampling time that failed to prevent adverse events

RR: Relative risk

Reference: Chen K, Li G, Zhai S. Efficacy and safety of therapeutic drug monitoring of voriconazole: a systematic review. *Chin J Clin Pharmacol*. 2017;33:80-83.

Participants: Patients using voriconazole

Intervention: Patients aged 2-12

Control: Patients aged >12

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Treatment response**3 cohort studies | Moderatea | None | None | Seriousb,c | Not detected | None | 20/34 | 42/57 | RR 0.86 [0.57, 1.30] | Very low |
| **Hepatotoxicity**2 cohort studies | Moderatea | None | None | Seriousb,c | Not detected | None | 3/28 | 1/20 | RR 1.41 [0.25, 7.87]  | Very low |
| **Nervous system/psychiatric disorders**2 cohort studies | None | None | Moderated | Seriousb,c | Not detected | None | 0/23 | 3/32 | RR 0.32 [0.04, 2.52] | Very low |
| **Visual disturbance**1 cohort study | None | None | None | Seriousb,c | Not detected | None | 5/15 | 4/6 | RR 0.50 [0.20, 1.25] | Very low |

a Some studies not reporting main cofounding factors; b Wide confidence interval; c Insufficient sample size; d Not Asians

RR: Relative risk

Reference: Guo Y, An L, Chen K, et al. Difference of efficacy, safety and pharmacokinetics of voriconazole in different age: a systematic review. *Chin J Clin Pharmacol*. 2016;32:261-263.

Participants: Patients using voriconazole

Intervention: Patients aged 2-12

Control: Patients aged <2

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | MD or RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Trough concentration**2 cohort studies | Moderatea | None | Moderateb | Seriousc,d | Not detected | None | 26 | 7 | MD -0.77 [-3.59, 2.05] mg·L-1 | Very low |
| **Attainment of target concentration**1 cohort study | Moderatea | None | Moderateb | Seriousc,d | Not detected | None | 14/41 | 4/17 | RR 1.51 [0.57, 3.99] | Very low |

a Some studies not reporting main cofounding factors; b Only pharmacokinetic outcomes; c Wide confidence interval; d Insufficient sample size

MD: Mean difference; RR: Relative risk

Reference: Guo Y, An L, Chen K, et al. Difference of efficacy, safety and pharmacokinetics of voriconazole in different age: a systematic review. *Chin J Clin Pharmacol*. 2016;32:261-263.

Participants: Patients using voriconazole

Intervention: Patients with CYP2C19 PM phenotype

Control: Patients with CYP2C19 non-PM phenotype

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Treatment response**4 cohort studies | None | None | None | Moderatea | Not detected | None | 190/262 | 29/33 | RR 0.88 [0.77, 1.01] | Low |
| **Hepatotoxicity**4 cohort studies | None | Moderateb | None | Seriousa,c | Not detected | None | 48/248 | 10/37 | RR 0.60 [0.20, 1.83] | Very low |
| **Nervous system/psychiatric disorders**3 cohort studies | Moderated | None | None | Seriousa,c | Not detected | None | 5/121 | 3/20 | RR 0.22 [0.04, 1.36] | Very low |

a Wide confidence interval; b Inconsistent results among studies; c Insufficient sample size; d Some studies not reporting cohorts baseline data

RR: Relative risk; PM: Poor metabolizer

Reference: Li X, Yu C, Wang T, et al. Effect of cytochrome P450 2C19 polymorphisms on the clinical outcomes of voriconazole: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2016;72:1185-1193.

Participants: Patients using voriconazole

Intervention: Patients with voriconazole blood concentration < 0.5 mg·L-1

Control: Patients with voriconazole blood concentration > 0.5 mg·L-1

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Treatment response**6 cohort studies | Moderatea | None | None | None | Not detected | Large effect | 8/26 | 241/328 | RR 0.49 [0.29, 0.81] | Moderate |
| **Prophylaxis failure**3 cohort studies | Moderatea | None | None | Seriousb,c | Not detected | None | 5/20 | 10/73 | RR 1.74 [0.70, 4.31] | Very low |
| **Infections-related mortality**1 cohort study | Moderatea | None | None | Seriousa,c | Not detected | None | 0/2 | 10/102 | RR 1.63 [0.12, 21.89] | Very low |

a Some studies not reporting cohorts baseline data; b Wide confidence interval; c Insufficient sample size;

RR: Relative risk

Reference: Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:1772-1785.

Participants: Patients using voriconazole

Intervention: Patients with voriconazole blood concentration < 1 mg·L-1

Control: Patients with voriconazole blood concentration > 1 mg·L-1

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Treatment response**9 cohort studies | Moderatea | Moderateb | None | Moderatec | Not detected | None | 48/91 | 261/345 | RR 0.69 [0.49, 0.98] | Very low |
| **Prophylaxis failure**4 cohort studies | Moderatea | None | None | Seriousc,d | Not detected | None | 13/72 | 12/114 | RR 1.49 [0.73, 3.01] | Very low |
| **Infections-related mortality**1 cohort study | Moderatea | None | None | Seriousc,d | Not detected | None | 0/11 | 10/93 | RR 0.37 [0.02, 5.97] | Very low |

a Some studies not reporting cohorts baseline data; b Inconsistent results among studies; c Wide confidence interval; d Insufficient sample size;

RR: Relative risk

Reference: [1] Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:1772-1785. [2] Kang HM, Lee HJ, Cho EY, et al. The Clinical Significance of Voriconazole Therapeutic Drug Monitoring in Children with Invasive Fungal Infections. *Pediatr Hematol Oncol*. 2015;32:557-567.

Participants: Patients using voriconazole

Intervention: Patients with voriconazole blood concentration < 1.5 mg·L-1

Control: Patients with voriconazole blood concentration > 1.5 mg·L-1

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Treatment response**6 cohort studies | Moderatea | Seriousb | None | Seriousc,d | Not detected | None | 79/112 | 150/200 | RR 0.94 [0.68, 1.30] | Very low |
| **Prophylaxis failure**3 cohort studies | Moderatea | None | None | Seriousc,d | Not detected | None | 9/50 | 6/65 | RR 1.55 [0.62, 3.84] | Very low |
| **Infections-related mortality**1 cohort study | Moderatea | None | None | Seriousc,d | Not detected | None | 0/25 | 10/79 | RR 0.13 [0.01, 2.30] | Very low |

a Some studies not reporting cohorts baseline data; b Inconsistent results among studies; c Wide confidence interval; d Insufficient sample size;

RR: Relative risk

Reference: Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:1772-1785.

Participants: Patients using voriconazole

Intervention: Patients with voriconazole blood concentration < 2 mg·L-1

Control: Patients with voriconazole blood concentration > 2 mg·L-1

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Treatment response**7 cohort studies | Moderatea | Seriousb | None | Seriousc,d | Not detected | None | 113/157 | 143/207 | RR 0.99 [0.77, 1.29] | Very low |
| **Prophylaxis failure**3 cohort studies | Moderatea | None | None | Seriousc,d | Not detected | None | 10/57 | 5/36 | RR 0.88 [0.26, 2.95] | Very low |

a Some studies not reporting cohorts baseline data; b Inconsistent results among studies; c Wide confidence interval; d Insufficient sample size;

RR: Relative risk

Reference: Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:1772-1785.

Participants: Patients using voriconazole

Intervention: Patients with voriconazole blood concentration < 3 mg·L-1

Control: Patients with voriconazole blood concentration > 3 mg·L-1

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Treatment response**7 cohort studies | Moderatea | Seriousb | None | Seriousc,d | Not detected | None | 166/228 | 91/137 | RR 1.05 [0.77, 1.44] | Very low |
| **Prophylaxis failure**2 cohort studies | Moderatea | None | None | Seriousc,d | Not detected | None | 3/18 | 2/4 | RR 0.38 [0.10, 1.38] | Very low |
| **Hepatotoxicity**4 cohort studies | None | None | None | None | Not detected | Large effect | 13/142 | 34/80 | RR 0.31 [0.16, 0.63]  | Moderate |
| **Nervous system/psychiatric disorders**1 cohort study | None | None | None | Seriousc,d | Not detected | None | 0/12 | 1/11 | RR 0.31 [0.01, 6.85] | Very low |
| **Visual disturbance**1 cohort study | None | None | Moderatee | Seriousc,d | Not detected | None | 7/15 | 2/6 | RR 1.40 [0.40, 4.91] | Very low |

a Some studies not reporting cohorts baseline data; b Inconsistent results among studies; c Wide confidence interval; d Insufficient sample size; e Pediatrics

RR: Relative risk

Reference: Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:1772-1785.

Participants: Patients using voriconazole

Intervention: Patients with voriconazole blood concentration < 4 mg·L-1

Control: Patients with voriconazole blood concentration > 4 mg·L-1

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Hepatotoxicity**6 cohort studies | Moderatea | Moderateb | None | None | Not detected | Large effect | 27/213 | 41/77 | RR 0.27 [0.11, 0.63] | Moderate |
| **Nervous system/psychiatric disorders**1 cohort study | None | None | None | Seriousc,d | Not detected | None | 0/13 | 1/10 | RR 0.26 [0.01, 5.82] | Very low |
| **Visual disturbance**1 cohort study | None | None | Moderatee | Seriousc,d | Not detected | None | 9/17 | 0/4 | RR 5.28 [0.37, 75.88] | Very low |

a Some studies not reporting cohorts baseline data; b Inconsistent results among studies; c Wide confidence interval; d Insufficient sample size; e Pediatrics

RR: Relative risk

Reference: Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:1772-1785.

Participants: Patients using voriconazole

Intervention: Patients with voriconazole blood concentration < 5 mg·L-1

Control: Patients with voriconazole blood concentration > 5 mg·L-1

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Hepatotoxicity**4 cohort studies | None | Moderatea | None | Moderate | Not detected | Large effect | 29/190 | 18/32 | RR 0.34 [0.13, 0.87] | Moderate |
| **Nervous system/psychiatric disorders**1 cohort study | None | None | None | Seriousb,c | Not detected | None | 0/15 | 1/8 | RR 0.19 [0.01, 4.14] | Very low |
| **Visual disturbance**1 cohort study | None | None | Moderated | Seriousb,c | Not detected | None | 9/19 | 0/2 | RR 2.85 [0.22, 37.31] | Very low |

a Inconsistent results among studies; b Wide confidence interval; c Insufficient sample size; d Pediatrics

RR: Relative risk

Reference: Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:1772-1785.

Participants: Patients using voriconazole

Intervention: Patients with voriconazole blood concentration < 5.5 mg·L-1

Control: Patients with voriconazole blood concentration > 5.5 mg·L-1

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Hepatotoxicity**4 cohort studies | None | Moderatea | None | None | Not detected | Large effect | 30/193 | 17/29 | RR 0.36 [0.17, 0.74] | Moderate |
| **Nervous system/psychiatric disorders**1 cohort study | None | None | None | Seriousb,c | Not detected | None | 0/15 | 1/8 | RR 0.19 [0.01, 4.14] | Very low |
| **Visual disturbance**1 cohort study | None | None | Moderated | Seriousb,c | Not detected | None | 9/19 | 0/2 | RR 2.85 [0.22, 37.31] | Very low |

a Inconsistent results among studies; b Wide confidence interval; c Insufficient sample size; d Pediatrics

RR: Relative risk

Reference: Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:1772-1785.

Participants: Patients using voriconazole

Intervention: Patients with voriconazole blood concentration < 6 mg·L-1

Control: Patients with voriconazole blood concentration > 6 mg·L-1

|  |  |  |
| --- | --- | --- |
| **No. of studies, design** | Quality assessment | Summary of findings |
| Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | RR, 95% confidence interval | Quality |
| Intervention | Control |
| **Hepatotoxicity**5 cohort studies | None | None | None | None | Not detected | Large effect | 34/217 | 18/30 | RR 0.36 [0.21, 0.63] | Moderate |
| **Nervous system/psychiatric disorders**1 cohort study | Moderatea | None | None | Seriousb,c | Not detected | None | 1/20 | 0/5 | RR 0.86 [0.04, 18.45] | Very low |
| **Visual disturbance**1 cohort study | None | None | Moderated | Seriousb,c | Not detected | None | 9/19 | 0/2 | RR 2.85 [0.22, 37.31] | Very low |

a Inconsistent results among studies; b Wide confidence interval; c Insufficient sample size; d Pediatrics

RR: Relative risk

Reference: Jin H, Wang T, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:1772-1785.

Participants: Patients using voriconazole

Intervention: Voriconazole plus CYP inducers or inhibitors

Control: Voriconazole alone

|  |  |  |
| --- | --- | --- |
| **Drug** | **No. of studies, design** | Summary of findings |
| Sample size | Study results [95% CI] | Quality |
| Intervention | Control |
| **Efavirenz (400 mg po. QD)** | **Cmax**,1 SBA | 16 | 16 | MD -1.91 [-2.57, -1.25] mg∙L-1 | Moderate |
| **AUC**, 1 SBA | 16 | 16 | MD -20.59 [-27.98, -13.20] mg∙h·L-1 | Moderate |
| **Ritonavir (400 mg po. Q12H)** | **Cmax**, 1 SBA | 13 | 13 | MD -2.38 [-3.03, -1.73] mg∙L-1 | High |
| **AUC**, 1 SBA | 13 | 13 | MD -22.55 [-29.66, -14.84] mg∙h·L-1 | High |
| **St John’s wort** | **Cmax**, 1 SBA | 16 | 16 | MD -0.69 [-1.34, -0.04] mg∙L-1 | Very low |
| **AUC**, 1 SBA | 16 | 16 | MD -13.87 [-25.46, -2.28] mg∙h·L-1 | Moderate |
| **Rifampin** | **Cmin**, 1 cohort study | 2 | 197 | Unstandardized β-coefficient -3.18 [-5.35, -1.01] mg∙L-1 | Moderate |
| **Phenobarbital** | **Cmin**, 1 cohort study | 3 | 196 | Unstandardized β-coefficient -2.63 [-4.52, -0.75] mg∙L-1 | Moderate |
| **Carbamazepine** | **Cmin**, 1 cohort study | 2 | 197 | Unstandardized β-coefficient -4.19 [-8.40, 0.01] mg∙L-1 | Very low |
| **Cimetidine** | **Visual disturbance**, 1 crossover RCT | 2/11 | 5/12 | RR 0.44 [0.11, 1.81] | Very low |
| **Cmax**, 1 crossover RCT | 11 | 12 | Geometric mean increased by 18% [90%CI 6%, 32%] | Low |
| **AUC**, 1 crossover RCT | 11 | 12 | Geometric mean increased by 23% [90%CI 13%, 33%] | Low |
| **Glucocorticoids** | **Cmin**, 6 cohort studies | NR | NR | Studies presenting inconsistent results | Very low |
| **Ritonavir (100 mg po. Q12H)** | **Cmax**, 1 SBA | 16 | 16 | MD -0.55 [-1.42, 0.32] mg∙L-1 | Moderate |
| **AUC**, 1 SBA | 16 | 16 | MD -7.30 [-16.08, 1.48] mg∙h·L-1 | Moderate |
| **Etravirine** | **Cmin**, 1 SBA | 14 | 14 | MD 0.17 [-0.54, 0.87] mg∙L-1 | Very low |
| **Cmax**, 1 SBA | 14 | 14 | MD -0.42 [-1.52, 0.69] mg∙L-1 | Very low |
| **AUC**, 1 SBA | 14 | 14 | MD -2.08 [-11.85, 7.69] mg∙h·L-1 | Very low |
| ***Ginkgo biloba* (CYP2C19 EM)** | **Cmax**, 1 crossover RCT | 7 | 7 | Median [Quartile]: 1.10 [0.98, 1.48] vs 1.45 [1.27, 2.72] mg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 7 | 7 | Median [Quartile]: 4.28 [3.63, 4.46] vs 5.17 [3.73, 6.88] mg∙h·L-1 | Low |
| ***Ginkgo biloba* (CYP2C19 PM)** | **Cmax**, 1 crossover RCT | 7 | 7 | Median [Quartile]: 1.60 [1.43, 2.01] vs 1.36 [1.33, 1.91] mg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 7 | 7 | Median [Quartile]: 22.85 [15.96, 32.53] vs 20.96 [18.81, 28.45] mg∙h·L-1 | Low |
| **Indinavir** | **Cmax**, 1 SBA | 8 | 8 | Geometric mean increased by 2% [90%CI -9%, 14%] | Very low |
| **AUC**, 1 SBA | 8 | 8 | Geometric mean increased by 7% [90%CI -2%, 18%] | Very low |
| **Omeprazole** | **Hepatotoxicity**, 1 cohort study | 16/92 | 2/51 | RR 4.43 [1.06, 18.52] | Very low |
| **Nervous system/psychiatric disorders**, 1 cohort study | 3/13 | 2/39 | RR 4.50 [0.84, 363.49] | Very low |
| **Visual disturbance**, 1 crossover RCT | 9/18 | 11/17 | RR 0.77 [0.43, 1.38] | Very low |
| **Pantoprazole** | **Cmin**, 2 cohort studies | NR | NR | Unstandardized β-coefficient 0.69 [0.33, 1.04] and 1.64 [0.91, 2.38] mg∙L-1 according to 2 studies, respectively | Low |
| **Rabeprazole** | **Cmin**, 1 cohort study | NR | NR | Unstandardized β-coefficient 1.41 [0.80, 2.03] mg∙L-1 | Low |
| **Esomeprazole** | **Cmin**, 2 cohort studies | NR | NR | Studies presenting inconsistent results | Very low |
| **Erythromycin**  | **Cmax**, 1 crossover RCT | 18 | 18 | MD 0.80 [0.30, 1.30] mg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 18 | 18 | MD 8.01 [-3.74, 19.76] mg∙h·L-1 | Low |
| **Erythromycin**  | **Cmax**, 1 SBA | 10 | 10 | Geometric mean increased by 7.7% [90%CI -9.4%, 28.0%] | Very low |
| **AUC**, 1 SBA | 10 | 10 | Geometric mean increased by 1.2% [90%CI -10.9%, 14.8%] | Very low |
| **Azithromycin** | **Cmax**, 1 SBA | 10 | 10 | Geometric mean increased by 17.5% [90%CI -1.2%, 39.7%]  | Very low |
| **AUC**, 1 SBA | 10 | 10 | Geometric mean increased by 7.7% [90%CI -4.9%, 22.4%] | Very low |
| **Cmin**, 1 cohort study | NR | NR | Regression index 0.877, significantly and positively correlated with voriconazole Cmin elevation | Very low |
| **Norethindrone/** **Ethinyl oestradiol** | Cmax, 1 SBA | 15 | 15 | MD 0.38 [-0.32, 1.08] mg∙L-1 | Very low |
| AUC, 1 SBA | 15 | 15 | MD 6.09 [-0.85, 13.03] mg∙h·L-1 | Very low |

CYP: Cytochrome P450; QD: Once daily; Q12H: Every 12 hours; SBA: Single-arm before-after study; RCT: Randomized controlled trial; MD: Mean difference; RR: Relative risk; CI: Confidence interval; AUC: Area under the curve; EM: Extensive metabolizer; PM: Poor metabolizer

Reference: [1] Li T, Liu W, Chen K, et al. The influence of combination use of CYP450 inducers on the pharmacokinetics of voriconazole: a systematic review. *J Clin Pharm Ther*. 2017;42:135-146. [2] Yang H, Chen K, Liang S, et al. Effect of cytochrome P-450 inhibitors on pharmacokinetics and safety of voriconazole. *J Chin Pharm Sci*. 2017;26:202-211.

Participants: People using voriconazole

Intervention: Dose-escalated voriconazole plus CYP inducers

Control: Voriconazole alone with normal dose

|  |  |  |
| --- | --- | --- |
| **Drug** | **No. of studies, design** | Summary of findings |
| Sample size | Study results [95% CI] | Quality |
| Intervention | Control |
| **Efavirenz 300 mg po. QD** | **Cmax**,1 SBA | 14 | 16 | MD 0.78 [-0.48, 2.04] mg∙L-1 | Very low |
| **AUC**, 1 SBA | 14 | 16 | MD 1.10 [-13.09, 15.29] mg∙h·L-1 | Very low |
| **Phenytoin** | **Cmax**, 1 SBA | 7 | 11 | Geometric mean increased by 34% [90%CI -10.8%, 100%] | Very low |
| **AUC**, 1 SBA | 7 | 11 | Geometric mean increased by 39% [90%CI -2.7%, 99%] | Very low |
| **Rifabutin** | **Cmin**, 1 case report | 1 | 1 | When using rifabutin, voriconzazole Cmin rising from 0.12 to 0.68 mg∙L-1 with voriconazole dose increasing from 300 mg iv. Q12H to 300 mg po. Q8H | Very low |

CYP: Cytochrome P450; QD: Once daily; SBA: Single-arm Before-after study; MD: Mean difference; CI: Confidence interval; Q12H: Every 12 hours; Q8H: Every 8 hours; AUC: Area under the curve

Reference: Li T, Liu W, Chen K, et al. The influence of combination use of CYP450 inducers on the pharmacokinetics of voriconazole: a systematic review. *J Clin Pharm Ther*. 2017;42:135-146.

Participants: Patients using CYP substrates

Intervention: CYP substrates plus voriconazole

Control: CYP substrates alone

|  |  |  |
| --- | --- | --- |
| **Drug** | **No. of studies, design** | **Summary of findings** |
| Sample size | Study results [95% CI] | Quality |
| Intervention | Control |
| **Oxycodone** | **Cmax**, 1 crossover RCT | 12 | 12 | MD 6.30 [-26.09, 38.69] μg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 12 | 12 | MD 1615.30 [1355.51, 1875.09] μg∙h∙L-1 | Moderate |
| **Methadone** | **Cmax**, 1 RCT | 16 | 7 | MD 95.00 [-4.03, 194.03] μg∙L-1 | Low |
| **AUC**, 1 RCT | 16 | 7 | MD 2440.00 [492.81, 4387.19] μg∙h∙L-1 | Low |
| **Fentanyl** | **AUC**, 1 crossover RCT | 12 | 12 | MD 2.40 [0.65, 4.15] μg∙h∙L-1 | Low |
| **Alfentani** | **AUC**, 1 crossover RCT | 12 | 12 | MD 444.00 [354.86, 533.14] μg∙h∙L-1 | Moderate |
| **Diclofenac** | **Cmax**, 1 crossover RCT | 10 | 10 | MD 0.83 [0.25, 1.41] mg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 10 | 10 | MD 0.71 [0.37, 1.05] mg∙h∙L-1 | Moderate |
| **Etoricoxib** | **Cmax**, 1 crossover RCT | 12 | 12 | Increased by 19% (*P* < 0.05) | Moderate |
| **AUC**, 1 crossover RCT | 12 | 12 | Increased by 49% (*P* < 0.01) | Moderate |
| **Meloxicam** | **Cmax**, 1 crossover RCT | 12 | 12 | MD 0.04 [-0.20, 0.28] mg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 12 | 12 | MD 14.80 [7.81, 21.79] mg∙h∙L-1 | Moderate |
| **Midazolam (iv. ONCE)** | **AUC**, 1 crossover RCT | 10 | 10 | MD 383.00 [323.09, 442.91] μg∙L-1 | Moderate |
| **Midazolam (7.5 mg po. ONCE)** | **AUC**, 1 crossover RCT | 10 | 10 | MD 764.00 [696.91, 831.09] μg∙h∙L-1 | Moderate |
| **Cmax**, 1 crossover RCT | 10 | 10 | MD 62.50 [45.66, 79.34] μg∙L-1 | Moderate |
| **Midazolam (3 mg po. QD)** | **AUC**, 1 SBA | 8 | 8 | MD 46.16 [39.37, 52.95] nmol∙h∙L-1 | High |
| **Etravirine**  | **Cmin**, 1 SBA | 14 | 16 | MD 222.00 [76.72, 367.28] μg∙L-1 | Very low |
| **Cmax**, 1 SBA | 14 | 16 | MD 267.00 [39.49, 494.51] μg∙L-1 | Very low |
| **AUC**, 1 SBA | 14 | 16 | MD 3125.00 [870.36, 5379.64] μg∙h∙L-1 | Very low |
| **Efavirenz** | **Cmax**, 1 RCT | 16 | 11 | MD 1.98 [1.08, 2.88] mg∙L-1 | Moderate |
|  | **AUC**, 1 RCT | 16 | 11 | MD 32.40 [15.46, 49.34] mg∙h∙L-1 | Moderate |
| **Cyclosporine** | **Cmax**, 1 crossover RCT | 7 | 11 | Geometric mean increased by 13% [90%CI -10%, 41%] | Low |
| **AUC**,1 crossover RCT | 7 | 11 | Geometric mean increased by 70% [90%CI 47%, 96%] | Moderate |
| **C/D**, 2 SBAs | 30 | 30 | SMD 0.93 [0.39, 1.47] | Very low |
| **Tacrolimus** | **Cmax**, 1 crossover RCT | 18 | 18 | MD 36.20 [28.11, 44.29] μg∙L-1 | Moderate |
| **AUC**, 1 crossover RCT | 18 | 18 | MD 403.10 [334.17, 472.03] μg∙h∙L-1 | Moderate |
| **C/D**, 2 SBAs | 35 | 35 | SMD 0.98 [0.48, 1.48] | Moderate |
| **Dose**, 3 SBAs | 108 | 108 | MD -1.87 [-3.69, -0.05] mg | Moderate |
| **Sirolimus** | **C/D**, 2 SBAs | 21 | 21 | SMD 0.97 [-0.03, 1.98] | Very low |
| **Dose**, 3 SBAs | 88 | 88 | MD -2.41 [-4.16, -0.65] mg | Moderate |
| **Everolimus** | **Cmin**, 2 case reports | 2 | 2 | Increased to 5 and 7.5 folds, respectively | Moderate |
| **C/D**, 1 case report | 6 | 4 | SMD 10.28 [4.35, 16.20] | Moderate |
| **Norethindrone** | **Cmax**, 1 SBA | 15 | 15 | MD 3.00 [-0.58, 6.58] μg∙L-1 | Very low |
| **AUC**, 1 SBA | 15 | 15 | MD 60.00 [25.64, 94.36] μg∙h∙L-1 | Very low |
| **Ethinyl oestradiol** | **Cmax**, 1 SBA | 15 | 15 | MD 43.00 [9.88, 76.12] ng∙L-1 | Very low |
| **AUC**, 1 SBA | 15 | 15 | MD 632.00 [218.26, 1045.74] ng∙h∙L-1 | Very low |
| **Glimepiride** | **Blood glucose**, 1 case report | 1 | 1 | Dropping to 40 mg∙L-1, not restoring after stopping glimepiride | Moderate |
| **Nifedipine** | **Blood pressure**, 1 case report | 1 | 1 | Dropping to 76/48 mmHg, restoring after stopping voriconazole | Moderate |
| **Simvastatin** | **Rhabdomyolysis**, 2 case reports | 2 | 2 | Rhabdomyolysis after concomitant use of voriconazole and simvastatin | Very low |
| **Vincristine** | **Adverse drug reactions**, 1 cohort study | 4/6 | 13/44 | RR 2.26 [1.09, 4.67] | Very low |
| **Warfarin** | **INR**, 1 SBA | 5 | 5 | Increased from 1.95 to 2.89 (*P* < 0.05) | Very low |
| **AUEC**, 1 crossover RCT | 14 | 13 | MD 929 [574, 1283] s∙h | Moderate |
| **Tilidine** | **Cmax**, 1 crossover RCT | 16 | 16 | MD 6.30 [-26.09, 38.69] μg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 16 | 16 | MD 1615.30 [1355.51, 1875.09] μg∙h∙L-1 | Moderate |
| **Buprenorphine** | **Cmax**, 1 crossover RCT | 12 | 12 | MD 0.26 [0.07, 0.45] μg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 12 | 12 | MD 3.90 [2.31, 5.49] μg∙h∙L-1 | Moderate |
| **Ibuprofen** | **Cmax**, 1 crossover RCT | 12 | 12 | MD 2.90 [-0.99, 6.79] mg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 12 | 12 | MD 69.80 [43.91, 95.69] mg∙h∙L-1 | Moderate |
| **Venlafaxine** | **Cmax**, 1 crossover RCT | 12 | 12 | MD 20.20 [-22.27, 62.67] μg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 12 | 12 | MD 488.00 [-773.54, 1749.54] μg∙h∙L-1 | Low |
| **Zolpidem** | **Cmax**, 1 crossover RCT | 10 | 10 | MD 23.00 [-19.53, 65.53] μg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 10 | 10 | MD 215.00 [-114.90, 544.90] μg∙h∙L-1 | Low |
| **Diazepam** | **Cmax**, 1 crossover RCT | 12 | 12 | MD -2.00 [-30.82, 26.82] μg∙L-1 | Low |
| **AUC**, 1 crossover RCT | 12 | 12 | MD 3380.00 [1661.54, 5098.46] μg∙h∙L-1 | Moderate |
| **Ritonavir**  | **Cmax**, 1 RCT | 14 | 15 | MD 0.20 [-2.64, 3.04] mg∙L-1 | Low |
| **AUC**, 1 RCT | 14 | 15 | MD 7.50 [-9.65, 24.65] mg∙h∙L-1 | Low |
| **Ritonavir**  | **Cmin**, 1 SBA | 20 | 22 | Geometric mean 28.3 vs 37.1 μg∙L-1 | Very low |
| **Cmax**, 1 SBA | 20 | 22 | Geometric mean 1429 vs 1597 μg∙L-1 | Very low |
| **AUC**, 1 SBA | 20 | 22 | Geometric mean 8280 vs 9572 μg∙h∙L-1 | Very low |
| **Indinavir** | **Cmix**, 1 crossover RCT | 16 | 16 | Geometric mean increased by 1% [90%CI -17.9%, 25%] | Low |
| **Cmax**, 1 crossover RCT | 16 | 16 | Geometric mean decreased by 8.6% [90%CI -1%, 17.3%] | Low |
|  | **AUC**, 1 crossover RCT | 16 | 16 | Geometric mean decreased by 12.5% [90%CI 0.2%, 23.3%] | Low |
| **Atazanavir** | **Cmin**, 1 SBA | 20 | 22 | Geometric mean 525 vs 674 μg∙L-1 | Very low |
| **Cmax**, 1 SBA | 20 | 22 | Geometric mean 4076 vs 4715 μg∙L-1 | Very low |
| **AUC**, 1 SBA | 20 | 22 | Geometric mean 38.28 vs 44.63 mg∙h∙L-1 | Very low |
| **Digoxin** | **Cmax**, 1 SBA | 12 | 12 | Geometric mean increased by 9.8% [90%CI -3%, 24.1%] | Very low |
| **AUC**, 1 SBA | 12 | 12 | Geometric mean increased by 0.5% [90%CI -8.6%, 10.5%] | Very low |

CYP: Cytochrome P450; SBA: Single-arm before-after study; RCT: Randomized controlled trial; MD: Mean difference; SMD: Standardized mean difference; RR: Relative risk; CI: Confidence interval; AUC: Area under the curve; C/D: Concentration/dose; INR: International normalized ratio; AUEC: Area under the effect curve; po.: Orally; QD: Once daily

Reference: [1] Liu Y, Liang S, Chen K, et al. Influence of voriconazole on pharmacokinetics and safety of combined drugs: a systematic review. *J Chin Pharm Sci*. 2016;25:785–798. [2] Liu P, Foster G, LaBadie RR, et al. Pharmacokinetic interaction between voriconazole and efavirenz at steady state in healthy male subjects. *J Clin Pharmacol*. 2008;48:73-84.