Table 1

Overview of the most commonly implicated antibiotics and their interactions

| Drug/Probability of Interaction[1] | Effect on Warfarin/Mechanism | Timing of Interaction/Recommendations |
|---|---|---|
| **Metronidazole:** highly probable<br>First case report published in 1976; four other case reports/series published after initial case report | Potentiates effect of warfarin<br>Mechanism: inhibition of cytochrome P450 (CYP) enzyme 2C9 and possibly displaces warfarin from albumin[2,3] | Thompson et al[2] reported an onset of five days (INR not measured earlier) in a patient taking warfarin concomitantly with metronidazole and levofloxacin. Tonna at al[3] reported an onset ranging between 2-4 days in patients who stopped taking warfarin and received metronidazole.<br>Recommendation: Santa Clara Valley Medical Center (SCVMC) the weekly dose of warfarin by 20%-30%. |
| **Trimethoprim/Sulfamethoxazole:** highly probable | Potentiates effect of warfarin<br>Mechanism: not well established; sulfonamide may impair hepatic metabolism of warfarin or it may displace warfarin from protein-binding sites[4,5] | Cook et al[4] cited seven other published case reports of this interaction and reported an onset ranging from 1 to 13 days; onset of three days cited in more recent literature.[5] Cook et al[4] reported an offset of the interaction of three days.<br>Recommendation: Ahmed et al[5] recommended warfarin dose by 10%-20%; SCVMC, warfarin dose by 20%-30%. |
| **Quinolones**<br>Ciprofloxacin: highly probable<br>Levofloxacin: probable<br>Moxifloxacin: probable | Potentiates effect of warfarin<br>Mechanism: ciprofloxacin most likely inhibits metabolism of R-enantiomer of warfarin;[6] other quinolones may disrupt intestinal flora responsible for vitamin K synthesis or displace warfarin from protein-binding sites.[7] | Carroll et al[7] summarized 21 publications of warfarin interactions with ciprofloxacin, levofloxavin, and moxifloxacin. Average time of onset for ciprofloxacin (earliest, three days) and for levofloxacin (earliest, 5.5 days) was 5 to 6 days; moxifloxacin interaction occurred earlier (2-4 days).<br>Recommendation: SCVMC, warfarin dose by 10% if taking ciprofloxacin; no recommendation for other quinolones. |
| **Rifampin:** highly probable | Decreases effect of warfarin<br>Mechanism: induction of warfarin metabolism through CYP1A2, CYP2C9, and CYP3A48 | Kim et al[9] stated that a total of 7 case reports (including her own) and 3 pharmacokinetic-pharmacodynamic studies described the interaction between rifampin and warfarin. Krajewski et al[10] published a detailed report on this interaction in 2010, stating an onset of the induction effect of days and an initial offset of the inducing effect of 6 days. The inducing effects of rifampin (after 6-week course) took 4 months to completely subside.<br>Recommendation: Krajewski et al.[10] the weekly dose of warfarin by ~ 30% after five days; warfarin dose by an additional 30% on days 7-16; warfarin dose by additional 25% on days 17-30; warfarin dose by additional 20% on days 31-37; warfarin dose by additional 30% on days 38-40; warfarin dose by additional 25% on days 41-45. Despite five-fold in warfarin dose over 45 days, INRs remained subtherapeutic. After rifampin dc'd: warfarin dose by 30% on day 6; dose by 30% on days 7-10; dose by 20% on day 11; checked INRs ~ every 2-4 weeks |

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| **Macrolides**<br>Erythromycin: highly probable<br>Clarithromycin: probable<br>Azithromycin: probable | Potentiates effect of warfarin<br>Mechanism: disruption of warfarin metabolism by CYP1A2 and CYP3A4 inhibition while receiving concomitant erythromycin or clarithromycin.[11-14] The proposed mechanism for the interaction with azithromycin not well-established, given the presence of confounding factors in various case reports. Possible mechanism might involve impairment of vitamin K production by gastrointestinal flora.[15-16] | Erythromycin: time of onset ranges from 0-18 days (median, 5 days).[12] One recent report showed that after 3 weeks of concomitant treatment with warfarin and ophthalmic erythromycin, a patient presented with elevated INR; offset of four days.<br>Clarithromycin: time of onset has ranged from five days[14] to 14 days.[11]<br>Azithromycin: six case reports with oral azithromycin[15] showed a range in onset of 3 days to 5 days after completion of azithromycin (five-day course). One case report of intravenous azithromycin[16] showed an onset of one day. Both reports showed multiple confounding factors such as use of prednisone, fever, decreased appetite, use of ampicillin, heart failure, decreased cigarette smoking, worsening liver function, and decreased albumin.<br>Recommendation: SCVMC, warfarin dose by 15%-30% if taking erythromycin; no changes for other macrolides |
| **Telithromycin:** one case report | Potentiates effect of warfarin<br>Mechanism: possibly through inhibition of the metabolism of R-enantiomer of warfarin, but is not established.[17] | Kolilekas et al1 seven showed an onset of five days in a patient who took warfarin and telithromycin. Possible confounding factor was the patient's illness, since infection can affect the activity of the CYP enzyme system. Also, fever catabolism of clotting factors.<br>Recommendation: enhanced monitoring of INR within five days |
| **Penicillins**<br>Dicloxacillin: probable<br>Amoxicillin: possible<br>Nafcillin: highly improbable | Dicloxacillin[18-20] and Nafcillin:[21] decreases effect of warfarin.<br>Amoxicillin:[22] potentiates warfarin effect<br>Mechanism: not established for dicloxacillin or nafcillin; possible induction of hepatic enzymes,[18,21] but not confirmed. Amoxicillin therapy may result in vitamin-K producing gut flora.[22] | Dicloxacillin: case reports[18-20] have shown an onset as early as 4-5 days and an offset of three weeks.<br>Nafcillin: Kim et al[21] summarized the interaction between warfarin and nafcillin in her case report; a total of seven published cases of this interaction exist at present. The time of onset is ~ 1 week, and the offset is ~ 4 weeks.<br>Amoxicillin: Davydov et al[22] summarized data from four case reports of warfarin interacting with amoxicillin ± clavulanic acid and found an onset between 7 days to 2.5 weeks after stopping amoxicillin therapy.<br>Recommendations: SCVMC, if taking nafcillin, may need to increase warfarin dose as much as four-fold. Gradually decrease dose of warfarin 1-4 weeks after stopping nafcillin. |

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| **Cephalosporins**<br>Cefazolin: highly improbable | Potentiates effect of warfarin<br>Mechanism: alteration of bacterial bowel flora; not well established. | Angaran et al[23] conducted a study that showed that after two days of treatment, the percentage change in PT for 20 cefazolin-treated patients was 51.1 ± 18.0% (nonsignificant). |
| **Tetracyclines**<br>Doxycycline: probable<br>Minocycline: theoretical<br>Tigecycline: no case reports | Potentiates effect of warfarin<br>Mechanism: not well-established for tetracyclines. Doxycycline:[24] competition for protein-binding displaces albumin-bound warfarin. | Doxycycline: Baciewicz et al[24] indicated a time of onset of 7-10 days and an offset of 3-7 days, based on a summary of three earlier case reports.<br>Recommendation: Monitor INRs more closely after seven days of doxycycline therapy. |