

Covid's INR conundrum: Unraveling the impact of covid-19 on warfarin management

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Background

COVID-19 is known to induce clotting cascade abnormalities, posing challenges in managing warfarin for patients with thromboembolic conditions like atrial fibrillation and pulmonary embolism [1]. Some studies suggest a hypercoagulation state in COVID-19, potentially resulting in a reduced International Normalized Ratio (INR) for patients on warfarin [2]. However, the literature does not conclusively demonstrate a clear association between COVID-19 and fluctuations in the International Normalized Ratio (INR), particularly an increase in INR.

Objective: This report will outline two cases of patients, previously with stable INR on warfarin treatment, who later tested positive for COVID-19 and encountered INR instability.

Case 1

A 43-year-old African female, previously stabilized on a weekly warfarin dose of 47.5 mg due to a history of pulmonary embolism and a diagnosis of protein S deficiency, was diagnosed with COVID-19 infection seven days before presenting to the clinic. On presentation, her INR was 4.4, with no identifiable factors influencing the change. Warfarin was withheld for two days, and upon resuming the normal dosing schedule, the INR returned to 2.5 after 10 days. However, when the patient returned 14 days later, her INR was 4.2, with no discernible contributing factors. Consequently, two doses were skipped, resulting in an INR of 2.5 six days later, prompting the patient to resume the total weekly warfarin dose of 47.5 mg. Nine days later, the INR rose to 3.2, and seven days after that, it reached 4.4, again without apparent contributing factors. Subsequently, the warfarin dose was reduced to a total weekly dose of 37.5 mg. The patient returned after 7 days, 14 days, and 41 days, demonstrating INR values of 2.0, 2.1, and 2.1, respectively.

Case 2

A 63-year-old Caucasian male diagnosed with atrial fibrillation, previously stabilized on a weekly warfarin dose of 52.5 mg, presented with an elevated INR of 6.6, contrasting with the recent INR of 2.7, following a positive COVID-19 test 14 days earlier. The patient denied medication use or any other identified factors contributing to the heightened INR. Withholding four warfarin doses led to an INR of 1.2. Resuming the previous regimen, the patient returned after 7 days with an INR of 2.0. At the subsequent visit 14 days later, the INR was 3.4; however, the patient revealed he had skipped his multivitamin containing Vitamin K for the past week. After reintroducing the multivitamin, the patient continued the total weekly warfarin dose of 52.5 mg and returned after 7 days with an INR of 2.3. Subsequently, his INR remained stable within the target range across three visits over the following 43 days.

Table 1: Case 1 INR/dosing chart.

Time frame	INR	Dosing schedule	Total weekly dose	Comments
41 days after change in dose	2.1	5 mg daily except 7.5 mg on Wednesday	37.5 mg	
14 days after change in dose	2.1	5 mg daily except 7.5 mg on Wednesday	37.5 mg	
7 days after change in dose	2.0	5 mg daily except 7.5 mg on Wednesday	37.5 mg	Held 2 doses
7 days after previous INR	4.4	7.5 mg daily except 5 mg on Tuesday and Thursday	47.5 mg	
9 days after previous INR	3.2	7.5 mg daily except 5 mg on Tuesday and Thursday	47.5 mg	
6 days after previous INR	2.5	7.5 mg daily except 5 mg on Tuesday and Thursday	47.5 mg	Held 2 doses as directed
14 days after previous INR	4.2	7.5 mg daily except 5 mg on Tuesday and Thursday	47.5 mg	
10 days after previous INR	2.5	7.5 mg daily except 5 mg on Tuesday and Thursday	47.5 mg	Held 2 doses after last visit
1 st INR post infection	4.4	7.5 mg daily except 5 mg on Tuesday and Thursday	47.5 mg	COVID19 infection 7 days prior to visit
March 2023 To July 2023	1.8 – 3.0	7.5 mg daily except 5 mg on Tuesday and Thursday	47.5 mg	Total of 7 INR values measured

Discussion

COVID-19 complicates the management of warfarin in patients with thromboembolic conditions, and previous studies have assessed the impact of the COVID-19 pandemic on INR testing [2,3]. The complex interplay of factors contributing to suboptimal anticoagulation is likely influenced by a combination of patient-specific elements and those directly associated with the COVID-19 virus. In studies conducted during the COVID-19 pandemic and lockdown, patient-specific factors like medication interactions with antibiotics and anti-pyretics, increased alcohol use, and social isolation's psychological burden resulted in altered INR, notably increased values [4]. Additionally, shifts in dietary intake, such as restricted access to leafy green vegetables during isolation amid the spread of illness, were identified as potential contributors to these fluctuations [4]. While these factors were denied by the patients in our case studies, it underscores the importance of meticulous individual risk evaluation and open communication between healthcare providers and patients.

Table 2: Case 2 INR/dosing chart.

Time frame	INR	Dosing schedule	Total weekly dose	Comments
39 days after previous INR	2.9	7.5 mg daily	52.5 mg	
28 days after previous INR	2.8	7.5 mg daily	52.5 mg	
15 days after previous INR	2.4	7.5 mg daily	52.5 mg	
7 days after previous INR	2.3	7.5 mg daily	52.5 mg	Resumed multivitamin
14 days after previous INR	3.4	7.5mg daily	52.5mg	Patient mentioned they ran out of multivitamin containing vitamin K a week ago.
7 days after previous INR	2.0	7.5mg daily	52.5mg	
4 days after previous INR	1.2	Holding doses	N/A	
1 st INR since COVID19	6.6	7.5 mg daily	52.5 mg	COVID19 infection diagnosed 14 days prior
February 2023 – June 2023	2.2-3.1	7.5 mg daily	52.5 mg	Total of 5 INR values measured

COVID-19 is also known to dysregulate proinflammatory cytokines, induce endothelial dysfunction, and cause subclinical impairment of the liver, potentially causing INR fluctuations in warfarin-treated patients [1,4]. Studies also note decreased extra-hepatic vitamin K in COVID-19 from heightened vitamin K demand for Matrix Gla protein-crucial for preventing lung elastic fibers' calcification and degradation [5]. This variation may be patient-specific, requiring further research into the link between inflammatory pathways and INR elevation. Close monitoring of warfarin-treated COVID-19 patients is crucial, as effects may persist weeks after symptom resolution. Further research is needed to understand the association between inflammatory and coagulation pathway dysregulation and higher INR in patients on warfarin, emphasizing the need for closer monitoring post-COVID-19 symptom resolution.

Conflicts of interest: None of the contributing Authors listed above have any conflicts of interest to disclose

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