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Fasting and warfarin

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Warfarin has been the dominant oral anticoagulant since its discovery and first clinical application in the middle of the 20th Century (1-2). Due to its mechanism of action that reduces the synthesis of active vitamin K-related clotting factors, oral intake of vitamin K rich food has a measurable impact on the anticoagulation effect of warfarin. It is therefore conceivable that periods of food abstinence in the form of fasting has long been suspected of affecting warfarin therapy (3).

In the 1970s, studies using rat models suggested that prolonged fasting increased plasma free fatty acid levels, displacing warfarin from plasma protein. The increased plasma concentration of warfarin led to higher anticoagulation intensity in rats (4-6).

It was later demonstrated that a vitamin K deficient state induced by reduced vitamin K intake or fasting led to hypoprothrombinemia, with increased susceptibility in male rats than female rats (7).

Despite the compelling results in rat models, the effect of fasting in warfarinized patients was uncertain. There has however been considerable interest in Muslim majority countries on the effect of fasting on patients with chronic disorders during the holy month of Ramadan. Studies have pointed towards significant physiologic and psychological changes in Muslim patients fasting during Ramadan (8-12). A number of studies had indirectly suggested that patients undergoing fasting during Ramadan may experience changes to their anticoagulation therapy.

Recently, we reported the findings of a study on the effects of Ramadan fasting on a group of 32 Muslim patients taking warfarin (13). Weekly INR (international normalized ratio) readings were taken from subjects with previously stable INRs over a three-month period spanning pre-Ramadan to post-Ramadan. We found a statistically significant increase in the mean INR by 0.23 (P=0.006) during Ramadan from the pre-Ramadan month and decreased by 0.28 (P<0.001) after Ramadan. There was no significant difference (P=1.000) in mean INR between the non-Ramadan months. Importantly, there was a decline in the time within therapeutic range (TTR) during Ramadan with a corresponding increase in TTR above the therapeutic target range. %TTR declined from 80.99% before Ramadan to 69.56% during Ramadan (P=0.453). The first out-of-range INR was seen around 12.1 days (95% CI 9.0-15.1) after the start of fasting and returned within range about 10.8 days (95% CI 7.9-13.7) after Ramadan. Time above range increased from 10.80% pre-Ramadan to 29.87% during Ramadan (P=0.027), while time below range increased from 0.57% during Ramadan to 15.49% post-Ramadan (P=0.006). This observation is directly attributable to the effects of fasting.

To conclude, warfarin may increase the INR of patients during religious fasting. This is inconsequential in the majority of fasting patients. However, among patients with labile INRs or at higher risk of bleeding, the potential harm of a higher INR should mandate more

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frequent monitoring or pre-emptive titration during periods of fasting.

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