Warfarin poisoning with delayed rebound toxicity

Abstract

Background: Intentional poisoning with warfarin is not the same as over-anticoagulation, for which guidelines exist [1]. The coagulopathy resulting from a warfarin overdose is reversed with vitamin K_1, the dose and timing of which is often guided by experience with the management of over-anticoagulation with warfarin therapy, rather than acute overdose.

Case report: We report a case of a 50 year old man who ingested an unknown amount of his warfarin, venlafaxine and paracetamol. He presented with an international normalised ratio (INR) of 2.5 which steadily increased over 24h to 7, despite an initial 1mg of vitamin K_1. He was then treated with 5mg vitamin K_1 and discharged home once the INR returned to 4.5, 40h post-ingestion. He was also treated with a full course of acetylcysteine for the paracetamol overdose. The following day his INR rebounded to 8.5 and he suffered a spontaneous epistaxis requiring readmission and was treated with low titrated doses of vitamin K_1. The warfarin concentration was 74.6µg/ml 26h post-ingestion and decreased to 3.7µg/ml over 72h.

Why should an emergency physician be aware of this?: Our case highlights the risk of a rebound elevated INR even 3 days after acute warfarin overdose despite treatment with vitamin K_1. Understanding the pharmacokinetics of vitamin K_1 in comparison to warfarin, repeat INR testing and continued treatment with oral vitamin K_1 may help avoid complications of rebound coagulopathy in warfarin overdose.

Keywords: Warfarin; poisoning; vitamin K1; overdose

Introduction

Acute anticoagulant poisoning is uncommon, but can potentially result in life-threatening bleeding [1]. Warfarin overdoses are often complicated by the fact that patients are on anticoagulant therapy for a reason, and complete reversal may be detrimental for the treatment of the underlying condition (e.g. prevention of pulmonary embolism). The anticoagulant coagulopathy resulting from a warfarin overdose is reversed with vitamin K_1. The dose and timing of vitamin K_1 is often guided by experience with the management of over-anticoagulation with warfarin therapy, rather than acute overdose [2]. There is little guidance on the best way to treat abnormal clotting in acute warfarin overdoses [1, 3]. We present a case that highlights these problems, the prolonged effect of warfarin and the rebound coagulopathy that can occur despite initial vitamin K_1 treatment.

Case report

A 50 year old man self-presented to the emergency department several hours after taking an overdose of unknown amounts of warfarin, venlafaxine and paracetamol with alcohol. He had a history of massive spontaneous pulmonary embolism four years earlier and was advised to remain on warfarin indefinitely. He also had a history of alcohol abuse and major depression with previous suicide attempts, including a warfarin overdose. He was prescribed 15mg warfarin, 225mg venlafaxine and 30mg mirtazapine daily.

On presentation the patient had slurred speech and a Glasgow Coma Scale of 13. His vital signs and physical examination were unremarkable (heart rate, 75bpm, blood pressure, 129/80mmHg, respiratory rate, 16, oxygen saturations, 99% on room air). He had no signs of bruising or active bleeding. His international normalised ratio (INR) was 2.5 measured 5h post-ingestion, and his blood alcohol level was 0.15g/100mL.

In the emergency department he was commenced on intravenous acetylcysteine (200mg/kg over 4h and then 100mg/kg over 16h; modified intravenous protocol ADD REF to OUR NAC paper) for the paracetamol ingestion (8hr paracetamol concentration, 1253µmol/L [188mg/L]) and admitted to the emergency short stay ward for monitoring of his INR and bleeding risk. He completed the full 20h course of acetylcysteine and his liver function tests remained normal.

The following morning his INR had risen to 5.1 and he was given 1mg vitamin K_1 intravenously (Figure 1). Despite this, the INR continued to increase and 5h later was 7. He was given a further 5mg vitamin K_1 intravenously. Twelve hours later the INR had decreased to 4.5 and after psychiatric assessment he was discharged about 40h post-ingestion for outpatient monitoring of the INR and a plan to recommence warfarin.

The following day (69h post-ingestion) the patient was readmitted to hospital due to an INR of 7.8 and reporting a self-resolving spontaneous epistaxis. He was commenced on regular low dose intravenous vitamin K_1 (1-2mg every 3h for a total of 18mg over 48h) with serial INRs for 3 days (Figure 1). He had no further episodes of bleeding. His INR decreased to 2.4 the following morning and remained below the therapeutic range. He was recommenced on warfarin (15mg) on day 6, but his INR did not increase for another 5 days. At follow up 12 months later he had not suffered any complications (thromboembolic or bleeding) and his INR had been stable and within the therapeutic range.

Blood was stored at the time and S-warfarin was measured using a gradient liquid chromatography-mass spectrometry method with a 5µm chiral Astec Chirobiotic V column on an API2000 triple quadrupole mass spectrometer in negative ion mode with multiple reaction monitoring. The method involved spiking 50µL aliquots of plasma with 4-nitro

phenol as internal standard, precipitating proteins with acetonitrile, injecting 5µL of supernatant onto the column and intra- and inter-day precision validation.

The concentration was 74.6µg/ml 26h post-ingestion and decreased to 3.7µg/ml over 72h where the therapeutic range is 0.6 to 3.1 µg/ml (Figure 1).

Discussion

Treatment with large early doses of vitamin K_1 will result in initial INR improvement, which can be falsely reassuring. If the patient's INR is not closely monitored there is a risk of a rebound increase in the INR. The reason for this rebound is that warfarin has a much longer half-life (estimates of 44h in overdose) than vitamin K_1 (elimination half-life of 1.7h) [3]. To maintain sufficient concentrations of vitamin K_1 a small dose of vitamin K_1 is required with a dosing interval of 3 to 6h, otherwise vitamin K_1 concentrations will drop to zero while the warfarin concentration remains high, resulting in the rebound coagulopathy[5]. Single large doses of vitamin K_1 may initially reduce the INR to 1 but will still not maintain high enough vitamin K_1 concentrations to prevent the INR increasing again. We chose a dose of 1 to 2 mg because of a trial by Hung et al which demonstrated that 0.5 to 2mg of vitamin K_1 will reduce the INR into the range 2 – 4 in the majority of over-anticoagulated patients (ADD Hung A, Singh S, Tait C. A prospective randomised study to determine the optimal dose of intravenous vitamin K_1 in reversal of over-warfarinization.) It is thus important to admit patients after the initial vitamin K_1 dose, continue to monitor the INR and give further vitamin K_1 as required for at least 48 hours. In this patient the warfarin concentration was over 20 times the therapeutic upper limit 26 hours after ingestion and should not have been discharged without further observation and INR measurements.

An alternative to giving large doses is to titrate small doses of vitamin K_1 in response to the INR result. The problem with this approach is that it uses a tail chasing method of regular

INR testing, close monitoring and active treatment based on the result, which results in a delay in correction of the INR. The approach used in this patient after they were re-admitted 72h post ingestion was to commence regular (3 hourly) low dose intravenous vitamin K_1 in an effort to prevent further rebounds with high INRs (e.g. >4.5). However, the patient received a further 18mg vitamin K_1 over 48h when the warfarin concentrations had already decreased into the therapeutic range of 0.6 to 3.1 µg/ml[6] (Figure 1). This resulted in a significant delay in re-establishing a therapeutic INR, probably because of the development of warfarin resistance due to increased liver stores of vitamin K_1.

Acetaminophen overdose and treatment with acetylcysteine can both cause an increased INR (REF: Whyte IM et al TDM 2000; Schmidt LE et al Lancet 2002). However, this is usually a mild effect with most patients only have increases in the INR to about 2, compared to the much higher INR that occurred in this patient and in other warfarin overdoses.

The management of intentional warfarin overdose in patients who require anticoagulation is complex. Multiple options exist, but admission and regular INR testing is essential, usually for 2 to 4 days or an initial observation period of 48 hours. Either regular low dose vitamin K_1 or titrating small doses of vitamin K_1 to the INR is reasonable. There is limited evidence to support the use of factor replacement, unless the patient has active bleeding, and it will not prevent rebound either (CAN YOU REF MY PAPER on this). Only vitamin K_1 (phytomenadione) should be used and the synthetic provitamin, vitamin K_3 (menadione), will not have the same effect. It is also important to remember that the treatment of warfarin overdose differs to over warfarinisation, and guidelines for the treatment of over-anticoagulation need to be interpreted with caution.

Why should an emergency physician be aware of this?

Over-anticoagulation from warfarin therapy is common and guidelines exist to help determine management.[2] In contrast, acute warfarin overdoses are rare with few published case reports and series describing the natural course and bleeding risks [1, 3-5]. In most overdoses, warfarin is ingested by people prescribed anticoagulation to prevent thromboembolism or for mechanical valve prophylaxis.[1] This complicates treatment because the emergency physician needs to balance the risks of inadequate anticoagulation reversal against the risks of thromboembolic events. The aim is to treat over-anticoagulation without complete reversal, but there is no standardised way to do this. Complete anticoagulation reversal plus heparinisation until adequate warfarinisation is re-established is an option, but results in prolonged hospital admission. Ideally, tailored vitamin K_1 dosing resulting in a therapeutic INR until warfarin concentrations normalise would ideal. However, such a treatment method can be complicated with rebounding INRs and warfarin resistance [1, 3].

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Figure Legend

Figure 1: Patients INR over time since ingestion (blue line). Warfarin levels since ingestion (red line). Vitamin K_1 doses in mg (green dots) and warfarin recommencement in mg (purple dots).