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WHEN NEW THERAPIES MEET OLD CHALLENGES: TIRZEPATIDE–WARFARIN INTERACTION IN A MECHANICAL MITRAL VALVE PATIENT

Raffaele Natale[1], Annadora Morena[1], Luca Maria Capece[1], Sofia Donnarumma[1], Ermenegilda Pagano[2], Fabrizio Pasanisi[1], Lidia Santarpia[1]

[1] Internal Medicine, Department of Clinical Medicine and Surgery, Federico II University Hospital, Naples, Italy
[2] Casa di Cura Santa Maria del Pozzo Hospital, Somma Vesuviana, Naples, Italy

Corresponding author's e-mail: raffaelenatale1993@gmail.com

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ABSTRACT

Tirzepatide is a medication capable of controlling blood glucose levels through the dual agonism of GIP and GLP-1 receptors. In particular, GLP-1 reduces food intake and delays gastric emptying. We report the case of a 66-year-old woman hospitalised with a medical history notable for grade III obesity and a mechanical mitral valve prosthesis.

Given the severity of obesity and the high overall cardiovascular risk, tirzepatide was initiated on the day after admission. After 10 days of therapy, routine blood tests revealed an unexpectedly significant reduction in INR values, despite the patient following a strict and stable diet. The therapeutic INR target was gradually achieved only after approximately three weeks of progressive increases in daily warfarin dosage.

Although tirzepatide has no known direct effects on INR, it could indirectly influence its values by delaying gastric emptying. In patients treated concomitantly with tirzepatide and warfarin, closer INR monitoring may therefore be advisable, even in the absence of dietary or pharmacological changes.

KEYWORDS

Tirzepatide, warfarin, INR

LEARNING POINTS

- Tirzepatide may indirectly affect the pharmacokinetics of warfarin.
- In patients receiving both warfarin and tirzepatide, closer INR monitoring may be required.
- Careful attention to potential drug interactions is warranted, even when no direct interaction is known.

INTRODUCTION

Tirzepatide is a novel dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. By enhancing insulin secretion, reducing food intake, delaying gastric emptying and improving lipid and blood pressure profiles, as shown

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in *Figure 1*, it has demonstrated significant benefits in patients with obesity and type 2 diabetes[1]. The adverse events most commonly associated with tirzepatide include nausea, vomiting, diarrhoea, constipation, upper abdominal discomfort, decreased appetite and abdominal pain. These effects are frequently observed in patients with irritable bowel syndrome and may suggest a potential influence of tirzepatide on the gut microbiota[2].

Although its metabolic efficacy is well established, limited data are available regarding potential pharmacological interactions with other therapies. Here we describe the case of an obese patient with a mechanical mitral valve prosthesis, in whom tirzepatide initiation was followed by unexpected alterations in international normalised ratio (INR) values during concomitant warfarin treatment.

CASE DESCRIPTION

A 66-year-old woman with grade III obesity and heart failure was hospitalised in a rehabilitation unit for weight and cardio-pulmonary rehabilitation. Among comorbidities were post-thyroidectomy iatrogenic hypothyroidism under replacement treatment, chronic obstructive pulmonary disease and severe mixed disventilatory syndrome. The patient had a mechanical mitral valve implanted approximately 10 years earlier. She had been maintained on warfarin 5 mg daily with stable INR values over time; on admission, INR was 3.1.and she was on therapy with warfarin 5 mg (one) tablet with stable INR over time. Given the presence of severe obesity, multiple previously unsuccessful dietary attempts and high overall cardiovascular risk, tirzepatide 2.5 mg subcutaneously once weekly was initiated the day after admission, with a plan to titrate the dose over four weeks.

After 10 days of therapy, routine blood tests revealed an INR of 1.19. The warfarin dose was therefore increased from 5 mg to 7.5 mg daily, and subcutaneous enoxaparin was administered twice daily as bridging anticoagulation until the target INR was achieved.

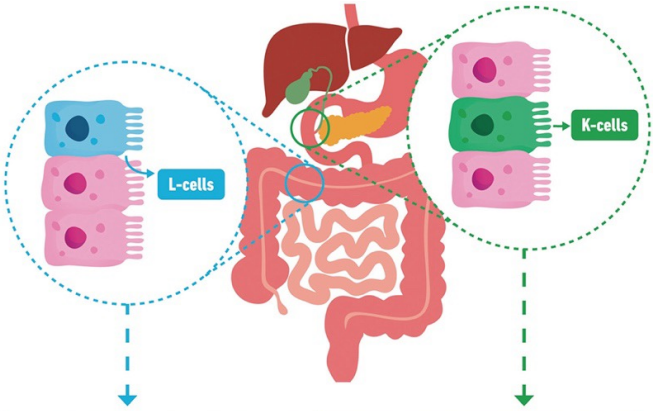
Despite the increased warfarin dosage, strict adherence to a stable diet and the absence of significant weekly variations, the patient's INR returned to the therapeutic range only after approximately three weeks. Serial INR measurements demonstrated the trend shown in *Figure 2*.

Enoxaparin was discontinued upon reaching the INR of 1.82.

DISCUSSION

Although the patient had shown good compliance with warfarin therapy for approximately 10 years, and despite adherence to a standard and rigorous diet as well as an increased warfarin dosage, achieving the target INR proved more challenging.

It should be considered in this case that the change of diet



	GLP-1	GIP
Brain	↓ Appetite ↓ Food intake ↑ Nausea	↓ Appetite* ↓ Food intake* ↓ Nausea*
Pancreas	↑ Insulin secretion ↓ Glucagon	↑ Insulin secretion ↑ Glucagon
Stomach	↓ Gastric emptying	↓ Gastric acid secretion
Adipose tissue	↑ Lipolysis	↑ Lipogenesis ↑ Lipid buffering capacity
Bone		↓ Bone resorption
Heart	↑ Cardioprotection	
Kidney	↑ Natriuresis ↑ Diuresis	

Figure 1. Effects of GLP-1 and GIP[1].

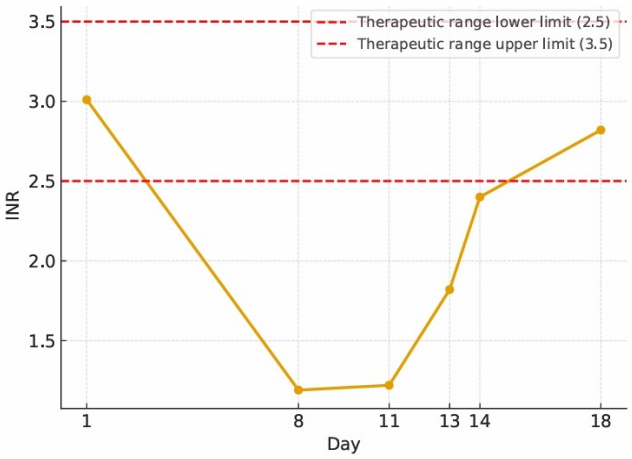


Figure 2. Trend of INR values during hospitalisation. The trend in INR values is shown below: day 1: 3.01; day 8: 1.19; day 11: 1.22; day 13: 1.82; day 14: 2.40; day 18: 2.82.

upon admission to hospitalisation may have interfered with the pharmacological action of warfarin; it should however be considered that a diet as similar as possible to that carried out by the patient was prescribed and that interfering foods were selected as little as possible with warfarin; in any case, considering the stability of the diet over the weeks, all this would not seem to explain the difficulty in reaching the INR target.

Tirzepatide has no known direct effects on INR; however, it may indirectly influence its course by delaying gastric emptying and thereby altering the absorption of both food and warfarin. This could result in slower attainment of peak plasma drug levels or modifications in the absorption of dietary components with potential anticoagulant interactions. In addition, tirzepatide may indirectly affect INR values through its side effects, such as nausea and vomiting, or by inducing changes in the intestinal microbiota[2].

CONCLUSION

Closer INR monitoring should be considered in patients treated with both tirzepatide and warfarin, even when no interfering dietary or pharmacological modifications are present.

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