CASE REPORT

Example of the drug interaction between ciclosporin and orlistat, resulting in relapse of Evan's syndrome

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SUMMARY

A man aged 35 years with a history of Evan's syndrome presented to the clinic with jaundice and shortness of breath, with further testing indicating a relapse of his previously well-controlled condition, for which he was taking ciclosporin. This followed shortly after he had started taking orlistat to prevent weight gain from a course of steroids, and once the orlistat was stopped, his platelets began to rise. The patient required 4 months of steroid treatment before his platelet levels finally stabilised and he could be put back on his regular medicine regime.

BACKGROUND

Ciclosporin is an immunosuppressant drug used in a variety of scenarios, including immune-mediated cytopenias and after organ transplantation to prevent rejection. Although very effective, a significant problem with ciclosporin is the large number of associated interactions. This report illustrates how interaction with orlistat, a lipase inhibitor used to treat obesity (and widely available over the counter in many countries), resulted in the reactivation of Evan's syndrome, and indicates why this is an important interaction for clinicians to be aware of in future.

CASE PRESENTATION

A man aged 35 years with a history of Evan's syndrome (immune thrombocytopaenic purpura, and autoimmune haemolytic anaemia) secondary to antiphospholipid syndrome presented to clinic with headache, jaundice and shortness of breath on exertion. He had been seen 2 months earlier by a respiratory physician with a 6-month history breathlessness, diagnosed to be due to restrictive lung disease after lung function tests—possibly caused by multiple massive pulmonary emboli he suffered 6 years earlier (which led to his diagnosis of antiphospholipid syndrome). Blood tests on admission showed a haemoglobin of 93 g/L, platelet count of 4×10^9 /L (figure 1), international normalised ratio (INR) of 3.4, direct antiglobin test+++, indicating a relapse of the Evan's syndrome. His condition had been well maintained for ~4 years taking ciclosporin 200 mg once a day.

Drug history elicited revealed him to have started taking orlistat, a lipase inhibitor used to treat obesity. This was started by the general practitioner at the patient's request, as he was worried about possible weight gain with steroids (recommended by the respiratory physician in an attempt to approve his lung function). The patient had been

taking the drug for 2 weeks, at the same time as his ciclosporin, prior to his admission, and it is undocumented whether he was experiencing the characteristic effect of steatorrhoea with the drug. He stopped taking the orlistat after noticing increasing jaundice and presented to hospital 4 days later, where his platelet count was 4×10^9 /L, and his ciclosporin levels were undetectable (his previous level, 1 month earlier, was 36 ng/mL).

As the initial management, his anticoagulation was reversed with vitamin K 5 mg intravenously, and prothrombin complex concentrates. He was started on 1 mg/kg of prednisolone. His platelet count gradually improved over the next few months. Once the platelet count reached 30×10^9 /L, he was started on dalteparin at prophylactic dose, which was increased to therapeutic level, once the platelet count was persistently over 50×10^9 /L. When his platelet count stabilised, he was restarted on warfarin. Ciclosporin for his Evan's Syndrome was reintroduced while he was continued on tapering doses of prednisolone; however, he required 4 months of steroid treatment before his platelet levels returned to the previous stable level $80\text{--}130 \times 10^9$ /L (figure 1).

DISCUSSION

Evans syndrome is defined as a combination of Coombs-positive autoimmune haemolytic anaemia and immune thrombocytopaenic purpura. First described in 1951 by Evans *et al*,¹ the exact pathophysiology remains unclear; however, it is thought to be due to the production of autoantibodies against red blood cells and platelets resulting in their destruction, and thus, episodes of haemolytic anaemia and thrombocytopaenia, respectively.

The first-line treatment of Evans syndrome involves intravenous corticosteroids and/or intravenous immunoglobulin;² however, as the syndrome runs a relapsing course, many patients require immunosuppressive drugs as second-line therapy. In our patient's case, this was ciclosporin.

The mechanism of action of ciclosporin involves interrupting the induction phase of the adaptive immune response by forming a complex with cyclophilin, which then binds to and inhibits calcineurin. Ciclosporin is a lipid-soluble drug, and its main site of absorption has been shown to be the small intestine.³ Hepatic metabolism of ciclosporin involves the cytochrome P450 system, with the main enzyme involved being CYP3A4,⁴ and its metabolism by this family of enzymes in part accounts for its wide range of interactions, as many

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Figure 1 Platelet levels plotted against time. The dotted line shows when the patient was started on orlistat, after which a few months of fluctuating levels can be seen, during which the patient was receiving steroid therapy, before his platelet levels were finally brought back to their previous steady count. Unfortunately, his platelet level directly prior to starting orlistat was not measured.

drugs are known to increase or decrease activity of the cytochrome P450 system.

Orlistat is a drug used in the treatment of obesity. Its mechanism of action involves inhibiting gastric and pancreatic lipases, which are responsible for hydrolysing triglycerides from the diet into readily absorbable free fatty acids.⁵

The reaction between ciclosporin and orlistat is thought to be related to orlistat's influence on lipid absorption. Orlistat has been shown to modestly increase CYP3A4 expression in human hepatocytes,⁶ indicating that absorbed orlistat may play a minor role in increasing ciclosporin metabolism. However, as the majority of orlistat is passed out in the stool, and is not absorbed systemically, it is unlikely for the key culprit of the interaction to be interference with its hepatic metabolism. The more likely causative factor for the interaction is therefore orlistat's reduction in lipid absorption from the small intestine, thereby limiting the vehicle by which ciclosporin enters the systemic circulation (as a highly lipid-soluble drug). Orlistat has been shown to reduce the absorption of ciclosporin by around a third⁷ and it can do so almost immediately after its administration. It has been considered whether this effect extends to other lipophilic drugs and drugs with narrow therapeutic indices, and Zhi *et al*^{7–9} have carried out a number of studies to this effect; however, a 2012 review found that the majority of these drugs were unaffected by concomitant administration of orlistat, but ciclosporin was significantly affected.¹⁰

The interaction between ciclosporin and orlistat has been previously reported, although almost exclusively in patients who have undergone solid organ transplantation,^{11–13} and the consequences of their concomitant administration cannot be underestimated. Indeed, their concomitant use is contraindicated in the current prescribing information for orlistat,¹⁴ however, this can easily go unnoticed by clinicians, hence the importance of highlighting this case as a learning tool for general clinicians. Patients undergoing transplant have been known to experience weight gain in the year following their surgery,¹⁵ which may cause general practitioners to consider prescribing orlistat, and

it is therefore important that they are aware of the possible consequences of their coadministration, as reduced plasma levels could lead to episodes of acute rejection. Patients who take ciclosporin to control autoimmune disorders are likely to also occasionally require corticosteroids for flare-ups of their condition, and as a significant side effect of corticosteroids is weight gain, it is important for physicians to be aware of the consequences of prescribing them together. It should also be noted that orlistat is available over the counter, and so clinicians prescribing ciclosporin should be careful to warn patients to be

Learning points

- ▶ The absorption of many drugs (in this case, ciclosporin) relies on their lipid solubility, and they can be metabolised and excreted through a variety of pathways; therefore, drugs that interfere with lipid absorption have the potential to interfere with the absorption of these drugs.
- ▶ Ciclosporin is used for a wide range of conditions, from organ transplant to severe psoriasis, however has a number of known associated interactions and should be regarded with caution.
- ▶ Orlistat is widely available for over-the-counter purchase around the world.
- ▶ Caution should be used when prescribing orlistat concomitantly with any drug whose absorption relies on its lipid solubility, and prescribing information should be consulted.
- ▶ As a broader learning point, clinicians should always check for interactions when prescribing any combination of drugs where there is any degree of unfamiliarity, and warn patients to be cautious when purchasing over-the-counter medicines.

cautious with over-the-counter medicines, as should pharmacists when requested to dispense orlistat by a patient.

To conclude, we have illustrated the case of a patient with Evan's syndrome who relapsed following the initiation of orlistat because its interaction with ciclosporin was overlooked. It is important that physicians are aware of this interaction to avoid serious consequences and prolonged hospitalisations, which was required in the present case.

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