Is there an interaction between erythromycin and statins?

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Background

Erythromycin is a macrolide antibiotic and an inhibitor of liver isoenzyme cytochrome P450 (CYP) 3A4 (1). Inhibition of CYP may result in reduced metabolism of medicines dependent on this isoenzyme and may lead to increased plasma concentrations and potentially cause toxic effects (2). There are other possible mechanisms of interactions between erythromycin and statins; erythromycin inhibits P-glycoprotein (P-gp) which may lead to an increase in statin absorption or reduced biliary secretion. Erythromycin also inhibits organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3); these uptake transporters play a role in the disposition of certain statins (3, 4).

There are currently 5 statin drugs available in the UK, for the management of high cholesterol: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin (5). They are all metabolised by various liver isoenzymes, therefore the potential for an interaction with erythromycin exists. Increased plasma concentrations of statins can increase the risk of muscle disorders such as myopathy and/or rhabdomyolysis (6-10).

Rhabdomyolysis is the breakdown of muscle fibres resulting in the release of muscle fibre contents (myoglobin) into the bloodstream. Myoglobin can be harmful to the kidney and raised plasma levels can result in kidney damage. Rhabdomyolysis is rare but can be fatal (11, 12). Cases of acute rhabdomyolysis have been noted in patients taking simvastatin with erythromycin or clarithromycin, as well as in patients taking other statins and a macrolide antibiotic (13).

Answer

Atorvastatin

Atorvastatin is metabolized by CYP3A4 and is a substrate of the OATP1B1 transporter (3-6). Co-administration of a single 10mg dose of atorvastatin and erythromycin (500mg four times daily) in 12 healthy subjects raised the maximum plasma concentration (Cmax) and systemic exposure as signified by the area under the curve (AUC) of atorvastatin by 38% and 33% respectively (6, 13, 14). The manufacturer of Lipitor® states that the risk of myopathy may be increased with moderate inhibitors of CYP3A4 such as erythromycin (6). The concomitant use of atorvastatin plus erythromycin or clarithromycin should be avoided if possible, with temporary suspension of atorvastatin if erythromycin is to be taken for a short period (15). If concurrent administration is unavoidable, lower doses of atorvastatin (maximum 20mg daily) should be considered (6, 15, 16). Appropriate clinical monitoring (unexplained muscle pain, tenderness or weakness or dark coloured urine) of these patients is recommended (6, 13).

Fluvastatin

Fluvastatin is substantially metabolised by CYP2C9 and is a substrate of the OAPT1B3 transporter (4). Concomitant administration with erythromycin has minimal effects on the bioavailability of fluvastatin (3, 4, 7). The results from an interaction study with a small number of healthy volunteers suggested that the steady state plasma levels of fluvastatin 40mg daily were not affected by a single dose of erythromycin 500mg and that fluvastatin and erythromycin do not appear to be metabolised by the same isoenzyme (7, 13). Therefore, fluvastatin can be used concomitantly with erythromycin without any need for dose adjustments or additional monitoring.

Pravastatin

Pravastatin is not metabolised to a clinically significant extent by the CYP isoenzymes (8). This has been shown in a short trial where pravastatin 40mg or lovastatin was given to 12 healthy subjects once daily for 14 days followed by a further week with erythromycin 500mg three times daily. The pharmacokinetics of pravastatin did not change (13, 17).

However, in another interaction study in healthy individuals, the administration of erythromycin 500mg three times daily with pravastatin 40mg daily resulted in a statistically significant increase in the Cmax (121%) and AUC (70%) of pravastatin (8). This suggests a different mechanism of interaction between erythromycin and pravastatin (13). Pravastatin is a substrate of both OATP1B1 and OATP1B3 transporters which could explain the increase in Cmax and AUC of pravastatin in the above study (3). Until more information is available, pravastatin should be used cautiously with erythromycin and patients should be warned to be alert for signs of myopathy (i.e. unexplained muscle pain, tenderness or weakness or dark coloured urine (8, 13, 15, 16).

Rosuvastatin

Rosuvastatin undergoes limited metabolism with approximately 90% of the dose being excreted unchanged in the faeces. The other 10% is metabolised principally by CYP2C9 (9, 12). Concomitant use of erythromycin (500mg four times daily for 7 days) and a single 80mg dose of rosuvastatin in 11 healthy subjects resulted in a 20% decrease in AUC and a 30% decrease in Cmax of rosuvastatin (9, 18). This interaction may be caused by the increase in gut motility caused by erythromycin, or that rosuvastatin is a substrate of both OATP1B1 and OATP1B3 transporters (3). It is not considered to be clinically relevant, if short-term courses of erythromycin are used (9, 13, 18). Therefore, rosuvastatin can be used concomitantly with erythromycin without any need for dose adjustments or additional monitoring.

Simvastatin

Simvastatin is metabolised by CYP3A4 and OATP1B1 (10, 13). Inhibitors of CYP3A4 such as erythromycin increase plasma levels of simvastatin, and significantly increase the risk of myopathy and rhabdomyolysis during concomitant treatment.

In an interaction study, a single dose of simvastatin 40mg was given to 12 healthy individuals. After 2 days of placebo or erythromycin (500mg three times daily), the plasma levels and AUC of simvastatin and its active metabolite were increased 6.2-fold and 3.9-fold respectively (19).

An 80-year old gentleman was admitted to hospital, following a one week history of myalgia and inability to walk. Investigations revealed elevated liver function tests, myoglobinuria and high creatine kinase. He subsequently developed renal failure requiring haemofiltration. His drug history showed a four week course of erythromycin whilst concurrently taking simvastatin. The authors concluded that the patient had experienced a delayed interaction between a past completed four week course of erythromycin and simvastatin. The patient made a full recovery (20).

A man aged 83-years who was receiving stable therapy with simvastatin 80mg per day was hospitalized with rhabdomyolysis for 1 to 2 weeks following treatment with erythromycin (500mg four times daily) for 10 days for pneumonia. Four weeks after taking the erythromycin he experienced myalgia, muscle weakness, functional disability and serum creatine kinase levels more than 60 times the upper limit of normal. He made a full recovery (21).

In another case, an 85 year man was treated as an outpatient for pneumonia with a 10 day course of erythromycin 500mg twice daily. His regular medication included simvastatin 80mg once daily. After several days he developed reduced mobility, lethargy and sustained two falls which were attributed to generalised weakness. He was admitted to hospital and further tests showed a serum creatine kinase level of 27813 IU (normal range 20-215 IU). The patient was diagnosed with simvastatin-associated

rhabdomyolysis. Both the simvastatin and erythromycin were stopped and the patient physical condition improved, allowing eventual discharge to home (22).

A 70-year old man developed myalgia and fatal rhabdomyolysis after receiving a 4 week course of erythromycin 250mg four times a day concomitantly with his regular simvastatin 40mg daily (23).

A population-based cohort study, with a primary outcome measure of hospitalisation within 30 days of antibiotic prescription being initiated, concluded that in older patients, co-prescription of either erythromycin or clarithromycin with a statin that is metabolised by CYP3A4 increases the risk for statin toxicity (24).

Due to this increased risk of myopathy and rhabdomyolysis, the Medicines and Healthcare products Regulatory Authority (MHRA) recommends against the concomitant prescribing of simvastatin and erythromycin (25). Both the manufacturers of erythromycin and simvastatin contraindicate this combination (10, 26). If erythromycin use is essential in patients prescribed simvastatin, then simvastatin therapy should be held for the duration of the course of erythromycin. If erythromycin use is going to be long-term, an alternative lipid-lowering agent with less potential for interaction should be considered.

Summary

- Erythromycin raises the plasma levels of statins which are metabolised by CYP3A4 (i.e. atorvastatin and simvastatin), but in practice not all patients are affected.
- Simvastatin is contraindicated in patients taking erythromycin and should be withdrawn if the antibiotic is required for the duration of the antibiotic treatment course and then restarted.
- Atorvastatin and erythromycin may be used together with caution. It may be prudent to withhold atorvastatin if erythromycin treatment is required to avoid any potential adverse effects. If concurrent administration is unavoidable, then a lower dose of atorvastatin (maximum 20mg daily) should be considered.
- The interaction between erythromycin and statins that are metabolised by CYP3A4 can be delayed such that the patient experiences the effects after the erythromycin course has been completed.
- Fluvastatin, pravastatin and rosuvastatin are not metabolised by CYP3A4, however pravastatin exposure is possibly slightly increased by erythromycin, suggesting that another mechanism of interaction may be involved such as inhibition of OATP1B1 and OATP1B3.
- Rosuvastatin and fluvastatin do not appear to be affected by erythromycin in pharmacokinetic studies, and therefore an increased risk of rhabdomyolysis with these statins and erythromycin would seem unlikely. However until more information is available in relation to other potential interaction mechanisms, caution is advised with the concomitant use of erythromycin with fluvastatin, pravastatin and rosuvastatin.
- If co-prescription with a drug that increases systemic exposure to statins is unavoidable, it is particularly important to start on the lowest statin dose. Any patient who is given a statin concomitantly with a macrolide antibiotic such as erythromycin should be warned to be alert for any signs of myopathy (i.e. unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately.

Limitations

The clinical significance of enzyme inhibition interactions depends on the extent to which the serum levels of the drug rise. Information on the interaction between erythromycin and statins is limited to reports of small interaction studies conducted in healthy individuals. Interactions between statins and other macrolide antibiotics have not been considered in this Q&A.

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Search strategy
1. In-house database/ resources (including British National Formulary, Martindale: the Complete Drug Reference, Drugdex, UpToDate, Stockley's Drug Interactions, Summary of Product Characteristics accessed via Electronic Medicines Compendium, Sanford guide and John Hopkin's ABX guide).

2. Embase: erythromycin(it) + (simvastatin OR atorvastatin OR pravastatin OR rosuvastatin OR fluindostatin) [Limit to: Publication year 2018-2020]

3. Medline: erythromycin + (simvastatin OR atorvastatin OR pravastatin OR rosuvastatin OR fluvastatin) + drug interactions [Limit to: Publication year 2018-2020]