Unexpected antimicrobial effect of statins

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Objectives: Epidemiological studies of statins have suggested a link between statin therapy and a decreased risk of sepsis. It has been proposed that the mechanism underlying this apparent protective effect of statins relates to their known immunomodulatory and anti-inflammatory effects. The aim of this study was to explore the antimicrobial effect of statins.

Methods: Simvastatin (Merck) and fluvastatin (Novartis) were both tested against six of each of methicillin-susceptible and -resistant Staphylococcus aureus (MSSA and MRSA), and vancomycin-sensitive and -resistant enterococci (VSE and VRE) using a microtitre dilution method. The test was repeated five times for both statins against all 24 isolates. Vancomycin, linezolid and propranolol were used as controls, as appropriate.

Results and discussion: Simvastatin showed a significant antimicrobial effect against MSSA (mean MIC 29.2 mg/L) and to a lesser extent against MRSA (mean MIC 74.9 mg/L). Fluvastatin had a significantly less marked antimicrobial effect. Propranolol showed no antimicrobial effect. Simvastatin has a considerable antimicrobial effect in vitro and further testing of it is warranted.

Keywords: antimicrobial activity, susceptibility testing, Staphylococcus aureus

Introduction

Statins are a class of lipid lowering drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase leading to decreased cholesterol and isoprenoid synthesis. Several recent studies have shown a link between statin use and a decreased risk of sepsis and inflammation. Pre-treatment with atorvastatin in one study was found to significantly reduce cytokine release and endothelial neutrophil adhesion to the venous endothelium in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Recent work has suggested that there is a 19% reduced risk of sepsis in patients with atherosclerosis who take statins. Patients taking statins at the time they develop pneumonia or other serious infections are less likely to go on to develop sepsis, die from sepsis or develop complications necessitating admission to an intensive care unit. These effects are thought to be due to the known pleiotropic properties of this class of drugs, including anti-inflammatory, immunomodulatory and antioxidant effects.

Another mechanism that may explain why patients on statin therapy appear to have better outcomes than patients not on statin therapy would be a direct antimicrobial effect.

Many drugs not thought of traditionally as antimicrobials have some effect in vitro. We hypothesized that some of the benefits apparently conferred by statins in sepsis might be due to a previously unrecognized antimicrobial effect. The aim of this study was to assess whether there was any direct antimicrobial effect of two statins on blood culture isolates of staphylococci and enterococci.

Materials and methods

Six of each of methicillin-susceptible Staphylococcus aureus (MSSA), methicillin-resistant S. aureus (MRSA), vancomycin-sensitive enterococci (VSE) and vancomycin-resistant enterococci (VRE) blood culture isolates were recovered from frozen or ambient stores by spreading on blood agar plates and inspecting for contamination after overnight incubation. Four to five colonies of pure isolate were frozen in Microbank beads (Pro-Lab Diagnostics, UK) at −80°C.

The night before each experiment, one bead was removed from each tube, thawed at room temperature and spread on to a blood agar plate which was then incubated at 35°C in air for 18–24 h. The test organisms from these plates were made up to a turbidity equivalent to that of a 0.5 McFarland standard then diluted 1:100 in Mueller–Hinton broth. These inocula were prepared immediately prior to each experiment. Testing was by a
method based on the classical microtitre broth dilution recommended by the CLSI (formerly the NCCLS).

Simvastatin (Merck) and fluvastatin (Novartis) were obtained from the manufacturer as pure drugs and dissolved in methanol to give an initial concentration of 1 g/L. The first test well therefore contained a concentration of 500 mg/L after the addition of isolate broth. There were eight further wells tested, each with half the concentration of the previous and the concentration in the final well tested was 1.95 mg/L. The range of concentrations of each test drug was duplicated on each microtitre tray and each tray repeated twice so that in total each drug had been tested against each isolate six times. The trays were read after 18–24 h of incubation at 37°C in air. Positive growth and negative sterility controls, and a methanol control were included on each microtitre tray.

Vancomycin was used as the antibiotic control for the four isolates except for VRE, where linezolid (Zyvox, Pharcma, UK) was used. Propranolol (Inderal, Astra Zeneca, UK) at an initial concentration of 0.1 mg/mL was also used as a control.

The MIC of the statin was taken to be that at which there was no visible growth. If the contents had precipitated, the plates for that isolate were repeated. If all the contents precipitated on repeating, no results were recorded for that isolate/drug combination.

Results and discussion

Figure 1 shows the average MICs achieved for simvastatin compared with fluvastatin against the four organisms. Both statins demonstrated antimicrobial activity; however, the MICs of fluvastatin were consistently higher compared with simvastatin. Propranolol showed no antimicrobial activity.

Many drugs used for non-infectious illnesses have been found to have in vitro antimicrobial activity against some bacteria. Statins have been reported to be beneficial in patients with sepsis. Immunomodulation has been postulated as the likely mechanism but may not be the only one. Our results demonstrate that part of the perceived benefits of statins in preventing infection may be due to their antimicrobial properties. HMG-CoA reductase, the target of statins, is essential in prokaryotes but it is required for the biosynthesis of isoprenes, not sterols as in eukaryotes. Furthermore, the bacterial HMG-CoA reductase is of a different structural class with an affinity for statins that is ~10,000 times weaker than the enzyme found in eukaryotes. Thus, it is highly unlikely that the antimicrobial effect we have seen can be attributed to a known mechanism of action of statins, and there is therefore the possibility that this represents a new and potentially important class effect.

Available evidence suggests that the typical peak plasma concentration of simvastatin attained in healthy adult volunteers after a 40 mg oral dose is 0.0209 mg/L and therefore many times lower than the MIC achieved in our study. Most people take statins for prolonged periods and it is therefore possible that the steady-state plasma simvastatin level would be higher. Most statin users are likely to be older, and this too may result in higher plasma simvastatin levels compared with healthy volunteers. An additional consideration is that simvastatin is a pro-drug which is converted in the liver to the active form and antimicrobial activity of the metabolites is not known. The circulating level of simvastatin is low but the levels or activity of metabolites may be higher. Thus, it would be premature to conclude that there is no antimicrobial effect of statins with normally attainable serum concentrations as used in current clinical practice.

There was a striking difference between the MICs achieved by the two drugs. One possible explanation could be related to how they are produced. Simvastatin is obtained after fungal fermentation, whereas fluvastatin is obtained by chemical synthesis. Many traditional antibiotics, for example penicillin, are fungal products or have been derived from them, so it is reasonable to speculate that simvastatin, as a natural product, might have more intrinsic antibacterial activity than a structurally related but synthetic compound such as fluvastatin.

These statins, in particular simvastatin, have an unexpected antimicrobial effect in vitro but require concentrations that are far higher than are probably achieved in vivo with traditional indications for statins. Therefore, statins probably do not exert a significant antimicrobial effect in patients, but these data have revealed an unanticipated class effect and further testing of statins and their metabolites is warranted.

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Transparency declarations

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References


