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 + MRSA), and vancomycin-sensitive and -resistant enterococci (VSE + 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 saves by spreading on blood agar plates and inspected 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 con-
centration 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 all the isolates
except for VRE, where linezolid (Zyvox, Pharmacia, 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 com-
pared with fluvastatin against the four organisms. Both statins
demonstrated antimicrobial activity; however, the MICs of flu-
vasatin 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 bac-
teria. Statins have been reported to be beneficial in patients
with sepsis. Immune modulation 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 pre-
venting infection may be due to their antimicrobial properties.
HMG-CoA reductase, the target of statins, is essential in prokar-
yotes 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 simvasta-
tin is low but the levels or activity of metabolites may be higher.
Thus, it would be premature to conclude that there is no anti-
microbial effect of statins with normally attainable serum concen-
trations 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 syn-
thesis. Many traditional antibiotics, for example penicillin, are
fungal products or have been derived from them, so it is reason-
able 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


