Neither moxifloxacin nor cefuroxime produces significant attenuation of inflammatory mediator release in patients exposed to cardiopulmonary bypass: a randomized controlled trial

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Objectives: In vitro and experimental studies in animals have established the anti-inflammatory effects of moxifloxacin. Cardiopulmonary bypass (CPB) leads to an inflammatory response. The aim of this study was to assess whether the inflammatory cytokine response to CPB is reduced with a perioperative antibiotic prophylaxis, either moxifloxacin or cefuroxime (the standard prophylaxis).

Patients and methods: Twenty-eight patients scheduled for elective coronary artery bypass grafting with CPB were randomly assigned to receive either moxifloxacin or cefuroxime as the perioperative antibiotic prophylaxis. Interleukin (IL)-6, -8, -10 and tumour necrosis factor-α (TNF-α) serum concentrations were determined at eight time points before and after CPB.

Results: In both groups, all cytokine concentrations significantly increased after the start of CPB. There were no statistically significant differences between the moxifloxacin and cefuroxime groups at any point; IL-6 concentrations [median (interquartile range)] 240 min after CPB, the primary endpoint, were 364 (192–598) and 465 (325–906) pg/mL (P = 0.323), respectively.

Conclusions: Neither moxifloxacin nor cefuroxime produced significant attenuation of the inflammatory cytokine response to CPB. The reasons why moxifloxacin did not have significant anti-inflammatory effects in this unique clinical situation may be: (i) the inflammatory response to CPB may be different from that of infectious disease states that were used to establish the immunomodulatory effects of moxifloxacin; and (ii) a single intravenous dose, which was used in this investigation, may not lead to high enough plasma and intracellular concentrations.

Keywords: fluoroquinolones, cephalosporins, inflammation, cardiac surgery

Introduction

In addition to its anti-infective properties, the fluoroquinolone moxifloxacin has immunomodulatory effects.1 For example, in lipopolysaccharide (LPS)-stimulated monocytes and neutrophils, moxifloxacin inhibited the release of interleukins (ILs) and tumour necrosis factor-α (TNF-α). Cerebral inflammation was reduced in rats exposed to cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA) at 15–18°C.2 The inflammatory response to CPB has been well described.3 It is triggered by the contact of blood with non-endothelial surfaces, ischaemia–reperfusion injury and endotoxaemia; a characteristic increase of ILs and TNF-α can be observed.4,5 Therefore, in this study we investigated whether there is an attenuation of the inflammatory cytokine response to CPB using either moxifloxacin as perioperative antibiotic prophylaxis or cefuroxime, the standard therapy.

Patients and methods

After approval by the local Ethics Committee and the regulatory authorities (EudraCT number 2006-000369-12), 30 patients scheduled for...
elective coronary artery bypass grafting (CABG) with CPB were selected. These patients were between 18 and 80 years old, gave their written informed consent and were enrolled in the study from February 2009 to December 2010. Exclusion criteria were: body mass index >30 kg/m²; ejection fraction <50%; heart rate <40 beats/min; symptomatic arrhythmia; intake of drugs that are associated with torsades de pointes and/or QT prolongation (e.g. amiodarone and tricyclic antidepressants); serum potassium <3.8 or >5.0 mmol/L; serum creatinine >1.3 mg/dL; serum glutamic pyruvic transaminase (SGPT) >50 U/L; steroid therapy; hypersensitivity to fluoroquinolones, cephalosporins or other drugs with the possible need for steroid therapy; antibiotic therapy for infection diseases within the previous 2 weeks; tendinopathy due to former fluoroquinolone therapy; pregnancy; and nursing mothers.

For perioperative antibiotic prophylaxis, the patients randomly received either 400 mg of moxifloxacin intravenously after induction of anaesthesia (moxifloxacin group) or 3 x 1.5 g of cefuroxime (after induction of anaesthesia, then 8 and 16 h thereafter) with an additional dose of 2.25 g in the CPB circuit (cefuroxime group). Antibiotic prophylaxis selection was not blinded. For unrestricted randomization, a list created by a random number generator was used. The whole implementation (generation of the random allocation sequence, enrolment and assignment of the participants to interventions) was done by the investigators. Two patients had to be excluded (one in each group): one operation was cancelled, and one patient had combined surgery (CABG and aortic valve replacement). No serious adverse events were observed.

All patients received a balanced anaesthetic. For extracorporeal circulation, a standardized CPB setup with a membrane oxygenator (Compactflo Evo®, Sorin, Mirandola, Italy) was used, with non-heparinized tubing and bovine heparin for anticoagulation. After cross-clamping of the aorta, cold blood cardioplegia was used for cardiac arrest. CABG surgery was performed with mild hypothermia (32°C).

As part of cardiac anaesthesia quality assurance, we recorded sex, age, height, weight, duration of CPB and aortic cross-clamping (AoX), need for catecholamine therapy after CPB (none, low or high dose), and rethoracotomy for any reason within the first 24 h. Low dose catecholamine therapy was defined as dopamine ≤5 μg/kg/min and/or epinephrine ≤200 μg/h and/or norepinephrine ≤500 μg/h; high dose was defined as levels above these.

Blood samples to determine the concentrations of IL-6, IL-8, IL-10 and TNF-α were obtained before induction of anaesthesia, 30 min after the antibiotic had been given, at the beginning of CPB, at the end of CPB, 30, 120 and 240 min after the end of CPB, and 24 h after the antibiotic had been given. The cytokines were measured using a solid-phase, enzyme-labelled chemiluminescent sequential immunometric assay (Immulite®, Siemens Healthcare Diagnostics, Eschborn, Germany). The lower limits of detection were 2 (IL-6), 4 (TNF-α) and 5 pg/mL (IL-8 and IL-10), respectively. For data evaluation, values below the detection limit were set to 0.

The difference in IL-6 concentration at 240 min after the end of CPB between the moxifloxacin and the cefuroxime groups was the primary outcome variable. Referring to a former study, a total sample size of 28 was necessary to detect a mean difference of 100 pg/mL (α within each group 100 pg/mL, α of 0.05 and a power of 0.8 (GPOWER for MS-DOS, Franz Faul & Edgar Erdfelder, Bonn, Germany)). All other differences in the cytokine concentrations between and within both groups were considered as secondary outcomes. Between group comparisons were performed with Fisher’s exact tests (sex and need for rethoracotomy), Freeman–Halton test (need for catecholamine therapy after CPB) and Student’s t-tests for normally distributed data (patient characteristics and perioperative data), and Mann–Whitney U-tests for non-normally distributed data (IL-6, IL-8, IL-10, TNF-α). The Wilcoxon test was used for the within-group comparisons of cytokine concentrations. P < 0.05 was considered significant, and the SPSS for Windows software package v17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

The patient characteristics and perioperative data are summarized in Table 1. There was a statistically significant continuous

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<td>Variable</td>
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<td>Need for rethoracotomy (n)</td>
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CPB, cardiopulmonary bypass; AoX, aortic cross-clamping.

αData are means ± SD.

βLow dose, dopamine ≤ 5 μg/kg/min and/or epinephrine ≤ 200 μg/h and/or norepinephrine ≤ 500 μg/h; high dose, above these levels.
increase in all cytokines after the start of CPB, in both groups. The concentration time course of IL-6 is shown in Figure 1. The maximum concentrations [median (interquartile range)] of IL-6 [57.6 (35.2–94.2) and 42.4 (31.0–85.1) pg/mL] and TNF-α [15.7 (12.2–24.2) and 21.5 (13.0–27.2) pg/mL], for moxifloxacin and cefuroxime groups, respectively, were both reached at 240 min after CPB. The corresponding values of IL-10 [37.8 (20.1–82.1) and 36.4 (14.4–80.3) pg/mL] were reached at the end of CPB. There was no time at which the IL or TNF-α concentration was statistically significantly lower in the moxifloxacin group compared with the cefuroxime group. The P value for the primary endpoint (IL-6: 240 min after CPB) was 0.323.

**Discussion**

Despite its well-established immunomodulatory properties, moxifloxacin did not prevent continuous increase in cytokines after CPB, nor did it produce statistically significantly lower concentrations than cefuroxime.

The immunomodulatory effects of fluoroquinolones depend on cell type, co-stimulation, stimulant, drug concentration and type of fluoroquinolone. For example, moxifloxacin inhibits the secretion of ILs and TNF-α in monocytes stimulated with LPS, but not if pan-sorbin is used instead of LPS. In human bronchial epithelial cells 24 h incubation with 8 mg/L moxifloxacin, in contrast to cefuroxime, reduced spontaneous IL-8 release. In the same study, the TNF-α-stimulated IL-8 release was reduced at a moxifloxacin concentrations of at least 4 mg/L. All these concentrations are higher than the maximum concentration that was observed (3.62 mg/L) after the recommended intravenous single daily dose (400 mg).

Recently, the influence of moxifloxacin on cerebral inflammation after CPB and DHCA was investigated in rats. Moxifloxacin, 6×100 mg/kg every 2 h intraperitoneally, reduced the number of hippocampal neurons positive for inflammatory markers, such as TNF-α, nuclear factor-κB and cyclooxygenase 2. Unfortunately, CPB without DHCA was not investigated.

Clinical studies in patients on the immunomodulatory properties of moxifloxacin have focused on immunodepression after stroke. In the PANTHERIS trial, Harms and co-workers investigated the immunodepression after 2. Unfortunately, CPB without DHCA was not investigated. The reason for this is unclear because this study was performed at the same institution (German Heart Centre Munich) under similar conditions. This greater variability reduces the power of our study, but it is in line with a recently published study dealing with cefuroxime, the standard antibiotic prophylaxis.

In conclusion, moxifloxacin failed to significantly attenuate inflammatory mediator release in the unique clinical situation of CPB. There are two possible reasons: firstly, contact activation, the major trigger during CPB, is different from the inflammatory pathways that are activated during infectious disease; and secondly, a single intravenous dose of 400 mg of moxifloxacin may not lead to plasma and intracellular concentrations that are high enough to have significant anti-inflammatory effects.

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**Transparency declarations**

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**References**

Moxifloxacin and cefuroxime effects on inflammatory response


