

CHANGES OF THE SERUM ANTIBIOTIC LEVELS DURING OPEN HEART SURGERY (ceftazidim, ciprofloxacin, clindamycin)

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Summary: **Background:** Wound, mediastinal and intracardiac infections are still very serious complications of open-heart surgery. The incidence of it is still in the range of 0,4%-5%. The aims of our study were to assess the adequacy of regimen using ceftazidim (CTZ), ciprofloxacin (CPF) and clindamycin (CLIN) as prophylactic antibiotics and to verify whether cardiopulmonary bypass (CPB) can modify the time of antibiotic serum concentrations. That is why the serum levels of them were measured during open heart procedures. **Methods:** The prospective study comprised 75 consequent coronary patients randomized in to three groups receiving 1 g of CTZ or 400 mg of CPF or 900 mg of CLIN i.v. with anesthesia induction. Routine coronary surgery with left internal mammary artery harvesting, moderate body hypothermic (30 °C) CPB with crystalloid cardioplegia was performed. Serum antibiotic levels were determined before application, with skin incision, prior CPB induction, after cardioplegia infusion, every 20 minutes of CPB, prior end of CPB, in time of chest closure. Conventional cylinder – plate microbiological assay was used for antibiotic level measurement. **Results:** All serum antibiotic concentrations showed a sharp decrease immediately after starting CPB and lasted until CPB ended. After initiating of CPB after cardioplegia administration serum concentrations of CTZ (105 min after initial dose) decreased by, on average 55%, CPF (97 min) by 42% and CLIN (116 min) by 78%. **Conclusion:** CPB can modify the time course of antibiotic serum concentrations. The serum levels of CTZ at the end of the longest procedures were found to be below the MICs for some of the suspected pathogens. We recommend to use higher antibiotic doses for prophylaxis and to administer the second dose with protamin sulphate to obtain maximum concentration in newly formed blood clots.

Key words: Cardiac surgery; Cardiopulmonary bypass; Antibiotic prophylaxis; Serum antibiotics concentrations

Introduction

Wound, mediastinal and intracardiac infections are still very serious complications of open-heart surgery. In a review article, Oakley and Wright (1,22) found a reported incidence varying from 0,4 to 5%. The reported prevalence rate for **all** nosocomial infections connected with cardiac procedures most commonly ranges from 5% to 20%, but can be significantly greater among patients requiring long postoperative intensive care (13). The mortality rate of patients developing nosocomial infection ranges between 10% and 50% (2,4,5).

The antibiotic (atb) prophylaxis of bacterial infections during cardiac surgery is widely used in clinical practice since Geraci, Dale, and McGoon (8) in 1963 reported about a 10% incidence of prosthetic endocarditis with staphylococci, and the benefit of it has been confirmed in the meantime in controlled studies by several authors (6,7,9,14,15,19,21,26,).

It is generally agreed that the success of prophylaxis is dependent on the ability to reach and maintain free antibiotic concentrations in tissues higher than the minimum inhibitory concentrations (MICs) for the most common suspected pathogens and must remain at these concentrations throughout the operation. There is also evidence that effective antimicrobial prophylaxis is mainly due to an exposure to antibiotics during the operation period, as continuation of therapy after surgery does not achieve better clinical results than single day administration (26).

Until recently *Staphylococcus aureus* and *epidermidis* are still the pathogens most frequently involved in infective complications of cardiopulmonary bypass (CPB) surgery (10,12,17,19,23,24,25,26). At present we can observe the increase of Gram-negative infections too, especially caused by *Pseudomonas aeruginosa*, *Enterobacter species*, *Acinetobacter species* (16).

The aims of our study were to assess the adequacy of our regimen using ceftazidim (CTZ) (KEFADIM LILLY, Eli

Lilly, Italia S.p.A., Sesto Fiorentino, Italy), ciprofloxacin (CPF) (CIPRINOL® KRKA p.o., Novo Mesto, Slovenia) and clindamycin (CLIN) (DALACIN C™ UPJOHN, s.a.-Puurs-Belgium) as prophylactic antibiotics and to verify whether CPB can modify the time course of antibiotic serum concentrations. That is why the serum levels of them were measured during open-heart procedures. Our results were compared to standard producers data obtained after administration of 1g of CTZ, 200 mg of CPF (we were not able to find in the literature the standard curve after the dose of 400 mg) and 900 mg of CLIN to healthy volunteers.

We have chosen three different types of antibiotics which represents three different groups of them (cephalosporin group, chinolone group and lincomycine group) for our study. Ceftazidim and ciprofloxacin are not routinely used for prophylaxis at our department and were used as the model ones only. Clindamycin we have routinely used for prophylaxis in former years as the antistaphylococcal agent.

Methods

The prospective study comprised 75 consequent coronary patients randomized in three groups. In *Group 1* - 1 g of CTZ i.v. (basic antibiotic dose) was given with anesthesia induction, 8 hours further dosage interval, 48 hours prophylaxis was used. In *Group 2* - 400 mg of CPF i.v. (medium antibiotic dose) was given with anesthesia induction, 12 hours further dosage interval, 48 hours prophylaxis was used. In *Group 3* - 900 mg of CLIN i.v. (medium antibiotic dose) was given with anesthesia induction, 8 hours further dosage interval, 48 hours prophylaxis was used. The doses of antibiotics were chosen on the basis of producers recommendation. The dose 1 g for CTZ is recommend for treatment of noncomplicated cases, the dose 400 mg of CPF and 900 mg of CLIN are recommend for treatment of complicated infective cases. We wanted to follow the antibiotic levels after different doses of them.

There were no detectable differences between each group of patients with regard to demographics in our operative details (age, sex, body surface, number of grafts etc.). We have performed routine coronary surgery with LIMA harvesting. Standard cardiopulmonary bypass, SAFE II closed oxygenating system (POLYSTAN A/S, Vaerlose, Denmark), 30 °C systemic hypothermia, 4 °C St. Thomas antegrade cardioplegic arrest, two-stage venous return and ascending aortic perfusion were used. Non colloid, antibiotic free priming is routinely used at our department (Tab. 1). The hematocrit levels were maintained between 20 - 25%.

Serum antibiotic levels were determined at the following intervals (Tab. 2). Blood samples (5 ml) were taken via arterial catheter.

Conventional cylinder-plate microbiological assay (modif. acc. Growe-Randall: „Assay Methods of Antibiotics Laboratory Manual”, 1958) was used for antibiotic levels

Tab 1: Oxygenator prime.

Hartmanns' solution	750 - 1000 ml (acc.weight)
Rheomacrodex 3%	500 ml
Mannitol 10%	1,0 g/kg
Natrium bicarbonate 8,4%	1 mmol/kg
Magnesium sulphuricum 20%	10 ml
Heparin	2500 U
Metylprednisolon	5 mg/kg
Ascorbic acid	1000 mg

Tab. 2: Sampling intervals,

1. Before atb application
2. Skin incision
3. Prior CPB institution
4. After cardioplegia administration
5. Every twenty minutes of CPB
6. Prior end of CPB
7. Chest closure

Tab. 3: Standard concentrations of ceftazidim after administration of 1 g i.v.

• After 1 hour	65 mg/l
• After 2 hours	28 mg/l
• After 4 hours	10 mg/l
• After 8 hours	2 mg/l

Tab. 4: Standard concentrations of ciprofloxacin after administration of 200 mg i.v.

• After 1 hour	3,5 mg/l
• After 2 hours	2,8 mg/l
• After 4 hours	1,1 mg/l
• After 6 hours	0,8 mg/l
• After 12 hours	0,1 mg/l

Tab. 5: Standard concentrations of clindamycin after administration of 900 mg i.v.

• After 30 minutes	10,5 mg/l
• After 1 hour	7,65 mg/l
• After 2 hours	6,9 mg/l
• After 4 hours	4,2 mg/l
• After 8 hours	2,4 mg/l

Tab. 6: MICs of ceftazidim (Univ. Teach. Hosp. Hradec Králové).

Staphylococcus aureus	4 - 8 mg/l
Staphylococcus epidermidis	16 mg/l
Pseudomonas aeruginosa	2 mg/l
Acinetobacter species	8 - 16 mg/l

Tab. 7: MICs of ciprofloxacin (Univ. Teach. Hosp. Hradec Králové).

Staphylococcus aureus	0,25 – 0,5	mg/l
Staphylococcus epidermidis	0,125 – 0,25	mg/l
Pseudomonas aeruginosa	0,063 – 0,25	mg/l
Enterobacter species	0,063 – 0,32	mg/l
Klebsiella pneumoniane	0,063 – 0,125	mg/l

Tab. 8: MICs of clindamycin (Univ. Teach. Hosp. Hradec Králové).

Staphylococcus aureus	0,063	mg/l
Staphylococcus epidermidis	0,125 – 1,0	mg/l

Tab. 9: Operation and cardiopulmonary bypass times.

	CTZ (n = 25)	CPF (n = 25)	CLIN (n = 25)
Operation times (min)	220±41 (130-310)	199±40 (145-300)	223±21 (185-260)
CPB times (min)	78±27 (40-155)	86±23 (55-140)	75±16 (50-155)

Tab. 10: Sampling times.

Times from atb administration to... (min)	CTZ (n = 25)	CPF (n = 25)	CLIN (n = 25)
...skin incision	45±8	41±12	45±10
...to prebypass phase	87±21	77±18	94±18
...to cardioplegia	105±24	97±20	116±20
...to the end of the longest procedures	298±6	266±22	235±14

measurement. *Morganella morganii* CRM 58/87 was used as the testing agent for ceftazidime, MAU 58/87 for ciprofloxacin and STAU 4223 for clindamycin. Our results were compared to standard curves (Tab. 3-5) and to MICs of some suspected pathogens (Tab. 6-8) isolated from various types of samples of patients treated at our hospital during last two years and which were the most frequent pathogens causing infective complications at our department.

Results

The mean operation times (including anesthesia induction) and cardiopulmonary bypass times are summarised in Table 9. There were no significant differences in times between our three groups of patients.

The times from antibiotic administration to various phases of operations are shown in Table 10. Time courses of mean antibiotic serum concentrations measured during procedures are in Fig. 1-3. After the initial doses of antibiotics, their levels rapidly increased and at the time of skin

Fig. 1: The mean serum concentrations of ceftazidim during open heart surgery.

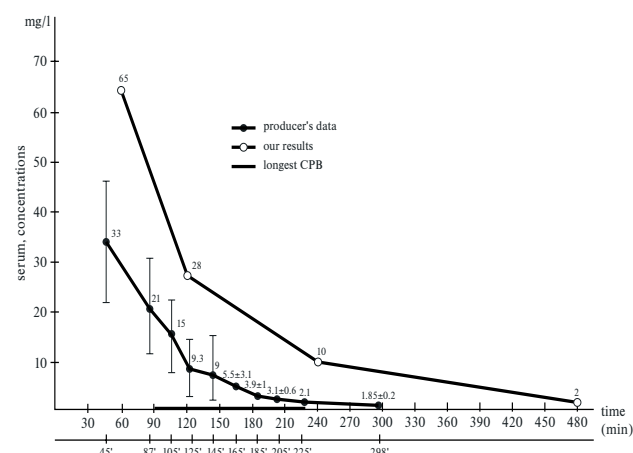


Fig. 2: The mean serum concentrations of ciprofloxacin during open heart surgery.

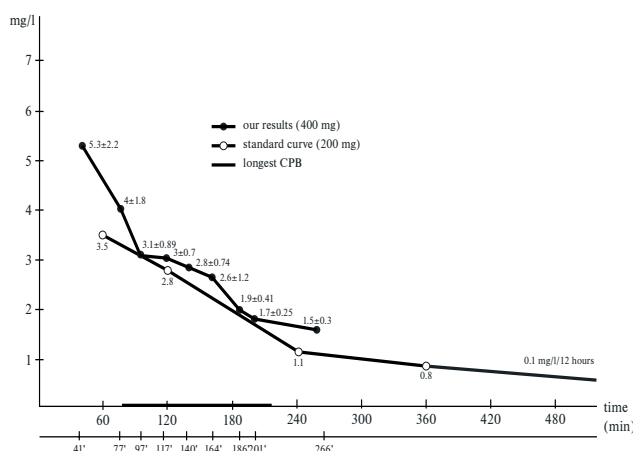
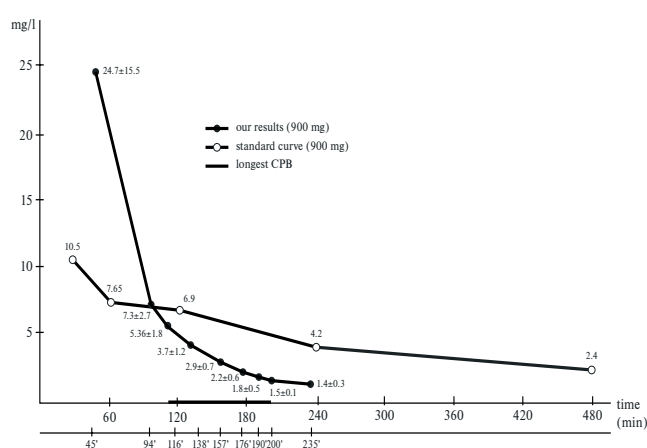


Fig. 3: The mean serum concentrations of clindamycin during open heart surgery.



incision were in sufficient antibacterial concentrations to protect the patients against suspected infection. The antibiotic levels of CPF and CLIN (Fig. 2-3) were, even, above the concentrations in standard groups of patients. All serum concentrations show a sharp decrease immediately after starting CPB and lasted until CPB ended. The corresponding expected antibiotic serum concentrations based on producers data after the same doses are called „standard curve” (in the group of CPF are our results after the dose of 400 mg compared to standard curve after the dose of 200 mg, because we could not find the producers data after the dose 400 mg) are shown in parallels (Fig. 1-3). After initiating of CPB after cardioplegia administration serum concentration of CTZ (105 min after initial dose) decreased by, on average 55%, serum concentrations of CPF (97 min after initial dose) decreased by, on average 42% and serum concentrations of CLIN (116 min after initial dose) decreased by, on average, 78% and the concentrations of all antibiotics remained significantly lower than the expected values throughout the operation.

Comparing the antibiotic serum levels to the MICs for some of suspected pathogens (Tab 6-8) we can see, that serum levels of CTZ at the end of the longest procedures were below the MICs for some of them. It means at the end of these procedures the prophylaxis was not adequate.

Despite of the low levels of antibiotics at the end of the longest procedures no infective complication in the group of CTZ was observed and only one wound infective complication in CLIN group of patients was found.

Discussion

The onset of cardiopulmonary bypass is associated with profound physiological changes affecting the pharmacokinetic behaviour of prophylactic antibiotics. Hypotension, hypothermia, haemodilution, lung isolation, the administration of other agents and ischaemic injury to the kidneys can alter the clearance and volume distribution (11).

As pointed out by Buylaert et al. (3) the decrease in drug serum concentrations at the onset of CPB is mainly due to an increase in volume of distribution. Many factors may underline this pharmacokinetic alteration such as an increase in blood volume, plasma protein dilution, drug binding to CPB apparatus, and drug-protein displacement by heparin-induced free fatty acid increase (19).

Our data shows that CPB can modify the time course of ceftazidim, ciprofloxacin and clindamycin serum concentrations. A sharp decrease in drug concentrations occurred at the start of CPB and lasted until CPB ended. We have found the initial decrease in serum concentrations of CTZ (- 55%), CPF (- 42%) and CLIN (-78%). The initial decrease in serum concentrations of teicoplanin (- 35%) and (- 40%) in connection with CPB has reported Miglioli et al. (19,20) and Wilson et al. (25,26).

The decrease of serum concentrations of cephalosporins and oxacilin in connection with CPB is described by the

author et al. (15). We have observed, that plasma levels fall below the MIC for antistaphylococcal action after 180 minutes and 150 minutes respectively. Comparing the antibiotic levels to the phase of operation, the lowest levels occurred at the end of the CPB.

On the other side Heylen et al. (11) assayed serum and urinary concentrations of gentamicin during open heart surgery and in the early postoperative period. Despite the effects of CPB, therapeutic serum gentamicin levels were maintained during surgery and reduced renal excretion in the postoperative period was associated with raised levels.

On the basis of our results and literature data we can conclude that as a result of the alteration that occur in drug distribution on cardiopulmonary bypass, standard antibiotic regimens may not be appropriate. In some situations the antibiotic prophylaxis can be inadequate. That is why some authors recommend to administer the second antibiotic dose during operation to keep the antibiotic concentrations above the MICs for suspected pathogens. Menges et al. (18) suggest to administer the second dose of 2g of cefamandole after onset of CPB. Lonský et al. (15) administer the second dose of antibiotic at the same time as Protamine Sulphate infusion after removing the aortic perfusion cannula to obtain maximum antibiotic concentration in newly formed blood clots.

Our dosage regimen in this study was based on producers recommendations. On the basis of our results we have changed our protocol of antibiotic prophylaxis. We have started to use the second dose of antibiotic prior to Protamine Sulphate infusion again and we use higher antibiotic doses.

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