International Journal of Antimicrobial Agents 49 (2017) 395–402

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Dosing antibiotic prophylaxis during cardiopulmonary bypass—a higher level of complexity? A structured review

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ARTICLE INFO

Article history:
Received 2 August 2016
Accepted 17 December 2016

Keywords:
Pharmacokinetics
Extracorporeal therapy
Cardiac surgery

ABSTRACT

In highly invasive procedures such as open heart surgery, the risk of post-operative infection is particularly high due to exposure of the surgical field to multiple foreign devices. Adequate antibiotic prophylaxis is an essential intervention to minimise post-operative morbidity and mortality. However, there is a lack of clear understanding on the adequacy of traditional prophylactic dosing regimens, which are rarely supported by data. The aim of this structured review is to describe the relevant pharmacokinetic/pharmacodynamic (PK/PD) considerations for optimal antibiotic prophylaxis for major cardiac surgery including cardiopulmonary bypass (CPB). A structured review of the relevant published literature was performed and 45 relevant studies describing antibiotic pharmacokinetics in patients receiving extracorporeal CPB as part of major cardiac surgery were identified. Some of the studies suggested marked PK alterations in the peri-operative period with increases in volume of distribution (V_d) by up to 58% and altered drug clearances of up to 20%. Mechanisms proposed as causing the PK changes included haemodilution, hypothermia, retention of the antibiotic within the extracorporeal circuit, altered physiology related to a systemic inflammatory response, and maldistribution of blood flow. Of note, some studies reported no or minimal impact of the CPB procedure on antibiotic pharmacokinetics. Given the inconsistent data, ongoing research should focus on clarifying the influence of CPB procedure and related clinical covariates on the pharmacokinetics of different antibiotics during cardiac surgery. Traditional prophylactic dosing regimens may need to be re-assessed to ensure sufficient drug exposures that will minimise the risk of surgical site infections.

1. Introduction

Patients undergoing major cardiac surgery are at significant risk of post-operative infections by virtue of the prolonged highly invasive procedure and the presence of multiple foreign devices (e.g. chest catheters as well as central venous and arterial catheters and pacing wires), which may remain in situ post-operatively [1,2]. In addition, the increased risk of bleeding further increases the likelihood of infection, the consequences of which may be catastrophic [3]. Particularly problematic infections that may occur include sternal wound infections (including mediastinitis), endocarditis and prosthetic implant (valvular and aortic graft prosthetic material) infections. These infections are associated with poor patient outcomes and escalating costs of care [4]. Mediastinitis alone has a mortality rate as high as 47% [5].

Antibiotic prophylaxis is therefore important in major cardiac surgery as it can reduce the incidence of surgical site infections (SSIs) and thereby minimise the associated morbidity and mortality. The choice of prophylactic regimen should be guided by local epidemiological data to ensure that the most likely pathogens are covered. The vast majority of SSIs are attributed to *Staphylococcus aureus* and coagulase-negative staphylococci, including *Staphylococcus epidermidis* [6,7]. Gram-negative pathogens including *Pseudomonas* spp., *Acinetobacter* spp. and Enterobacteriaceae such as *Proteus mirabilis* are isolated in less than one-third of mediastinitis cases [8,9]. Rare causes of SSIs include *Propionibacterium acnes* [10] and fungi [11]. In addition to selecting a prophylactic agent of sufficient spectrum, it is important that the associated dosing regimen ensures adequate plasma and tissue concentrations throughout the entire intraoperative period. However, this is considered highly challenging due to likely changes in antibiotic pharmacokinetics caused by surgery and intraoperative interventions including

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http://dx.doi.org/10.1016/j.ijantimicag.2016.12.014
0924-8579/

cardiopulmonary bypass (CPB). Indeed, the present uncertainty in antibiotic dosing requirements for prophylaxis during major cardiac surgery is manifest in the lack of consensus between available guidelines in terms of antibiotic choice, dose, frequency and total duration [12–15]. The lack of standardised dosing raises concerns of insufficient dosing, risking failure of prophylaxis and the emergence of resistant organisms. It is therefore important to understand and meet the dosing challenges present in complex situations such as CPB.

The aim of this structured review is to describe the impact of pharmacokinetic (PK) changes on antibiotic dosing requirements during CPB and the relevant pharmacokinetic/pharmacodynamic (PK/PD) considerations for optimal antibiotic prophylaxis.

2. Method

The MEDLINE database was searched through Web of Science™ for the keywords (i) 'cardiac surgery' or 'heart surgery' or 'coronary artery bypass' or 'cardiopulmonary bypass', (ii) 'prophylaxis' or 'antibiotic*' and (iii) 'pharmacokinetic*' or 'dose' or 'dosing regimen', and the searches (i), (ii) and (iii) were combined with the Boolean operator 'AND'. Search results were then refined with a MeSH qualifier 'Pharmacokinetics', language 'English' and publication type 'Journal Article'. A total of 87 original research articles were retrieved and further screened, with 45 relevant articles identified for full review. The references of these articles were also screened and relevant articles were included.

3. How does cardiopulmonary bypass affect dosing of antibiotic prophylaxis?

3.1. Overview of cardiopulmonary bypass procedure

CPB refers to the use of an extracorporeal machine to temporarily take over cardiorespiratory function during heart surgery. The CPB machine, whilst bypassing the patient's heart and lungs, maintains adequate circulatory flow and oxygen content to the rest of the body. The system uses the gravitational drainage of venous blood from the cannulation of the right side of the heart (usually the right atrium, but the vena cava may also be used) and the return of oxygenated blood to the ascending aorta (or occasionally to the femoral artery) as illustrated in Fig. 1. Some situations may require the use of additional cannulation, e.g. femoral venous cannulation for poor access or for direct administration of cardioplegia and myocardial protection agents. The cannulae are connected to the CPB circuit via a series of large-bore tubes. This extensive silicone or poly vinyl chloride (PVC) tubing is initially primed with a crystalloid solution or occasionally with blood. The venous blood drains via large-bore tubing into a venous reservoir.

A centrifugal or roller pump propels the reservoir blood forward through the membrane oxygenator and heat exchanger so that oxygenated blood is returned to the arterial side of the patient. Following the cannulation process when adequate flows are achieved, mechanical lung ventilation is terminated and the aorta is cross-clamped. This effectively isolates the lungs from the circulation. At this time, fluids, blood, anaesthetic agents and drugs may be administered directly via the CPB circuit. The circuit may be used to cool or re-warm the blood, as hypothermia (28–32 °C) is required during the procedure. During hypothermia, CPB flow is reduced. Heparin, with or without protamine, may be administered to control anticoagulation in the circuit and prior to decannulation. The entire CPB intervention may span a period of <1 h to several hours. Given the variation in surgical practice and use of CPB, which may not always be predictable at the beginning of surgery, it is clear that significant changes to antibiotic pharmacokinetics are likely.

3.2. Cardiopulmonary bypass factors affecting antibiotic concentrations

Generally, there is limited understanding of the influence of CPB on antibiotic pharmacokinetics. However, emerging PK data from other related extracorporeal therapies such as veno-arterial extracorporeal membrane oxygenation (VA-ECMO) suggest that significant PK changes can be expected [16]. These two technologies are considerably similar in terms of possible factors affecting pharmacokinetics, with the main difference being that CPB is restricted to intraoperative use and is of a much shorter duration than VA-ECMO, which is indicated in the critical care setting for a relatively longer duration. Accumulating data from clinical and ex vivo PK studies highlight the marked PK changes that can occur during ECMO procedures for several antibiotics [16]. The PK alterations manifest mostly as an increase in volume of distribution (V_d) and an increase or decrease in drug clearance (CL). Fig. 2 summarises the

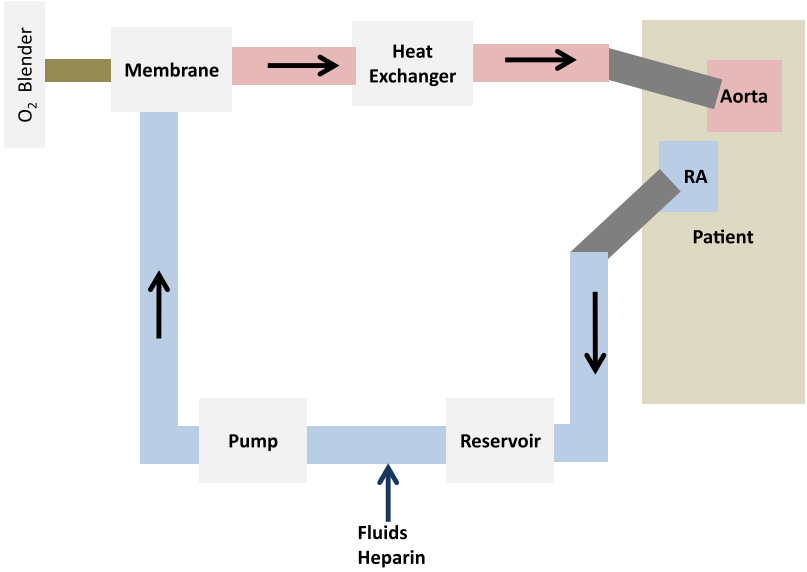

Fig. 1. Cardiopulmonary bypass circuit. RA, right atrium.