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Penetration of cephradine into heart valves, subcutaneous tissue and muscle of patients undergoing open heart surgery

F. D. Daschner,* H. Langmaack, G. Spillner, A. Ahmadi and V. Schlosser

Department of Hospital Epidemiology, Department of Cardiac Surgery, University Hospital, Freiburg, Germany

Concentrations of cephradine in heart valves, subcutaneous tissue and muscle were determined in 28 adult patients undergoing open heart surgery.

Within 120 min of intravenous injection of 1 g cephradine antibiotic concentrations reached levels of between 1·5 and 8·6 μg/g in subcutaneous tissue and muscle; concentrations in heart valves were even higher varying between 3·8 and 15·0 μg/g at 50 to 140 min following administration of the drug. Cephradine concentrations in heart valves exceeded 8 μg/g for an average of 120 min; this concentration inhibited 91% of 64 *Staphylococcus epidermidis* and 100% of 69 *Staphylococcus aureus* strains isolated from wounds and the air of the operating theatre.

Introduction

Antibiotics are now almost routinely administered to patients undergoing open heart surgery for the insertion of prosthetic heart valves in order to prevent wound infection and endocarditis. *Staphylococcus aureus*, *Staph. epidermidis* and Gram-negative bacilli are the most common organisms causing prosthetic valve endocarditis (Dismukes, Karchmer & Buckley, 1973; Slaughter, Morris & Starr, 1973). Because of their broad spectrum which includes these bacteria, cephalosporins have been recommended as prophylactic antibiotics during open-heart surgery (Eigel *et al.*, 1978). Very few studies however have been done to prove the efficacy of the various cephalosporin prophylaxis regimens. The present study was designed to investigate the distribution of cephradine in serum, heart valves, subcutaneous tissue and muscles of patients undergoing open heart surgery; the activity of cephradine against bacteria which usually cause endocarditis and wound infections was also determined.

Materials and methods

Twenty-eight adult patients, all with normal renal function (18 males, 10 females;

*Address correspondence and reprint requests to: Prof. Dr med. F. D. Daschner, Dept. Hospital Epidemiology, Universitätsfrauenklinik, Universitätsklinikum, Hugstetter Str. 55, 7800 Freiburg, Germany.

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mean age 50 years, mean weight 67·8 kg) with valvular (19 patients) or coronary heart disease (9 patients) were given 1 g cephradine as a 5 minutes intravenous bolus injection at the time of induction of anaesthesia. Patients with valvular heart disease had prosthetic valves inserted in either the aortic (12 patients) or mitral position (7 patients). All surgery was performed by the same team. Patients were followed postoperatively for signs of wound-, respiratory tract-, or urinary tract infections by an Infection Control Nurse until discharge from hospital, a mean of 11·2 days after surgery, and thereafter for an average of 1 year for evidence of prosthetic valve infection by a member of the surgical team.

Nonpulsatile blood flow was maintained at 50 ml/kg per minute during cardiac bypass and blood temperature was 25 to 35°C. The mean arterial pressure varied from 60 to 80 mm of Hg. The pump was primed with 1000 ml Ringers lactate solution, 500 ml whole blood, 200 ml Osmofundin (Braun Melsungen) plus 40 ml tris buffer. The beginning of bypass was assumed to occur when the venous clamp was opened, the end of bypass coincided with clamping of the venous return.

Blood, obtained from the venous line, subcutaneous fat and muscle were taken simultaneously at various intervals following injection of the drug, usually at the beginning of the operation, while valvular tissue and blood were taken at the time of valve replacement. Specimens were assayed within the next 4 weeks by an agar diffusion method using *Bacillus subtilis* ATCC6633 as the test organism (Grove & Randall, 1955). (Spore suspension: BBL; antibiotic agar No. 5, Merck AG, Darmstadt Germany). Tissue fluid in 1 : 3 dilution (wt/vol.) with 0·15 molar phosphate buffer, pH 8, was obtained by use of a Coleworth Stomacher No. 80 (Daschner, Reiss & Engert, 1977).

Standards for plasma antibiotic assays were made in phosphate-buffered bovine serum albumin (1 : 1), for tissue fluid in phosphate buffer, pH 8. All determinations were done in triplicate and read by the same technician. The lower limit of sensitivity for the plasma and tissue assay was 0·125 mg/l (or g tissue). The average haemoglobin content of fluid obtained from heart valves was zero, from muscle 0·68 g% and from subcutaneous fat 0·42 g%. Minimum inhibitory concentrations of cephradine against 64 *Staph. epidermidis* and 69 *Staph. aureus* strains isolated from wounds or the air of the operating theatre were determined by an agar diffusion method.

Results

Tissue and concomitant serum antibiotic concentrations are shown in Table I. No corrections for the serum content of tissue specimens have been made. Up to 49 min specimens were obtained prior to, and from 50 to 185 min during cardiopulmonary bypass. Within 185 min cephradine plasma concentrations had declined slowly from 43·3 mg/l to 3·8 mg/l.

Subcutaneous tissue and muscle concentrations varied between 1·5 and 8·6 µg/g. However no specimens were obtained at the end of the operations.

Cephradine concentrations in cardiac valvular tissue were higher than those in muscle and fat. The decline in concentration almost paralleled that in plasma suggesting rapid diffusion and exchange of cephradine between plasma and valvular tissue. Histologic examination revealed small capillaries in only 4 out of 19 valves, in all of which hyaline deposits, scars and old inflammatory reactions were seen. No haemoglobin could be found in any of the valves tested.

The minimum inhibitory concentrations of cephradine for 69 strains of *Staph. aureus* and 64 strains of *Staph epidermidis* are summarized in Table II.

Ninety-seven per cent of the *Staph. aureus* and 92% of the *Staph. epidermidis* strains were inhibited at 4 mg/l, only one out of 69 *Staph. aureus* strains had a MIC of 8 mg/l, a concentration which still can readily be obtained in heart valves.

Table I. Plasma (mg/l) and tissue (μg/g) concentrations of cephradine in cardiac surgery patients after a single 1 g i.v. injection (number of specimens in parenthesis)

	Min after administration					
	10–29	30–49	50–69	70–120	121–140	185
Plasma	43·3 (5)* (19–74)†	23·1 (4) (17–25)	19·3 (9) (12·5–24)	16·3 (13) (10–38)	9·1 (5) (8–11)	3·8 (1)
Heart valve	—	—	15·0 (4) (9–21)	10·4 (10) (7–25·2)	3·8 (4) (6·6–11·4)	0 (1)
Muscle	5·7 (5) (0–10)	8·6 (3) (6·4–9)	4·3 (11) (0–7·5)	4·6 (4) (0–9)	—	—
Subcutaneous tissue	7·7 (6) (0–11·6)	5·4 (3) (0–8)	3·4 (11) (0–8)	1·5 (4) (0–6)	—	—

—No specimen assayed.
*Mean values.
†Range.

Table II. Minimum inhibitory concentrations of cephradine for 69 *Staphylococcus aureus* and 64 *Staphylococcus epidermidis* strains

Bacteria	Number of strains with MIC (mg/l) of:					
	0·5	1	2	4	8	>128
Staphylococcus aureus		1	45	22	1	
Staphylococcus epidermidis	2	5	28	21	2	6

Discussion

Bacteria, expecially *Staph. epidermidis*, diphtheroids and *Staph. aureus* are recovered from cardiac tissue in up to 71% of patients undergoing open heart surgery (Kluge *et al.*, 1974).

The reason for giving antibiotic prophylaxis during cardiac surgery is to obtain antibacterial activity at the site of possible bacterial contamination in order to prevent implantation and subsequent wound infection caused by these organisms; the major aim of prophylaxis however is to prevent infection around the prosthetic valves. We therefore determined antibacterial activity of cephradine not only in muscle and subcutaneous tissue (mostly fat), but also in cardiac valvular tissue during open-heart surgery at times when bacterial contamination was most likely. Cephradine plasma concentrations during cardiopulmonary bypass were higher than those in healthy adults given the same dosage intravenously (Simon, 1974). Cardiopulmonary bypass thus seems to increase the serum half-life of cephradine: this is in agreement with a study of Polk, Archer & Lower (1978), who found a significantly increased serum

half-life of cefamandole *during* cardiopulmonary bypass as compared to prior to bypass or in normal subjects. Their data indicated an apparent 'break' in the plasma level curves between the pre-bypass and intra-bypass period suggesting decreased elimination of the antibiotic during bypass. The same authors compared cephalothin and cefamandole prophylaxis during the insertion of prosthetic heart valves and found that plasma levels of both drugs fell less than 25% during a mean of 2 h on cardiopulmonary bypass (Archer *et al.*, 1978).

Between 0·5 and 2 h after antibiotic administration cefamandole and cephalothin produced average valvular tissue concentrations of 39% and 12% of the corresponding plasma level. The relationship between cephradine valvular and plasma concentration during the same time interval was significantly higher (on average 60%). This might be due to lower protein binding of cephradine as compared to cefamandole or cephalothin. Mean tissue concentrations of cephradine in heart muscle were 10 times higher than those of cephalothin after equal doses of both drugs (Adam *et al.*, 1976). The explanation for the higher valvular as compared to muscle tissue concentrations are not readily apparent. The almost parallel decline of valvular levels to those in plasma would suggest rapid exchange of cephradine, which is weakly protein bound, between plasma and valve tissue. Vascularisation of tissue is only one factor among others determining antibiotic tissue concentrations. Barza *et al.* found that in fibrin clots, concentrations of weakly bound agents were strikingly two to four times higher than those of strongly bound agents (Barza, Samuelson & Weinstein, 1974).

Ninety-seven per cent of *Staph. aureus* and 87% of *Staph. epidermidis* strains isolated from wounds or the air of the operating theatre in which the open heart surgery was performed were inhibited at 4 mg/l. Staphylococci inoculated on muscular or subcutaneous tissue during cardiopulmonary bypass would be exposed to 2 μg/g cephradine for an average of 110 min and to 4 μg/g for about 60 min. Cephradine concentrations in heart valves exceed 8 μg for an average of 120 min and 2 μg for at least 140 min.

Cephradine, whose antistaphylococcal activity is lower than that of cephalothin and cefamandole (Naumann, 1975), penetrates better than these cephalosporins even into damaged heart valves without any significant blood supply. Cephradine also reaches high concentrations in the pericardial exudate (Adam *et al.*, 1977). This cephalosporin therefore seems to be an appropriate antibiotic for prophylaxis during open-heart surgery; its ability to prevent wound infection and endocarditis however must be evaluated in prospective clinical trials.

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