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Concentrations of Flucloxacillin in Heart Valves and Subcutaneous and Muscle Tissues of Patients Undergoing Open-Heart Surgery

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Thirty-seven patients were given a single, 2-g intravenous bolus injection of flucloxacillin prior to open-heart surgery. Within 12 h, flucloxacillin concentrations in serum and heart valves declined from 125.2 to 4.4 μg/ml and from 16.5 to 3.7 μg/g, respectively. Concentrations in subcutaneous tissue and muscle were almost identical, declining from 14.7 or 14.2 μg/g to undetectable levels after 8 to 10 h.

Cardiac surgeons presently administer antibiotics to virtually all patients undergoing intracardiac surgery in attempts to prevent both wound infections and prosthetic valve endocarditis. Current recommendations call for parenteral administration of antistaphylococcal drugs just prior to the operation and continued administration for one or two further doses. Because the therapeutic efficacy of the isoxazolyl penicillins in the treatment of staphylococcal and streptococcal infections is well established (6, 8), flucloxacillin, the most recent member of this group, may be chosen for antibiotic prophylaxis in open-heart surgery and for treatment of infective endocarditis. The present study was designed to investigate the penetration of flucloxacillin into serum, heart valves, subcutaneous tissue, and muscle of patients undergoing open-heart surgery.

Thirty-seven adult patients were given 2 g of flucloxacillin as a 5-min intravenous bolus injection prior to open-heart surgery. The patients included 20 males (mean age, 59 years; mean body weight, 73 kg) and 17 females (mean age, 62 years; mean body weight, 61 kg). Each patient underwent a complete history and physical examination. Laboratory tests performed before surgery included complete blood count; urinalysis; and tests for blood urea nitrogen, transaminases, bilirubin, and creatinine. These values were normal in all patients. Informed consent was obtained from each patient. Flucloxacillin was administered between 12 h and immediately before open-heart surgery. No other antibiotics were given. The operations were always performed by the same surgical team. Nonpulsatile blood flow was maintained at 50 ml/kg of body weight per min during cardiac bypass; blood temperature reached 25 to 35°C (77 to 95°F). Mean arterial pressure varied between 60 and 80 mm Hg. The pump was primed with 1,000 ml of Ringer lactate solution, 500 ml of whole blood, 200 ml of Osmofundin (Braun Melsungen, Melsungen, Federal Republic of Germany), and 40 ml of Tris buffer. The mean extracorporal circulation time was 80 min. Samples of venous blood, subcutaneous fat, and muscle were taken once or twice simultaneously at various intervals after injection of the drug. Valvular tissue and blood samples were collected during valve replacement. Specimens were frozen at −72°C (−98°F) and assayed during the next 4 to 6 weeks by an agar diffusion method with antibiotic medium no. 2 (Oxoid Ltd., Basingstoke, England) supplemented with 3 g of sodium citrate per liter. *Bacillus subtilis* ATCC 6633 was used as a test organism. This method for antibiotic assays is well established (3, 5). It allows the testing of large numbers of clinical specimens in a minimal time and provides a 95% certainty that a reported concentration is within ±10% of the true concentration of the sample (1). Tissue fluid in 1:3 (wt/vol) dilution with phosphate buffer (pH 7) was obtained by use of a Coleworth Stomacher no. 80 (Seward and Co. Ltd., London, England) (10). Standards for plasma antibiotic assay were prepared in phosphate-buffered human serum (1:1 [vol/vol]); standards for tissue antibiotic assay were prepared in phosphate buffer (pH 7). There was a linear relationship between mean zone diameters of inhibition and the log of the antibiotic concentrations of each standard. No substantial interday variation of the assay could be observed. All determinations were done three times by the same technician. Histological examinations of all excised heart valves showed scars, remnants of old inflammations, and hyaline deposits but no vascularization. No corrections for the serum content of any tissue specimen were made.

Concentrations in tissues and serum are shown in Table 1. Peak flucloxacillin concentrations in serum of 125.2 μg/ml were reached within 0 to 1 h after administration of the antibiotic. Peak flucloxacillin concentrations were reached within 0 to 1 h in subcutaneous tissue and muscle and within 1 to 2 h in heart valves. Concentrations in subcutaneous tissue and muscle were almost identical, declining from 14.7 and 14.2 μg/g, respectively, to undetectable levels after 8 to 10 h. The flucloxacillin concentrations in heart valves declined from 16.5 to 3.7 μg/g within 12 h.

As described in previous studies (4, 7), intramuscular or intravenous administration of a single 500-mg dose of flucloxacillin resulted in relatively low concentrations in serum, heart tissue, and wound exudate. In our study, flucloxacillin concentrations in serum after a single, 2-g intravenous bolus injection during cardiac surgery resembled those found in healthy volunteers (2). Thus, the pharmacokinetics of the drug did not seem to be influenced by cardiopulmonary bypass.

While the results in vitro do not necessarily reflect the situation in vivo, and data should be interpreted cautiously, our results suggest that penicillinase-producing strains of *Staphylococcus aureus*, for which the flucloxacillin MIC range is between 0.25 and 5.0 μg/ml, would be inhibited after flucloxacillin administration for more than 6 h in serum and heart valves and for more than 3 h in muscle and subcutaneous tissue. However, many coagulase-negative staphylo-

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cocci are less susceptible to the isoxazolyl penicillins, and methicillin-resistant staphylococci are usually resistant (9, 11). When there is a low prevalence of methicillin resistance, flucloxacillin may be one of the drugs of choice for antibiotic prophylaxis in open-heart surgery, as well as for initial therapy for gram-positive coccal infections before identification and susceptibility testing has been performed.

TABLE 1. Concentrations of flucloxacillin in samples taken from open-heart surgery patients after a single, 2-g intravenous bolus injection[a]

Sample	Flucloxacillin concn (no. of samples) at the following time after administration:								
	0–1 h	1–2 h	2–3 h	3–4 h	4–5 h	5–6 h	6–7 h	7–8 h	8–10 h	10–12 h
Serum	125.2 ± 11.7 (31)	70.1 ± 11.5 (15)	43.0 ± 4.4 (11)	24.3 ± 6.3 (8)	14.0 ± 2.2 (12)	11.6 ± 3.1 (9)	6.1 ± 2.5 (6)	6.1 ± 2.0 (4)	3.9 ± 1.9 (4)	4.4 ± 0.6 (3)
Heart valve tissue	15.4 ± 1.1 (11)	16.5 ± 2.6 (9)	10.9 ± 1.9 (3)	8.3 ± 2.4 (2)	6.7 ± 1.9 (3)	6.7 ± 4.0 (2)	4.5 ± 1.7 (3)	4.0 (1)	3.5 ± 2.5 (2)	3.7 (1)
Muscle tissue	14.2 ± 1.7 (20)	10.4 ± 1.6 (6)	8.4 ± 1.4 (8)	3.6 ± 1.4 (6)	2.3 ± 0.8 (8)	1.4 ± 0.9 (6)	0.8 ± 0.8 (4)	0.6 ± 0.3 (3)	≤0.2 (2)	≤0.2 (2)
Fat tissue	14.7 ± 1.7 (20)	9.3 ± 1.3 (6)	9.7 ± 1.2 (7)	3.1 ± 1.1 (6)	2.3 ± 0.6 (8)	0.8 ± 0.5 (6)	0.9 ± 0.6 (4)	0.8 ± 0.4 (3)	≤0.2 (2)	≤0.2 (2)

[a] Data are means ± the standard error of the mean. Concentrations in serum are in micrograms per milliliter; concentrations in tissue are in micrograms per gram.

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