ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1996, p. 1785–1789 Vol. 40, No. 8
0066-4804/96/$04.00+0

Gentamicin Concentrations in Human Subcutaneous Tissue

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Received 14 July 1995/Returned for modification 1 December 1995/Accepted 10 May 1996

Wound infections frequently originate from the subcutaneous tissue. The effect of gentamicin in subcutaneous tissue has, however, normally been evaluated from concentrations in blood or wound fluid. The aim of the present study was to investigate the pharmacokinetic properties of gentamicin in human subcutaneous adipose tissue by a microdialysis technique. Seven healthy young volunteers each had four microdialysis probes placed in the fat (subcutaneous) layer of the abdominal skin. After the administration of a 240-mg gentamicin intravenous bolus, consecutive measurements of the drug concentrations in serum and subcutaneous interstitial fluid were obtained simultaneously for 6 h. The tissue gentamicin concentration peaked after 10 to 30 min. The peak concentration in the tissue was 6.7 ± 2.0 mg · liter^{-1} (standard deviation), equivalent to 39.1% of the peak concentration in serum. The area under the concentration-versus-time curve for the first 6 h in the tissue was 1,281.7 ± 390.0) mg · min liter^{-1}, equivalent to 59.7% of the area under the concentration-versus-time curve in serum. It is concluded that the microdialysis technique can be used to make dynamic and quantitative measurements of the gentamicin concentration in human subcutaneous tissue. In this adipose tissue, the peak concentrations of gentamicin were approximately seven times the MIC for *Pseudomonas aeruginosa* and 33 times the MIC for *Staphylococcus aureus* after the administration of an intravenous bolus of 240 mg, indicating the presence of sufficient concentrations in the adipose tissue to be effective against common bacteria.

The development of infection is primarily dependent on the type and virulence of the bacteria, the size of the inoculum, and the resistance of the tissue against infection. In certain types of surgery the use of a therapeutic concentration of antibiotics is an important precaution against wound infection.

Gentamicin is a widely used antibiotic, having antibacterial activity against aerobic gram-negative bacteria including members of the families *Enterobacteriaceae* and *Pseudomonadaceae*, which includes the human pathogen *Pseudomonas aeruginosa* and the gram-positive organism *Staphylococcus aureus*. Nosocomial pathogens most often obtained in cultures of specimens from surgical intensive care units and burn patients belong to this group (1, 11, 24, 28). The serum half-life of gentamicin necessitates a comprehensive understanding of the distribution of gentamicin into the interstitial fluid space of the subcutaneous tissue, because this compartment is the initial focus of the majority of wound infections.

Investigations with a dynamic in vitro pharmacokinetic model have demonstrated that the aminoglycoside netilmicin could prevent bacterial regrowth within 24 h when the concentration in the deep compartment exceeded the MIC eight times (7). The peak serum aminoglycoside concentration: MIC ratio (peak/MIC ratio) was significantly higher in patients with a clinical response to therapy than in patients not showing a clinical response (20). In a murine pneumonitis and thigh infection model, the log area under the concentration-versus-time curve (AUC)/MIC was the only parameter predictive of efficacy for the first 6 h, and the peak concentration in itself was not predictive of efficacy (17).

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Various techniques have been used to investigate interstitial drug concentrations. Biopsy specimens (9, 12, 13, 29) and tissue cages (6, 22) are not suitable for dynamic studies in humans. Skin blisters (12) are primarily applicable to dermal studies and might cause alterations in the dynamics of microvascular fluid. Subcutaneous paper disks (21) and subcutaneous threads do not allow for successive samplings from the same site. Microdialysis, which is minimally invasive, was developed in the field of brain research in animals (5), but it has recently been applied to investigations of various human tissues. The principle in microdialysis is to flush a fluid by means of a high-precision pump through a tube that allows the diffusive exchange of endogenous or exogenous compounds across a selectively permeable membrane (Fig. 1), thus enabling dynamic measurements of the concentration in interstitial fluid to be made.

The aim of the present investigation was to perform precise dynamic measurements with a high-level time resolution of the gentamicin concentration in the interstitial fluid of human subcutaneous tissue without inducing considerable tissue damage.

MATERIALS AND METHODS

Volunteers. Seven healthy young individuals with normal renal function (p-creatinine, <100 mmol · liter^{-1}) and between 25 and 36 years of age entered the study after providing informed consent. The study was performed in accordance with the Helsinki II Declaration and was approved by the Ethical Committee for Copenhagen, Copenhagen, Denmark (file number KF 01 263/93).

Microdialysis probe. A Gambro GFE-18 dialysis fiber (inner diameter, 0.119 mm; outer diameter, 0.180 mm; molecular mass cutoff, 2,000 Da) was inserted into and glued to polyethylene tubes (inner diameter, 0.28 mm; outer diameter, 0.61 mm). The microdialysis probe (Fig. 1) was designed to have a 35-mm free fiber length, giving an area of 19.8 mm^2 available for diffusive exchange.

For standardization of permeability the glycerol coating of the fiber material was rinsed with isotonic saline before measurements were performed. The probes were aseptically prepared.

Equipment for the collection procedure. Polyethylene tubes were used to

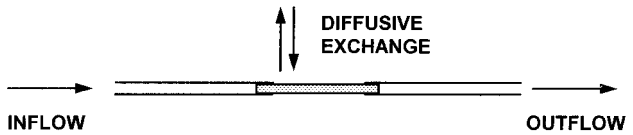

FIG. 1. The microdialysis probe. The exchange area and the adjacent polyethylene tubes were placed in the adipose tissue of the abdominal wall. The depth was approximately 2 cm, and the probes were parallel to the skin surface.

connect the probes to the 1-ml syringes held in the pump (Carnagie CMA-100 high-performance pump; Carnagie Medicine, Stockholm, Sweden). The efferent (outlet) fluid was collected in 0.3-ml glass injection vials (type 33001; Microlab, Århus, Denmark). In order to minimize evaporation, samplings were performed in a sealed system.

Drugs and chemicals. For the 240-mg intravenous bolus we used three 2-ml injection bottles with a gentamicin concentration of 40 mg/ml (Garamycin; Schering-Plough). For manufacturing the microdialysis inlet solutions we used purified gentamycin not containing preservatives and antioxidants (Garamycin for intrathecal use; concentration, 10 mg/ml; volume, 5 ml; Schering-Plough), because preservatives could bind (5, 16, 31) to the probe material and possibly subsequently precipitate the gentamicin.

Perfusate concentrations manufactured. Afferent solutions of 0.93, 1.33, 1.68, 2.28, 4.22, and 8.80 mg of gentamicin liter^{-1} for intrathecal use with the addition of 1% albumin were used.

Analysis. Afferent and efferent fluid solutions and plasma samples were analyzed on a drug analyzer (Solaris System; Syva) by a homogeneous spectrophotometric immunoassay technique requiring at least 100-μl samples. The lower detection limit was 0.6 mg · liter^{-1}, and the higher detection limit was 10 mg · liter^{-1}. Inter- and intra-assay variations were less than <10%.

Placement of the microdialysis probes. While the subjects were under local lidocaine analgesia, four probes were inserted into the subcutaneous fat layer of the abdominal wall 10-cm lateral to the umbilicus. A cannula (gauge 18) was placed through the skin to a depth of 2 cm and was guided into the adipose tissue at this depth for ca. 5 cm, where the skin was penetrated again from below. A microdialysis probe was guided through the cannula, and the cannula was carefully withdrawn, leaving the probe in place. No bleeding from the cannula or the skin penetration areas was observed.

Tissue convalescence. In order to let the tissue recover from the slight insertion trauma, a period of 2 h was allowed before starting the experiment (3, 5). During this period the four probes were continuously perfused with isotonic saline at a rate of 2.5 μl · min^{-1}.

Tissue and serum samples. After the intravenous administration of a 240-mg gentamicin bolus, microdialysis samplings were continuously obtained. In order to increase the time resolution in the first hour, sampling (50 μl) was performed at 20-min intervals, with subsequent dilution of the samples to 100 μl. Over the subsequent 6 h, samplings were performed at 60-min intervals. The afferent fluid had a gentamicin concentration of 1 mg · liter^{-1} in order to prevent exhaustion of gentamicin from the tissue surrounding the probes. The perfusion rate was 2.5 μl · min^{-1}. Dead-space time, i.e., the time for the efferent fluid to go from the diffusion exchange area situated in the subcutaneous tissue to the collection point at the outlet tube, was adjusted for. Blood samples were drawn from an intravenously placed cannula (Venflon) in a forearm vein.

Calibration of the probes. We used the purely empirical zero net flux technique (14, 19) to determine the relative recovery [extraction fraction = relative recovery = $(C_{out} - C_{in})/(C_{tissue} - C_{in})$ where C_{out} is the outlet concentration, C_{in} is the inlet concentration, and C_{tissue} is the unknown concentration in tissue]. By varying the inlet concentration and plotting the concentration increment (outlet concentration minus inlet concentration) against the inlet concentration, the recovery is calculated as the numeric value of the slope (linear regression coefficient) of the best-fitting line. The correlation coefficient was calculated to demonstrate the fit to a linear model. The concentration in tissue was calculated as $C_{tissue} = C_{in} + \Delta C/RR$ (27), where ΔC is the increment in concentration after the passage of the probe's exchange area, i.e., $C_{out} - C_{in}$, and RR is the relative recovery.

Pharmacokinetic parameters. Visual inspection of the data for drug concentrations in serum made a one- or two-compartment model fitting of the data most likely. Nonlinear iterative least-squares regression by using the inverse of the concentration as the weighting scheme was performed. The Akaike information criterion (32) was used for model discrimination. Data processing and curve fitting were performed by a computer program based on MULTI (33). Half-lives for the serum elimination phase were calculated as ln 2/b, where b is the slope of the elimination phase. The AUC for the first 6 h and total AUC were calculated by the trapezoidal method. In contrast to the concentration of drug in blood samples measured at discrete time points, each tissue gentamicin concentration was obtained from recovery-adjusted microdialysis samples. The concentration in one of these samples reflected a geometric mean for the single sampling period. When the sampling interval is small compared with the half-life of the drug, the geometric mean approaches the arithmic mean, meaning that the recovery-adjusted concentration of a sample can be assigned to the time point midway through the individual sampling period (25). These concentration-versus-time points were used to calculate the half-life of the concentration in tissue by the formula half-life = ln 2/β, where β is the tissue elimination rate constant that was obtained from the best-fitting curve [$C = C_0 \cdot \exp(\beta \cdot t)$, where C is the final concentration of drug in tissue, C_0 is the initial concentration, and t is time]. Tissue AUC was calculated by the trapezoidal rule.

Statistics. Recovery was calculated for each subject as the numeric value of the regression coefficient of the linear regression analysis in which the independent variable was four different afferent fluid concentrations and the dependent variable was the increment in the concentration after the passage of the probe.

The pharmacokinetic measures used to summarize the results were drug half-life, the peak concentration, time to reach the peak concentration, and AUC. Paired t tests were performed for comparison of the peak concentrations and half-lives in serum and tissue.

TABLE 1. Pharmacokinetic constants obtained from non-linear regression analysis and derived values[a]

Volunteer	A (mg · liter^{-1})	B (mg · liter^{-1})	a	b	$t_{1/2a}$ (min)	$t_{1/2b}$ (min)
1		16.3		0.0066		103.9
2		21.3		0.0087		80.1
3		13.5		0.0062		111.9
4	19.3	8.1	0.0314	0.0035	22.1	198.7
5	749.4	11.1	0.1476	0.0055	4.8	125.8
6	17.1	6.9	0.0149	0.0028	46.6	246.1
7	200.3	13.3	0.0919	0.0042	7.5	163.5
Mean	246.5	13.0	0.0714	0.0054	20.2	147.1
SD	346.0	4.9	0.0606	0.0020	19.1	58.8

[a] A and B, distribution and elimination phase intercepts, respectively; a and b, distribution and elimination phase slopes, respectively; $t_{1/2a}$ and $t_{1/2b}$, distribution and elimination phase half-lives, respectively.

RESULTS

Concentrations in serum. By using the Akaike information criterion, a two-compartment model was fitted to measurements for volunteers 4 to 7, while a one-compartment model fitted better to data for volunteers 1 to 3 (Table 1). The measured peak concentration was 18.0 ± 4.0 mg · liter^{-1} (standard deviation). The serum elimination half-life was 147.1 ± 58.8 min.

Calibration of probes. The 16 ideal measurements (four separate concentrations for each of four probes) were not established for any of the volunteers because of damage to the probes caused by the frequent manipulation of the probe inlets and outlets during calibration or accidental damage caused by the volunteers. Linear correlation coefficients R and P values for R (Table 2) demonstrate that the zero net flux method based on a linear regression model was applicable to the data. Recovery was 34.9% ± 17.4% and ranged from 17 to 65%.

TABLE 2. Calibration of microdialysis probes[a]

Volunteer	RR (% [mean ± SEM])	No. of samples	df	R	P
1	33.5 ± 7.3	11	9	−0.88	<0.01
2	65.0 ± 5.0	12	10	−0.97	<0.01
3	17.0 ± 5.7	11	9	−0.71	<0.02
4	25.8 ± 6.2	11	9	−0.77	<0.01
5	19.6 ± 8.2	8	6	−0.70	0.05
6	51.2 ± 6.2	15	13	−0.92	<0.01
7	32.2 ± 4.5	12	10	−0.91	<0.01

[a] Relative recovery (RR) was calculated as the numeric value of the slope of the concentration increment-versus-inlet concentration line. The fit of a linear model to the data was substantiated by the correlation coefficient and the significance level for a linear model. df, degrees of freedom.

TABLE 3. Measured peak concentrations in serum and adipose tissue interstitial fluid and AUC for the first 6 h

Volunteer	Serum[a]		Tissue AUC_6
	AUC_{TOTAL}	AUC_6	
1	2,287.4	2,057.9	1,080
2	2,235.5	2,128.8	786
3	2,036.5	1,802.8	1,249
4	2,869.3	2,212.7	1,278
5	2,105.1	1,826.4	1,691
6	3,308.3	2,380.4	994
7	3,308.1	2,610.0	1,894
Mean	2,595.7	2,150.7	1,281.7
SD	558.0	289.4	441.4

[a] The serum AUC for the first 6 h (AUC_6) was calculated as serum AUC_{TOTAL} − the concentration at 360 min/β.

Concentrations is tissue. The peak concentration in tissue was 6.7 ± 2.0 mg · liter^{-1}, equivalent to 39% ± 16% of the peak concentration in serum ($P = 0.0005$).

The tissue AUC for the first 360 min was 1,281.7 ± 390.0 mg · min liter^{-1}, equivalent to 60% of the serum AUC for the first 360 min (Table 3). Encompassing all individual samples, this ratio is proportional to the amount of gentamicin having passed through the fat tissue and serum, respectively.

Curves of the concentrations eliminated from serum and tissue approximated each other after ca. 240 min (Fig. 2). The ratio of the concentration in serum: concentration in tissue was 3.6 ± 1.2 30 min after administration of the bolus and 0.9 ± 0.6 240 min after administration of the bolus, indicating continued distribution to this compartment. The half-life of the concentration in the adipose tissue was 227.0 ± 96.2 min, corresponding to 65% of the half-life in serum ($P = 0.13$). Visual inspection (Fig. 2) suggests that distribution and elimination from the adipose tissue and serum assume a common course at the end of the observation period.

DISCUSSION

The microdialysis probe may be considered analogous to an artificial capillary. The difference from normal capillary dynamics is that the transit time of the perfusing fluid is insufficient for diffusion equilibrium to occur. The concentration in the efferent fluid (dialysate) is proportional to the concentration in the interstitial fluid, but the choice of perfusion rate represents a compromise between the desired time resolution and the relative recovery. When performing in vivo microdialysis, the relative recovery is dependent on a tortuosity factor (the ratio of diffusion path in the extracellular fluid to the diffusion path in water; i.e., the degree of zigzagging necessary for a compound to diffuse from point *A* to point *B*) and the fraction of the total tissue volume made up by the extracellular fluid (4). At a constant microdialysis flow rate, relative recovery is determined by the resistance to diffusion imposed by the surrounding medium (tissue), by the microdialysis probe membrane, and by the fluid in the probe lumen (2, 8). In vivo the tissue component is the determining factor (2, 8). Diffusion of gentamicin is restricted to the extracellular fluid. Interpersonal differences in the sizes of the fat cells are likely to cause variation in the tortuosity factor and the fraction of the volume of adipose tissue made up by interstitial fluid. Therefore, interindividual differences in recoveries were expected. We observed a range of recoveries from 17 to 65%. In a thesis by Jansson (14), relative recovery for lactate varied 90% and relative recovery for adenosine in subcutaneous tissue ranged from 40 to 78% (18). Ståhle et al. (26) found recoveries ranging from 22 to 40% for caffeine in fat tissue. In our study the concentrations in four samples collected simultaneously from four microdialysis probes varied less than 15%, indicating that the differences in recoveries represented true differences rather than artifacts. Unlike the previous studies cited above, both males and females participated in the present study and sex-stratifying recoveries produced significant differences (males, 23.7 ± 6.8 [$n = 4$]; females, 49.9 ± 15.8 [$n = 3$]; $P < 0.05$). These differences may be related to diversity in the adipose tissue composition between males and females.

The pharmacokinetics for the values in tissue were calculated by using the formulas for pharmacokinetics in serum. Each microdialysis measurement, when adjusted for recovery, represents an AUC for that period. The concentration in the sample is a geometric mean of an underlying true concentration-versus-time course [the mean value theorem, C_{mean} (Δt = $AUC/\Delta t = \int[A \cdot \exp(-at) + B \cdot \exp(-bt)]/\Delta t$ and when the elimination phase dominates, $\int(B \cdot e - bt)/\Delta t$, where C_{mean} is the mean concentration, *A* and *B* are the distribution and elimination phase intercepts, respectively; *a* and *b* are distribution and elimination phase slopes, respectively; and all other abbreviations were defined above]. The time point at which the mean concentration equals the underlying concentration is between the beginning and the time point midway through the period. In the present study the time point halfway through the times that the individual microdialysis samples were obtained were used. Ståhle et al. (26) demonstrated that the error due to this approximation is negligible when the sampling period is small compared with the drug's half-life (25).

The measured peak concentration obtained in the samples in the first 20 min reflects a minimum value, because the concentrations increase from time zero to reach a maximum above the geometric mean concentration in the first sample.

The measured peak concentration in tissue, 6.7 ± 2.0 mg · liter^{-1} results in peak/MIC ratios of 7.4:1 for *P. aeruginosa* (MIC, 0.9 mg · liter^{-1}); 33.5:1 for *S. aureus* (MIC, 0.2 mg · liter^{-1}), and 4.8:1 for *Klebsiella* spp. (MIC, 1.4 mg · liter^{-1}), which are representative values for members of the family *Enterobacteriaceae* (11).

Moore et al. (20) found that the peak/MIC ratio was significantly higher in patients with good clinical responses to therapy than in patients with poor clinical responses. Blaser et al. (7) demonstrated that a netilmicin peak/MIC ratio exceeding 8:1 prevented the selection and growth of netilmicin-resistant bacterial subpopulations. This 8:1 ratio was obtained in vitro, and the in vivo efficacy might be even more pronounced because of postantibiotic leukocyte enhancement (23). Craig and colleagues (17, 30) found that the AUC/MIC ratio rather than the peak/MIC ratio in itself was predictive of clinical outcome. We found that the adipose tissue AUC from 0 to 6 h was 1,281.7 ± 441.4 mg · min liter^{-1}, which was 60% ± 19.3% of the serum AUC. Eisenberg et al. (10) found a tissue AUC-to-serum AUC ratio in rat bronchial epithelium of 36% ± 12% for gentamicin. This difference might be explained by the difference in tissue, but the fact that an in vitro calibration was used might have been contributory.

The elimination of gentamicin from the adipose tissue of the abdominal wall was investigated in volunteers at thermal steady state and neutral body temperature, conditions in which the skin receives approximately 5% of the cardiac output. Gentamicin distribution may be different under hypothermic conditions, with fever, or during a stress response.

Gentamicin concentrations in serum and microdialysis samples were analyzed by an antibody-based technique, giving the

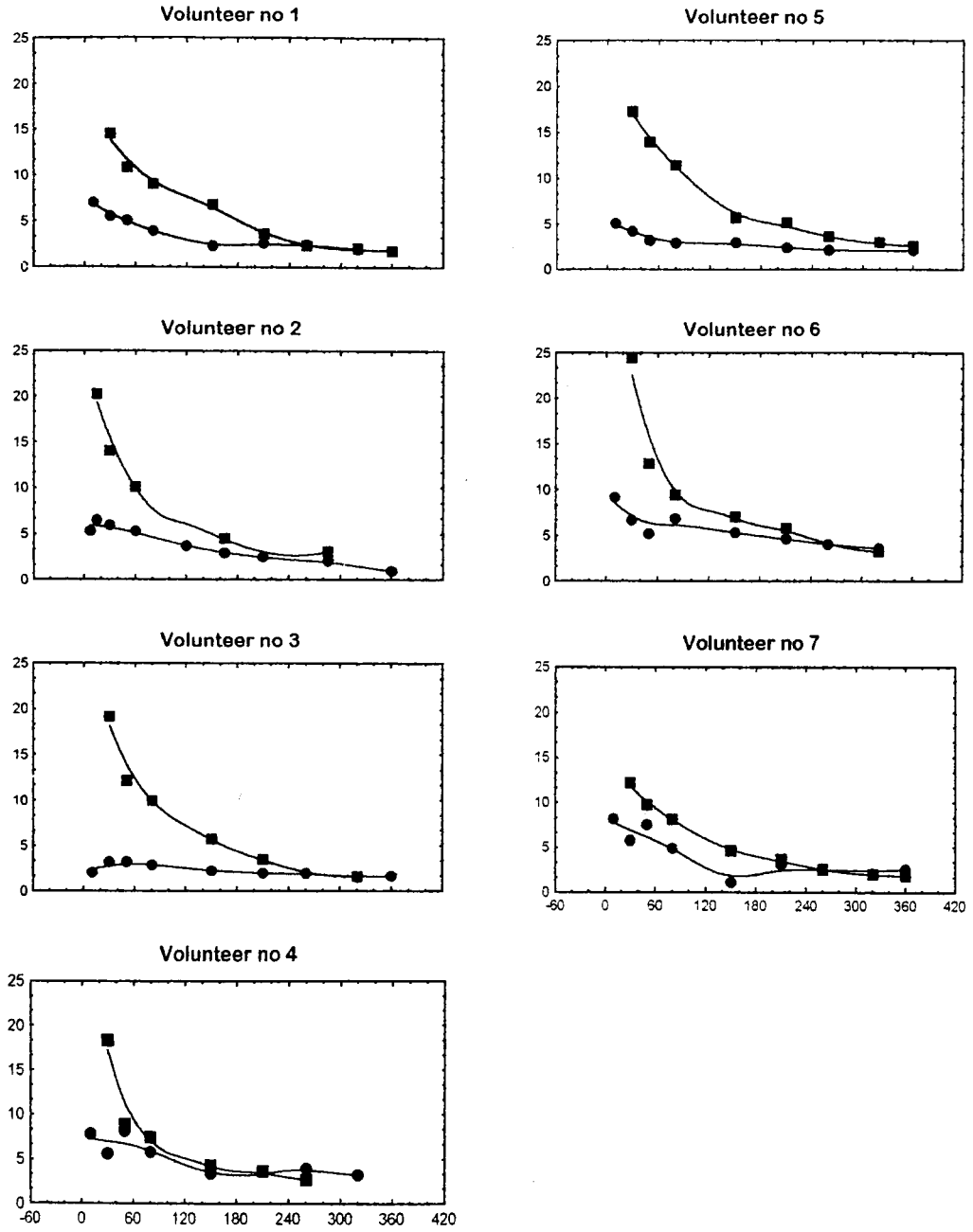

FIG. 2. Drug concentrations in serum (■) and fat tissue extracellular fluid (●) at various time points after the administration of an intravenous bolus of 240 mg of gentamicin. The concentrations in tissue were sampled over 20 to 40 min and were subsequently reduced to a single time point. Abscissa, time (in minutes) after administration of the bolus; ordinate, concentration (in milligrams · liter^{-1}).

chemical rather than a biologically titrated value obtained from culture media. This was considered pharmacokinetically more correct, but it implies that results cannot be extrapolated to conditions such as abscesses or tissue necrosis, in which the local environment may be acidic compared with normal subcutaneous tissue.

In conclusion, the microdialysis technique provided a method for performing pharmacokinetic studies of gentamicin directly in the adipose tissue. The concentrations of gentamicin in the extracellular fluid could be followed dynamically and quantitatively in humans. The peak concentration in the tissue was sufficient to be effective against common pathogens found in surgical and burn patients. The time to reach the peak concentration in the tissue was 10 to 30 min, stressing the relevance of administering gentamicin immediately before starting surgery or shortly after the induction of anesthesia.

ACKNOWLEDGMENTS

This work was supported by Coloplast A/S, Copenhagen, Denmark; Schering-Plough; and grants from the Danish Hospital Foundation for Medical Research, Region of Copenhagen; The Faeroe Islands and Greenland; and The Danish Medical Research Council (grant 5 22 04 05).

We thank the laboratory technicians in the Department of Microbiology, Hvidovre Hospital, and laboratory technician Annie Høj for their skillful work. We also thank Søren N. Rasmussen, the Royal Danish School of Pharmacy, Copenhagen, Denmark, for pharmaceutical assistance.

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