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THE PHARMACOKINETICS OF METHICILLIN AND DICLOXACILLIN IN WOUND FLUID FOLLOWING INTERNAL FIXATION OF TROCHANTERIC FRACTURES

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Prior to the operation, patients undergoing internal fixation of pertrochanteric fractures were given a single intravenous dose of either 2 g methicillin (5 patients) or 1 g dicloxacillin (5 patients). During the postoperative period the concentrations of the two antibiotics were examined in the serum and wound fluid. Based on the concentrations obtained per gram of antibiotics administered there was no difference between the two antibiotics. For both antibiotics the wound fluid concentration was higher than the serum concentration. The elimination from the wound fluid was significantly slower than from the serum. Thus the half-life in wound fluid was found to be approximately 1½ times that of the half-life in serum.

Key words: antibiotics; dicloxacillin; hip fractures; methicillin; pharmacokinetics; wound infection

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The kinetics of systemically administered antibacterial drugs in surgical wounds, i.e., the ability of penetration to and the rate of elimination from the wound, is related to the ability of the drug to eradicate or prevent wound infections. The ability to penetrate wounds following orthopaedic surgery has been investigated for only a few antibiotics (Nelson et al. 1975, Reichelt et al. 1976), and no studies of the kinetics in the wounds has been performed so far.

The present work is an investigation of the kinetics of methicillin and dicloxacillin in wound fluid following internal fixation of trochanteric fractures.

PATIENTS AND METHODS

Based on informed consent, 10 patients with trochanteric fractures (7 females and 3 males) took part in the investigation. Five of these patients were given methicillin and five dicloxacillin. All patients underwent internal fixation, 7 with a Jewett nail and 3 with a McLaughlin apparatus. In the week prior to the commencement of the investigation none of the patients had received antibacterial medicine. All patients had normal serum creatinine.

Suction drainage was employed at all the operations. The initial wound fluid specimen was taken, immediately after the wound had been closed, by aspiration through a syringe attached to the drain. The drain was then connected to a vacuum suction bottle (Steritex Vacu-Drain®), and the subsequent fluid samples were obtained by exchanging the suction bottle 1, 2, 3, 4½, 6 and 8 hours after closure of the wound. Depending on the amount of wound fluid secreted, the suction bottle was changed two to four times during the course of the next 16 hours (a minimum of 2.5 ml wound fluid was necessary for the subsequent assay procedure). For each collection period the volume of the secreted wound fluid was measured, and the fluid was centrifugated and the supernatant usèd for the measurements.

The antibiotics were given as a single intravenous treatment immediately prior to the start of the operation. The dose for methicillin (Lucopenin®) was 2 g and for dicloxacillin (Diclocil®) 1 g. The interval between the intake of antibiotics and the collection of

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the first wound fluid and serum specimen was 60 minutes in the case of methicillin (range 50–65) and for dicloxacillin 75 minutes (range 55–110).

Four samples of venous blood were collected. The first was taken immediately after closure of the wound (at the same time as the collection of the first wound fluid specimen), and the subsequent samples were taken 1, 3 and 6 hours later. Serum was used for the measurements.

In the determination of the concentrations an agar-cup method was employed. *Sarcina luthea* was used as the test organism and trypticase agar as test medium. Standard concentrations of antibiotics dissolved in pooled wound fluid supernatants from 10 patients were used for the measurement of antibiotics in the wound fluid supernatants. These 10 patients had undergone operations similar to those of the patients in the investigation but had not been treated with antibiotics. Antibiotics dissolved in pooled human serum were used as standard concentrations for the measurement of antibiotics in the serum samples. The smallest concentration of antibiotics in serum and wound fluid supernatant that could be measured was 0.6 μg/ml. All the samples were kept at 4°C, and the concentrations were measured within 24 hours of the collection.

The concentrations of the antibiotics in the suction bottles reflect the concentrations in the fluid of the operation wound itself with a certain time lag. This delay will partly depend on the secretion rate of the wound fluid and partly on the capacity of the drain. Since the capacity of the drains employed was 2.5 ml, the mean time-lag for a collection period becomes $2.5/H$ or $2.5/V \times (t_2 - t_1)$, where H is the mean secretion rate for the collection period from t_1 to t_2, and V is the secreted wound fluid volume for the same period. Assuming with some approximation that the concentration measured in the fluid from the suction bottle (C_b) is equal to the concentration in the fluid that is sucked into the bottle in the middle of the collection period ($t_2 + t_1/2$), we arrive at the following connection between C_b and the concentration (C_w) in the fluid of the operation wound itself:

$$C_w \left(\frac{t_2 + t_1}{2} - \frac{2.5}{V} \times (t_2 - t_1) \right) = C_b \left(\frac{t_2 + t_1}{2} \right)$$

This formula was used to calculate the concentrations of antibiotics in the fluid of the operation wound itself based on the measured concentrations in the fluid from the suction bottles.

The Mann-Whitney Test was used for the statistical evaluations.

RESULTS

Both methicillin and dicloxacillin are eliminated from the organism predominantly through the kidneys. To evaluate the comparison between the two groups of patients Table 1 shows the mean values of serum creatinine, age and weight. Since the elimination of antibiotics from the operation wound is influenced by the rate of secretion of the wound fluid, Table 1 shows the mean value of the rate of secretion 1, 6 and 12 hours after the completion of the operations for each of the two groups of patients. It can be seen from the Table that no significant difference was found between the two groups of patients as regards the investigated parameters.

The concentrations obtained in serum and operation wound fluid, of methicillin and dicloxacillin, respectively, are shown in Figures 1 and 2. The elimination of the antibiotics from the operation wound fluid was significantly slower than from the serum, and from 1/2 to 3/4 of an hour after completion of the operations the concentrations of the antibiotics in the wound fluid were higher than in the serum.

Table 1. Data for patients in the methicillin and dicloxacillin groups respectively, expressed as mean values and range

	Age (years)	Weight (kg)	Serum-creatinine (μmol/l)	Rate of secretion of wound fluid ml/minute Hours after closure of wound		
				1	6	12
Methicillin	81 (72–90)	63 (45–80)	84 (80–100)	0.38 (0.14–0.59)	0.085 (0.044–0.17)	0.034 (0.020–0.084)
Dicloxacillin	73 (61–89)	68 (43–82)	84 (60–100)	0.54 (0.20–1.1)	0.094 (0.068–0.14)	0.066 (0.018–0.16)
P-value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

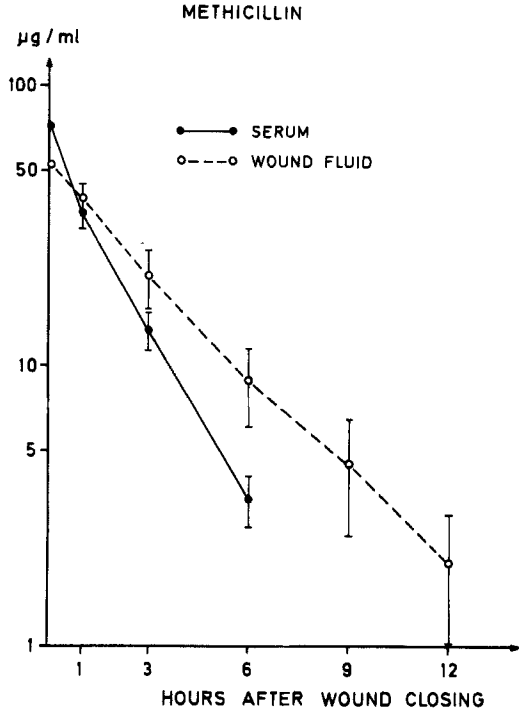

Figure 1. Concentration of methicillin in serum and wound fluid (mean value ± 2 × standard error) after an intravenous injection of 2 g. The starting point for measuring the concentration was the completion of the operations, and methicillin was administered 60 minutes prior to this (range 50–65).

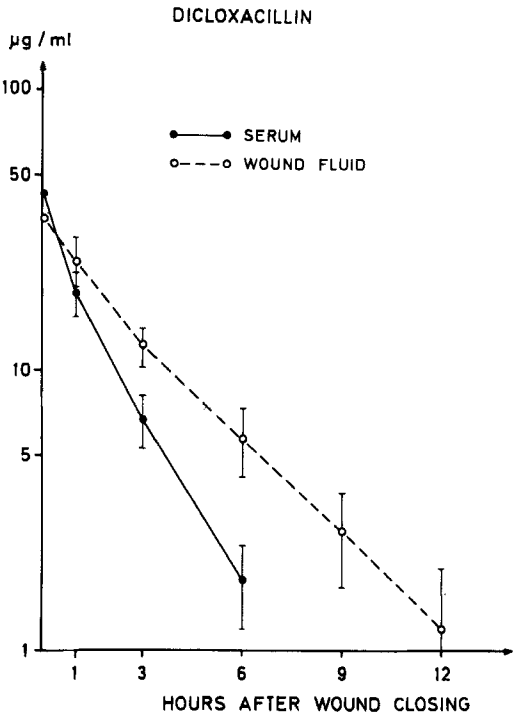

Figure 2. Concentration of dicloxacillin in serum and wound fluid (mean value ± standard error) after intravenous injection of 1 g. The starting point for measuring the concentrations was the completion of the operations, and dicloxacillin was administered 75 minutes prior to this (range 55–110 min).

Table 2 lists the mean value of the half-life in serum and wound fluid for both methicillin and dicloxacillin. In addition Table 2 shows the mean values of the concentrations obtained in the serum and wound fluids 2 hours after administration of antibiotics calculated per gram administered. As shown, the half-lives in serum for the two antibiotics were identical, and the same applied to the half-lives in wound fluid. The half-lives in wound fluid were found to be approxi-

Table 2. Pharmacokinetic data in serum and operation wound fluid, for the methicillin and dicloxacillin groups, respectively, expressed as mean values and range

	Half-life minutes		Concentration 2 hours after administration per gram administered (µg/ml)	
	serum	fluid	serum	fluid
Methicillin	91 (75–101)	147 (113–178)	18 (13–20)	20 (16–25)
Dicloxacillin	85 (71–97)	148 (126–186)	25 (15–42)	26 (19–36)
P-value	>0.05	>0.05	>0.05	>0.05

mately 1½ times the half-lives in serum. There was no difference between the obtained concentrations of methicillin and dicloxacillin, when these were calculated per gram of the quantities administered.

DISCUSSION

In clinical controlled investigations it has been found that systemically administered antibiotics are able to reduce the frequency of postoperative wound infection in orthopaedic surgery (Boyd et al. 1973, Ericson et al. 1973, Lindberg & Tjörnstrand 1978, Burnett et al. 1980). *Staph. aureus* is responsible for the major part of the postoperative wound infections. When selecting antibiotics for infection prophylaxis one must therefore choose those which have an antibacterial spectrum that includes *Staph. aureus*. It is however not only the antibacterial spectrum which determines how suitable an antibiotic is in such prophylaxis. The penetration to and the elimination from the wound fluid must also be taken into account, as well as the antibacterial effect of the antibiotic in the wound fluid.

Very few investigations have been undertaken so far on the penetration of systemically administered antibiotics to operation wound fluid. Nelson et al. (1975) examined the penetration ability of oxacillin, lincomycin and cephalothin to wound fluid following total hip replacement. They found the concentrations in wound fluid to be lower than in serum. Reichelt et al. (1976) examined the penetration of gentamycin to the wound fluid in the same category of patients and likewise found lower concentrations in fluid than in serum.

Both the antibiotics tested in the present study have a narrow antibacterial spectrum, which includes *Staph. aureus*. Other penicillins, nafcillin and oxacillin, have been proved to be able to reduce the frequency of postoperative wound infections caused by *Staph. aureus* (Boyd et al. 1973, Ericson et al. 1973). Based on the concentrations obtained in serum and wound fluid per gram of administered antibiotic, we found no difference between the two antibiotics. For both antibiotics, we found that from ½ to ¾ of an hour after completion of the operations there was a higher concentration in the wound fluid than in the serum, and that the elimination of the two antibiotics from the wound fluid was slower than from the serum.

As far as we know, there have been no investigations published, which throw light on the antibacterial effect of methicillin and dicloxacillin in operation wound fluid. This question has been investigated in our laboratory. In *in vitro* tests we have determined the lowest concentration in wound fluid of each of the two antibiotics, which prevent growth of *Staph. aureus*, and likewise determined the lethal effect on *Staph. aureus* of concentrations in excess of this minimal inhibitory concentration. From these tests we have not been able to prove any difference between the antibacterial effect of the two antibiotics. The minimal inhibitory concentrations of the two antibiotics in wound fluid were in these *in vitro* tests found to be 1–2 μg/ml. This is in agreement with the minimal inhibitory concentrations found by Reller & Stratton (1977) when a serum protein containing test medium was used. In the present study, it was found that the mean concentration in the wound fluid was above the minimal inhibitory concentration for *Staph. aureus* for about 12 hours in the methicillin group of patients (dose 2 g) and for about 10 hours in the dicloxacillin group (dose 1 g).

As to the question of whether methicillin or dicloxacillin should be used as prophylaxis against postoperative wound infections, we must conclude that there are no valid grounds for any preferences to be given. It must be stressed, however, that this conclusion is based on the pharmacokinetic characteristics after a single preoperative injection of the antibiotics, and that the conditions may be different in the case of multiple dosage in the postoperative period.

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