TRANSFER OF CEFMENOXIME FROM BLOOD INTO HUMAN SKIN BLISTER FLUIDS INDUCED BY SUCTION

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Cefmenoxime concentrations in blister fluid induced by suction were determined in 12 adult burn patients after an intravenous bolus injection (50 mg/kg body weight) of the drug. The cefmenoxime concentration in the suction blister fluid reached its maximum level (25.8 μg/ml) at 1 hr. Using a two-compartment open model, C_{max} (maximum concentration), T_{max} (time of maximum concentration) and apparent transport ratio (F) ($k_1 \cdot V_s/k_2 \cdot V_e$) were calculated as 26.6 μg/ml, 2.14 hr, and 0.54, respectively.

We compared the data with those on exudates from excoriated skin wounds and burn wounds, and with the data on burn blister fluids given in our previous paper. The pharmacokinetic parameters of cefmenoxime concentrations in suction blister fluids resembled those in burn blister fluids of burn patients. It appears from this study, that suction blister fluids are a useful model for burn blister fluid.

INTRODUCTION

In burn patients, antibacterial activity in skin exudates may give useful clinical and pharmacological information. Previously we studied the transfer of antibiotics such as tobramycin[1], cefmenoxime[2], cefoperazone[3], fosfomycin[4], and latamoxef[5] from the blood to burn blister fluid. We also reported the transport of cefmenoxime into three kinds of exudates (from excoriated skin wounds, burn wounds, and burn blister fluids) from the blood after injection. Except in the case of burn blister fluid, however, the sampling of a small amount of exudate from burn patients is usually difficult.

In this study we accordingly induced blister fluid by suction in burn patients and determined the cefmenoxime concentrations in the fluids after a bolud injection of the drug. Detailed results are described in this paper.

MATERIALS AND METHODS

The study comprised 12 adult burn patients, 7 males and 5 females, ranging from 19 to 70 years (mean : 43 years), and in body weight from 40 to 60 kg (mean : 55.2 kg). Liver and renal function tests were all within the normal range. All subjects were in-patients of Aichi Medical University Hospital who had agreed to take part in the study after it was explained to them.

In each subject, 8 skin blisters were produced by suction. Perspex cups (diameter 18 mm) were tightly strapped to the abdominal area and controlled suction (−200 mmHg) was applied to each cup. After 2 hours, a hemispherical blister containing approximately 1 ml of serous fluid was produced beneath each cup by dermo-epidermal separation induced by suction. From each blister 1 ml of fluid was aspirated by syringe. Cefmenoxime, a cephalosporin derivative, was provided for use in this study by Takeda Chemical Industries Ltd. (Osaka, Japan). The dose given to patients was determined as 50 mg/kg administered intravenously by bolus injection. After injection, blister fluids were taken at 30 minute, 1 hr and thereafter hourly for

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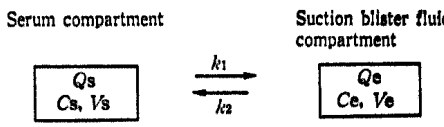
Fig. 1 Two-compartment open model for analysis of distribution of cefmenoxime in serum and suction blister fluid



Qs, Qe : amount of drug in serum or suction blister fluid
Cs, Ce : concentration in serum or suction blister fluid
Vs, Ve : distribution volume of serum or suction blister fluid
k_1, k_2 : transport rate constant

8 hr. Samples for the determination of antibiotic concentration were immediately frozen and stored at −20°C until the bioassay (using *Escherichia coli* NIHJ JC-2, as reported previously[6]) could be performed.

The data were pharmacokinetically analyzed with a modified two-compartment open model using an IBM 3081 computer. In this model the relationship (Fig. 1) of Q_s, C_s, and V_s represent the amount, concentration, and distribution volume of the drug in the central compartment (serum); Q_e, C_e, and V_e are the respective values in the peripheral compartment (blister fluid); k_1 and k_2 represent the ratio constants of the equilibrium, and F (apparent transport ratio) is $k_1 \cdot V_s / k_2 \cdot V_e$. F is the veritable transport ratio for serum to blister fluid when the V_s/V_e ratio is constant. The rate of drug transfer from serum to the blister fluid can be expressed by the equation (1):

$$\frac{dQ_e}{dt} = k_1 \cdot Q_s - k_2 \cdot Q_e \qquad (1)$$

The rate of increase in the concentration of the drug in blister fluid can be expressed by the equation (2):

$$\frac{dC_e}{dt} = \frac{k_1 \cdot V_s}{V_e} C_s - k_2 \cdot C_e = k_2 (F \cdot C_s - C_e) \qquad (2)$$

RESULTS

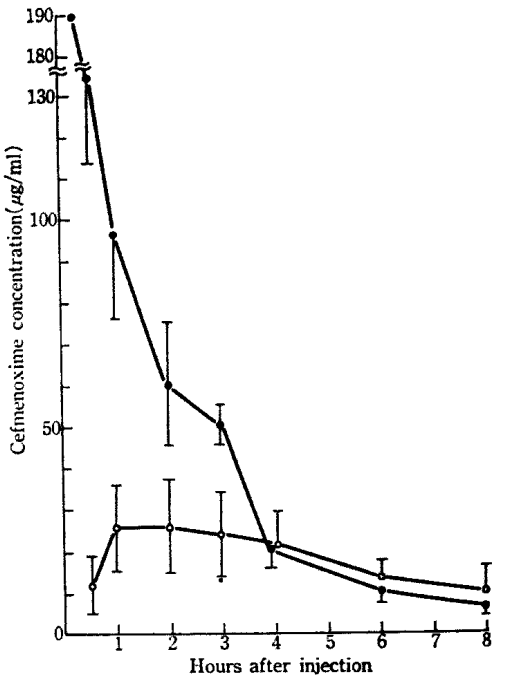
1. Changes in cefmenoxime concentrations in serum and suction blister fluid after bolus injection of cefmenoxime

The changes in cefmenoxime concentrations in serum after bolus injection of the drug (50 mg/kg) are shown in Table 1 and Fig. 2. The concentration in serum reached 189±29.7 μg/ml (mean±SD) at 15 min and then decreased to 4.8±1.3 μg/ml by 8 hr. The concentration in suction blister fluid increased gradually, being 25.8 μg/ml at 1 hr and 25.5 μg/ml at 2 hr, then decreased slowly to a higher level than that in serum at the same time point (Table 1 and Fig. 2).

Table 1 Cefmenoxime concentrations in serum and suction blister fluid after bolus injection (50 mg/kg) of the antibiotic to burn patients (n=12)

hrs	Serum (μg/ml)	Suction blister fluid (μg/ml)
0.25	189.2±29.7	
0.5	133.5±20.3	11.9± 7.0
1	96.0±18.0	25.8±10.0
2	59.5±15.3	25.5±11.4
3	30.0± 4.7	24.3± 9.9
4	20.9± 4.8	21.3± 8.3
6	9.7± 2.6	12.8± 4.3
8	4.8± 1.3	9.1± 6.5

Fig. 2 Cefmenoxime concentrations in serum (●) and suction blister fluid (○) after bolus injection (50 mg/kg) of the antibiotic to burn patients (n=12)



2. Pharmacokinetic analysis of cefmenoxime concentrations in serum and suction blister fluid after bolus injection

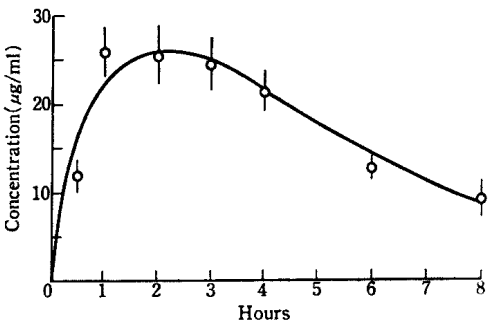
Changes in concentration in serum were analyzed using a two-compartment open model to obtain the

Table 2 Pharmacokinetic parameters of cefmenoxime in various exudates after bolus injection (50 mg/kg) of the antibiotic to burn patients

Parameters / Exudates	C_{max} (μg/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	k_2[b] (hr^{-1})	F[c]
Suction blister fluid[a] (n=12)	26.6±8.2	2.14±0.52	2.22±0.73	0.38±0.19	0.54±0.21
Burn blister fluid[a,d] (n=8)	22.9±6.6	2.03±0.35	1.94±0.45	0.40±0.12	0.43±0.14
Exudates from excoriated skin[a,d] (n=15)	34.9±7.8	1.39±0.46	1.58±0.18	0.78±0.36	0.47±0.10
Exudate from burn wound[a,d] (n=8)	19.7±3.3	1.47±0.47	1.59±0.23	0.71±0.33	0.28±0.07

[a] : Data represent the arithmetic mean ± standard deviation.
[b] : Transfer rate constant from exudate to serum.
[c] : Apparent transport ratio.
[d] : Data from our previous report (ref. 6).

Fig. 3 Simulation curve of cefmenoxime concentrations (mean±SD) in suction blister fluid by two-compartment open model after bolus injection (50 mg/kg) of the antibiotic to burn patients (n=12)



pharmacokinetic parameters. The half-life of the elimination phase was 1.53 hr. The distribution volume was 0.33 l/kg, and the AUC (area under the curve) of plasma concentration versus time was 346 μg·hr/ml. Changes in concentration in suction blister fluid were then similarly analyzed, as described in MATERIALS AND METHODS (Table 2 and Fig. 3). C_{max}, T_{max}, and F were calculated as 26.6 μg/ml, 2.14 hr, and 0.54, respectively.

DISCUSSION

Transfer of various antibiotics administered systemically to the skin of patients or to exudates elicited from them have been studied using homogenates of skin[7,8] or exudates (blister) induced artificially by the skin window technique (dermabrasion)[9,10,11] dermal suction[12,13] or application of cantharidin ointment[14,15,16,17].

In our previous paper, we studied the transport of cefmenoxime from the blood into three kinds of exudates (from excoriated skin wounds, burn wounds, and burn blister fluids). Though these exudates were useful for the determination of drug concentration in the interstitial-like fluid of the skin after administration, the volume of this fluid was not constant. Thus, to analyze with greater accuracy the drug concentration in the peripheral compartment, we artificially induced a constant volume (1 ml) of blister fluid by suction, and compared the data on suction blister fluid with those on exudates from excoriated skin wounds, from burn wounds, and from burn blister fluids. C_{max}, T_{max}, and F of suction blister fluid (26.6 μg/ml, 2.14 hr, 0.54) resembled those of burn blister fluid (22.9 μg/ml, 2.03 hr, 0.43). However, there was a difference between T_{max} (2.14 hr) in suction blister fluids and in exudates from excoriated skin wounds (1.39 hr) or from burn wounds (1.47 hr). The four kinds of exudates can therefore be divided into two groups in terms of their pharmacokinetic parameters. That is, the concentration of cefmenoxime in exudates from excoriated skin or from burn wounds increases quickly, so that the T_{max} and $t_{1/2}$ obtained are shorter than in burn blister fluid or suction blister fluid. Also, epidermis is lost in the case of excoriated skin wounds or burn wounds, while it remains on blisters produced by

burns or suction.

RAEBURN[9] reported that the acute inflammatory exudates induced by dermabrasion contain the highest level (2.1 mg/l) of clindamycin during the first hour of inflammation, while the chronic exudates from leg ulcers contain a gradually increasing concentration of clindamycin.

The exudates from excoriated skin wounds and from burn wounds probably correspond to the acute inflammatory exudates ; whereas burn blister fluid and suction blister fluid may correspond to the chronic exudates. This hypothesis should, however, be supported by further clinical and histological studies.

Staphylococcus aureus and *Pseudomonas aeruginosa* are commonly found in the skin wounds of burn patients in our hospital. Cefmenoxime minimum inhibitory concentrations (50%) against these organisms were reported by VINCENT[18] to be 8 μg/ml for *Staphylococcus aureus* and 16 μg/ml for *Pseudomonas aeruginosa*.

In the present experiment, the drug concentration found in suction blister fluid was over these concentrations (8-16 μg/ml) for approximately 3-4 hr after the antibiotic administration, so these results indicate that cefmenoxime should be a useful antibiotic for burn patients to avoid infection of their burn wounds, provided the drug is given at a sufficient dosage (50 mg/kg).

From this study, we concluded that suction blister fluid is a useful model for the study of the pharmacodynamics of antibiotics in burn blister fluid when the antibiotic is administered by bolus injection.

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静脈内投与された Cefmenoxime のヒト吸引水疱液内への移行

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12 名の熱傷患者に Cefmenoxime を体重 kg 当り 50 mg，静脈内に single-dose 静注し，吸引により惹起された水疱液への薬物の移行を調べた。

吸引水疱液中の Cefmenoxime 濃度は投与 1 時間後に最高濃度 25.8 μg/ml に達した。Two-compartment model により薬動力学的に解析した結果，最高濃度 (C_{max})，最高濃度到達時間 (T_{max})，みかけの移行率 (F) はそれぞれ 26.6 μg/ml，2.14 時間，0.54 と計算された。

今回，得られた結果を熱傷植皮術の際の皮膚剥離創滲出液，熱傷創面滲出液，熱傷水疱液の Cefmenoxime 濃度と比較した。吸引水疱液中の Cefmenoxime 濃度変化は薬動力学的に熱傷水疱液中の動態に類似しており，他の 2 種の滲出液とは異なる結果が得られた。

今回の結果から，吸引水疱液中の薬物濃度を調べることは臨床的に熱傷水疱液中薬物濃度の予測に有用であることが示唆された。