

Investigation of the CET Levels in the Serum During and after Cardiopulmonary Bypass

AKITO NAKAGAWA, MASANORI ARAKI, TOSHIMI OHSHIMA, YOICHI UENO,
KIYOSHI SAKAMOTO and MASANOBU AKAGI

Second Department of Surgery, Kumamoto University Medical School, Kumamoto

(Director: Prof. MASANOBU AKAGI)

Received for Publication, Nov. 10, 1983.

Introduction

Post-operative infectious disease is considered to be one of the most formidable complications of heart disease because of difficulty of the treatment and high mortality. As applications of heart operation become more extensive and operations become available for more complicated and serious cases, the significance of post-operative infectious disease increases. To examine adequate dosage of antibiotics, CET (sodium cephalothin) concentrations in blood serum during and after bypass were measured.

Subjects and Methods

1) Subjects

Data on the 11 patients entered into this study are shown in Table 1.

2) Methods

CET (3 g) was added to the filling liquid of pump-oxygenator regardless of the subjects' weight. For measuring CET concentration in serum, blood was drawn every 20–30 minutes after a 5–10 minute bypass and every 30–60 minutes after bypass until the antibiotic was supplementally administered in the recovery room or ICU. The concentration of CET was measured by a fractionation method, using streptococcus hemolytic denken as an assayed bacterium.

Results

Each measured value was plotted semilogarithmically with the vertical axis and horizontal axis representing CET concentration (logarithmic gradient) and time, respectively (Fig. 1). In each case, the CET concentration reached 200–700 $\mu\text{g/ml}$ after 5–10 minutes of bypass and then decreased with time by a certain decrement. The concentration in adult patients was initially lower than that of children because the amount of CET per body weight was less in adults.

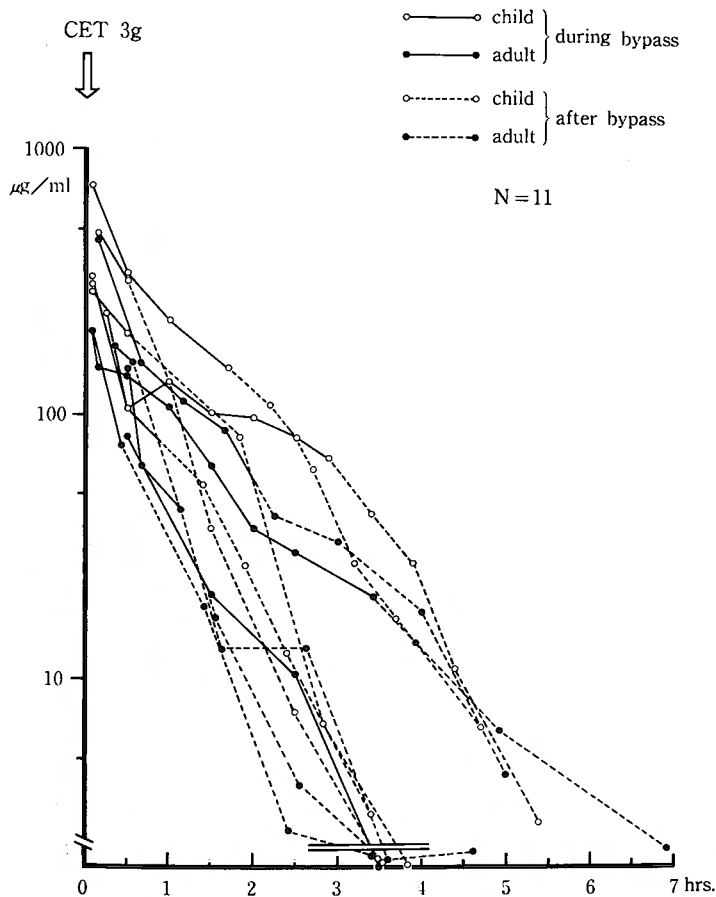
Key Words: Adequate dosage of antibiotics, Bypass, CET concentration in blood serum, Logarithmic gradient, Minimum inhibitory concentration.

索引語: 抗生物質の適正投与量, 体外循環, 血清中 CET 濃度, 対数勾配, 最小発育阻止濃度.

Present address: Second Department of Surgery, Kumamoto University Medical School, Kumamoto, 1-1-1 Honjo, Kumamoto-city, 860 in Japan.

Table 1. material

case No.	patient				name of disease	bypass time
	name	age	sex	wt. (kg)		
1.	OT	4	M	16.0	A S D + V S D	1° 42'
2.	NT	6	F	16.5	A S D + P S	30'
3.	OM	6	F	19.5	E C D	2° 53'
4.	TY	8	F	19.5	V S D	30'
5.	ME	8	F	20.0	A S D	54'
6.	MS	21	F	56.0	A S D	34'
7.	YN	21	F	58.0	Two chambered R.V.	1° 08'
8.	YT	21	F	58.7	T O F	3° 30'
9.	WK	25	M	54.0	T O F	3° 25'
10.	SH	32	M	51.5	Valsalva	2° 00'
11.	OK	35	F	52.0	A S D + P H	25'

**Fig. 1.** CET levels in serum

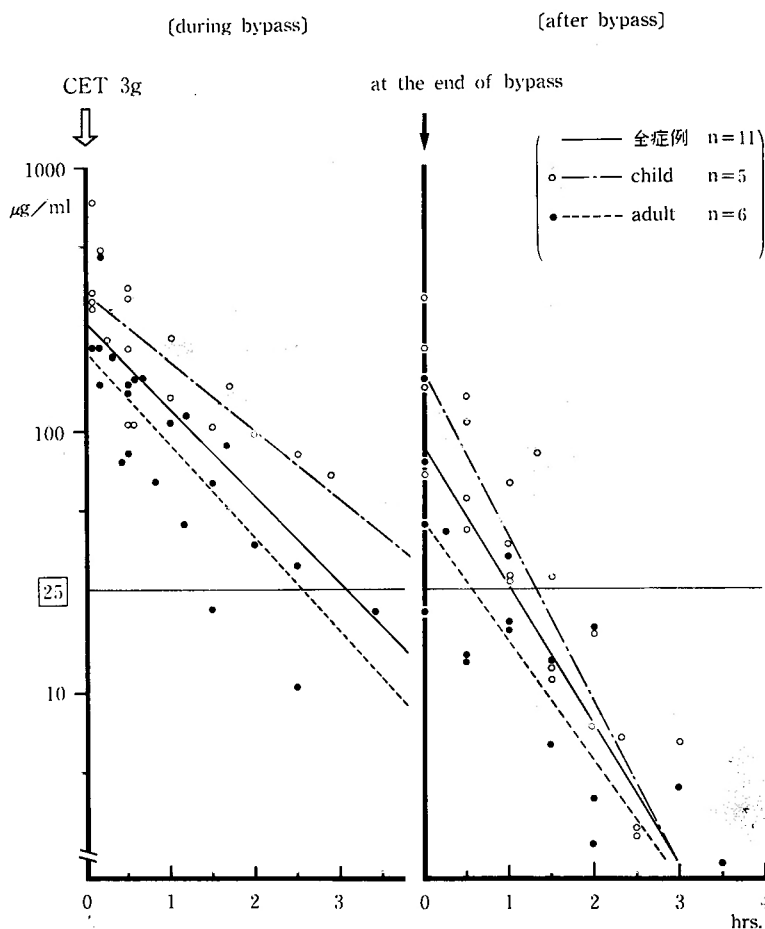


Fig. 2. CET levels in serum

According to the regression lines in the left diagram of Fig. 2, decrements were calculated to be:

$$\log y = -0.0043x + 2.5140 \text{ (T } 1/2 = 70 \text{ min.) for children;}$$

$$\log y = -0.0058x + 2.2913 \text{ (T } 1/2 = 52 \text{ min.) for adults; and}$$

$$\log y = -0.0055x + 2.4098 \text{ (T } 1/2 = 55 \text{ min.) for all cases.}$$

Although adult patients showed a larger decrement than children, no significant ($p > 0.05$) difference was observed between them.

As for CET level after bypass, shown in the right diagram of Fig. 2, the decrements were:

$$\log y = -0.0104x + 2.2121 \text{ (T } 1/2 = 29 \text{ min.) for children;}$$

$$\log y = -0.0075x + 1.6457 \text{ (T } 1/2 = 40 \text{ min.) for adults; and}$$

$$\log y = -0.0088x + 1.9350 \text{ (T } 1/2 = 34 \text{ min.) for all cases.}$$

There was a significant difference ($p < 0.05$) in decrements between children and adults.

The decrements were larger after bypass than during bypass in all cases, with a significant change ($p < 0.05$) shown in children from -0.0043 to -0.0104 (Fig. 2). In the case of only adults,

however, no significant difference was observed. In total, decrements increased significantly ($p < 0.05$) after bypass (Fig. 2).

Discussion

In the field of general surgery as well as heart surgery, the principles of administering preventive antibiotics seem to be, firstly, to identify the distribution of infectious agents and their sensitivity to medicine, and then to administer antibiotics effective at the initial stage during or after operation.

Accordingly, CET, an antibiotics effective to gram-negative bacteria and penicillin-resistant staphylococcus as well as gram-positive bacteria has been administered via the perfusion fluid during bypass, the time with the largest potential for bacterial contamination^{4,5,6,8,9,11}.

No examination has been made so far, however, on the CET concentration, which is a determining factor with respect to the amount, the method, and the scheduling of additional doses of CET. It still remains questionable whether the present regimens for administering CET are adequate or not.

To establish the optimal dosage of CET, the minimum inhibitory concentration (MIC) and the effective serum concentration under various conditions should be firstly examined.

Typical segregated bacteria of post-operative infectious diseases include gram-positive bacteria (staphylococcus and streptococcus) and gram-negative bacteria (colitis bacteria and Klebsiella^{6,8}). A fairly high MIC of CET is required against gram-negative bacteria, compared with the negligible amount needed against gram-positive bacteria. For example, 90% of colitis bacteria, 80% of Klebsiella, and 100% of all the gram-positive bacteria were destroyed by CET at a concentration of 25 $\mu\text{g/ml}$ ^{1,2,3}. Consequently, this concentration was considered to be effective in preventing post-operative infectious diseases.

Concerning the changes in CET serum concentrations, in the adult cases, the concentration remained over 25 $\mu\text{g/ml}$ within 2 hours 34 minutes of bypass, and after which it decreased to less than 25 $\mu\text{g/ml}$, implying the need for additional administration to maintain the effective concentration level (Fig. 2). In children, on the contrary, the CET concentration remained over 25 $\mu\text{g/ml}$ for 3 hours of bypass (Fig. 2). This discrepancy occurred because the CET concentration per body weight was initially lower in adults and because the rate of decrease was almost identical between two cases.

As to the CET levels after bypass, they remained over 25 $\mu\text{g/ml}$ for 78 minutes in children, while the same level was maintained for only 33 minutes in adults, as illustrated by each regression line. These results suggest that an additional dose by administered 30 minutes after bypass for adults and about 80 minutes after bypass for children (3.4).

There are several reports on supplemental administration after transfer to ICU^{6,8}. SHAH found in his in vitro experiment that with 10 $\mu\text{g/ml}$ on CET, a concentration which exceeds the MIC, 99% of the colitis bacteria were killed in 73 minutes¹⁰. According to EAGLE's report, when gram-positive bacteria are exposed for 1–1.5 hours to penicillin at concentration greater than MIC, the surviving bacteria are so damaged that no proliferation takes place for 3 hours in

mediums without antibiotics and for 6 hours in normal animals^{1,2,3)}.

Thus, it is desirable to constantly maintain the CET concentration over the MIC. However, SHIMADA recommended that an additional dose of CET should be administered so as to maintain the effective CET level for at least 3–6 hours. Thus, the effect of antibiotics depends on time and dosage, though the scheduling of dosage may vary with the concentration as well as the conditions of the patient.

A comparison of the rate of decrease in CET during bypass with that after bypass demonstrated higher values in the latter period. The difference was significant in children. The functional process of the change is as follows: The hemodynamics returned to normal after bypass, the transfusion was well-balanced, and renal blood flow and urine increased, triggering the increase in CET excretion and accordingly, a rapid decrease in CET concentration.

Conclusion

- a) General change in CET concentration in blood serum during and after bypass
A sharp decrease in the concentration was observed in a logarithmic plot, in which the vertical axis represents CET concentration (logarithmic gradient) and the horizontal axis, time.
- b) Comparison of the rate of decrease in CET concentration in serum during and after bypass
In children, the rate of decrease is significantly ($p < 0.05$) higher after bypass than during bypass. No significant difference was observed in adult cases.
- c) Comparison between children and adults in terms of decrements of CET concentration in serum during and after bypass.
There was no considerable difference between them during bypass, but after bypass, a significantly ($p < 0.05$) higher rate of decrease was observed in children.

References

- 1) Eagle H, Fleischman R, et al: "Continuous" vs "Discontinuous" therapy with penicillin. The effect of the interval between injection on therapeutic efficacy. *The New England J of Medicine* **248**: 81–88, 1953.
- 2) Eagle H, Fleischman R, et al: Effect of schedule of administration on the therapeutic efficacy of penicillin. Importance of the aggregate time penicillin remains at effectively bactericidal levels. *Am J Medicine* **9**: 280–299, 1950.
- 3) Eagle H, Fleischman R, et al: The bactericidal action in vivo of penicillin: The participation of the host, and the slow recovery of the surviving organisms. *Ann Intern Med* **33**: 544–571, 1950.
- 4) Fong IW, Baker CB, et al: The value of prophylactic antibiotics in aorta-coronary bypass operations. *J Thorac Cardiovasc Surg* **78**: 908–913, 1979.
- 5) Ilves R, Cooper JD, et al: Prospective, randomized, double-blind study using prophylactic cephalothin for major, elective, general thoracic operations. *J Thorac Cardiovasc Surg* **81**: 813–817, 1981.
- 6) Ino T, Aoki K, et al: Antibiotics prophylaxis for open heart surgery—Comparison of ABPC and CET—The *Jpn of Thorac Surg* **35**: 337–342, 1982.
- 7) Komatsu H, Ebine K, et al: Clinical experience with cephalothin after cardiac surgery. *The Jpn Saishin Igaku* **29**: 944–954, 1974.
- 8) Ohtaya H: Sensitivity of staphylococcus aureus and escherichia coli to antibiotics. V. *The J of Antibiotics* **27**: 686–695, 1974.
- 9) Stille W, Shah P: Kinetik der Bakterizidie von Ampicillin, Penicillin G, Carbenicillin, Cephalothin, Kanamycin, Gentamycin, Polymyxin B und Sulfamethoxazol/Trimethoprim gegenüber E. coli: *Arazneim Forsch*

23: 58-60, 1973.

10) Shimada K: Clinical evaluations of large dosis on cephalothin. The Jpn Saishin Igaku 20: 867-887, 1974.

和文抄録

体外循環中および終了後における血清中 CET 濃度の経時的变化について

熊本大学医学部第二外科（主任：赤木正信教授）

中川 昭十，荒木 昌典，大嶋 寿海，上野 洋一

酒本喜与志，赤木 正信

体外循環開心術11例を対象に，体重に関係なく，CET 3.0 g を人工心肺回路の充填液中に混入し，体外循環中および終了後の血清中 CET 濃度を経時的に測定し，2，3の知見を見た．縦軸に CET 濃度（対数目盛），横軸に時間を示す半対数グラフでみると，体外循環中および終了後の血清中 CET 濃度は，ほぼ直線的に下降していった．体外循環中と終了後における血清中 CET 濃度減少の速度の比較では，小児においては体外循環中より終了後の CET 濃度減少速度の方が有意に大きくなっているが，成人例では有意差はな

かった．また，体外循環中の血清中 CET 濃度減少速度については小児と成人の間に有意差はなかったが終了後には小児の方が成人より有意に大きかった．最後に体外循環中の血清中 CET 濃度が 25 $\mu\text{g/ml}$ 以上の時間についてみると，成人例では，循環開始後2時間34分であったが，小児では3時間以上であり，また終了後では，成人で約33分であり，小児では78分までは，25 $\mu\text{g/ml}$ 以上を維持した．このように血清濃度減少速度の状態を検討することは，適正なる抗生物質投与法の1つの参考となり得ると考えられる．