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Pharmacokinetic (PK) Characteristics in Critically Ill Patients

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<http://dx.doi.org/10.5772/60619>

1. Introduction

Recently, it was evidenced that application of the PK in critical patients has been growing. We reported previously that pharmacokinetic (PK) properties of 1) an aminoglycoside for Methicillin Resistance *Staphylococcus Aureus* (MRSA) and 2) an antithrombin preparation for DIC (disseminated intravascular coagulation) are remarkably different in critically ill patients from the normal condition ($\frac{1}{2}$). Therefore, we need to recognize these aspects on the treatments for such patients. So in this chapter, we review PK profile along with our previous reports and update pharmacological concept for critically ill patients.

2. Antibiotics

2.1. Background of ABK, an aminoglycoside

Arbekacin (ABK) is an aminoglycoside for methicillin-resistant *Staphylococcus aureus* (MRSA) [3]. The bactericidal effect of ABK depends on the peak serum concentrations like other aminoglycosides [4]. In this regard, several reports demonstrated antibiotic pharmacokinetics in burn or septic patients, in whom conventional dosing led to treatment failure due to the increased distribution volume (V_d) of the antibiotics [5, 6]. On the other hand, the maintenance dosage of antibiotics, especially aminoglycoside, should be adjusted according to the patients' CCR when the agent is administered to patients with chronic renal dysfunction [7]. Furthermore, such antibiotic adjustment has been performed even in patients with acute renal dysfunction followed by the conventional regulation [7]. Interestingly, V_d in chronic renal failure patients does not increase in contrast to patients with acute renal dysfunction, as

previously reported [8, 9]. Thus, in critically ill patients with acute renal dysfunction, there would be certain differences in antibiotic dosing with those of chronic renal insufficiency.

3. PK of ABK in critically ill patients

We examined pharmacokinetics of ABK in critical patients with acutely lowered CCR as well as in healthy volunteers. The serum concentrations of ABK were measured using fluorescence polarization immunoassay in ten critically ill patients (patient group) and six healthy volunteers (control group). MRSA infection in patients in this study developed from 14 to 22 days after admission (Table 1). The patients were given ABK at the recommended dose for subjects with normal CCR: 2 mg/kg with 100 ml normal saline for 30 minutes twice a day [10]. In six normal volunteers (control group), ABK at the same dosage as in the patient group was administered intravenously for 30 minutes. Data were analyzed with a two-compartment model program for ABK [10].

Patient group									
	Age	Gen.	BW	Ht.	Prim. Dis.	CCR	APACHE II	MRSA	Prog.
	(Y)		(kg)	(cm)		(ml/min)		Develop (days)	
1.	85	F	45	140	Pneumonia	48.7	24	14	surv.
2.	64	F	47	155	SAH	70	23	15	surv.
3.	55	M	50	155	ICH	50	24	15	surv.
4.	70	M	58	165	Pneumonia	40.3	22	16	surv.
5.	55	M	50	163	TBI	80	22	17	surv.
6.	89	F	45	150	SAH	60	25	21	surv.
7.	50	F	70	150	BURN (2W)	44.2	20	14	dead
8.	50	M	68	165	post CPR	65.4	30	18	dead
9.	60	M	65	168	TBI	70	26	20	surv.
10.	86	F	45	153	Sev. Ac. Panc.	53.1	35	22	surv.
Control group									
	Age	Gen.	BW	Ht	CCR				
	(Y)		(kg)	(cm)	(ml/min)				
1.	49	M	66.5	169	100				
2.	40	M	76	172	95				
3.	45	M	60	160	110				
4.	41	M	67.5	166	95				

Patient group								
	Age	Gen.	BW	Ht.	Prim. Dis.	CCR	APACHE II	MRSA
	(Y)		(kg)	(cm)		(ml/min)		Develop (days)
5.	32	M	59	163	106			
6.	48	F	53	169	98			

Gen.: gender, BW: body weight, Ht: height, CCR: creatinine clearance, SOFA: score to describe organ dysfunction/failure at the time of MRSA infection developing, MRSA Develop: MRSA infection development day, SAH: subarachnoid hemorrhage, ICH: intra-cerebral hemorrhage, TBI: traumatic brain injury, CPR: cardiopulmonary resuscitation, Sev. Ac. Panc.: severe acute pancreatitis

Table 1. Demographic Data of patients of ABK study

-ABK Study-			
Patient group (N=10)		Control group (N=6)	
Age	66±15	42±6	p<0.05
Gender (F/M)	5/5	1/5	NS
B.W. (kg)	60±7	63±8	NS
Ht. (cm)	153±15	165±5	NS
CCR (ml/min)	61±15	100±6	p<0.05

Abbreviations: F, female; M, male; BW, body weight; Ht, height; CCR, creatinine clearance. Data represent as mean±SD.

Table 2. Comparisons of demographic data between patient and control groups

CCR, which was calculated using Cockcroft and Gault's equation of the patient group (CCR: 61±15 ml/min), was significantly lower than that of the control group (CCR: 100±6 ml/min). Despite low CCR, the ABK dosage suitable for CCR of normal range did not increase the maximum serum level (C_{max}) to the effective range in the patient group. Although there were no significant changes in the drug clearance (CL) between the groups, V_{ss}/BW (the percentage of the distribution volume to body weight) of the patients was remarkably increased to 69±26 as compared to the control group of 18.7±3.6% (Figure 1A). The transfer rate constant to peripheral compartment ($k_{1/2}$) in the patient group was much higher than in the control (Figure 1B). A significant correlation between CCR and CL was found in the control group, but not in the patient group (Figure 1C).

These results indicate that in critical patients with lowered CCR, even ABK dose for normal CCR subjects does not elevate its serum concentration to effective levels due to augmented V_d caused by increased $k_{1/2}$. The present results suggest that adjustment of the antibiotic dosing according to CCR, as recommended generally, further lowers C_{max} , which results in ineffectiveness of the drug in the critically ill patients having reduced CCR.

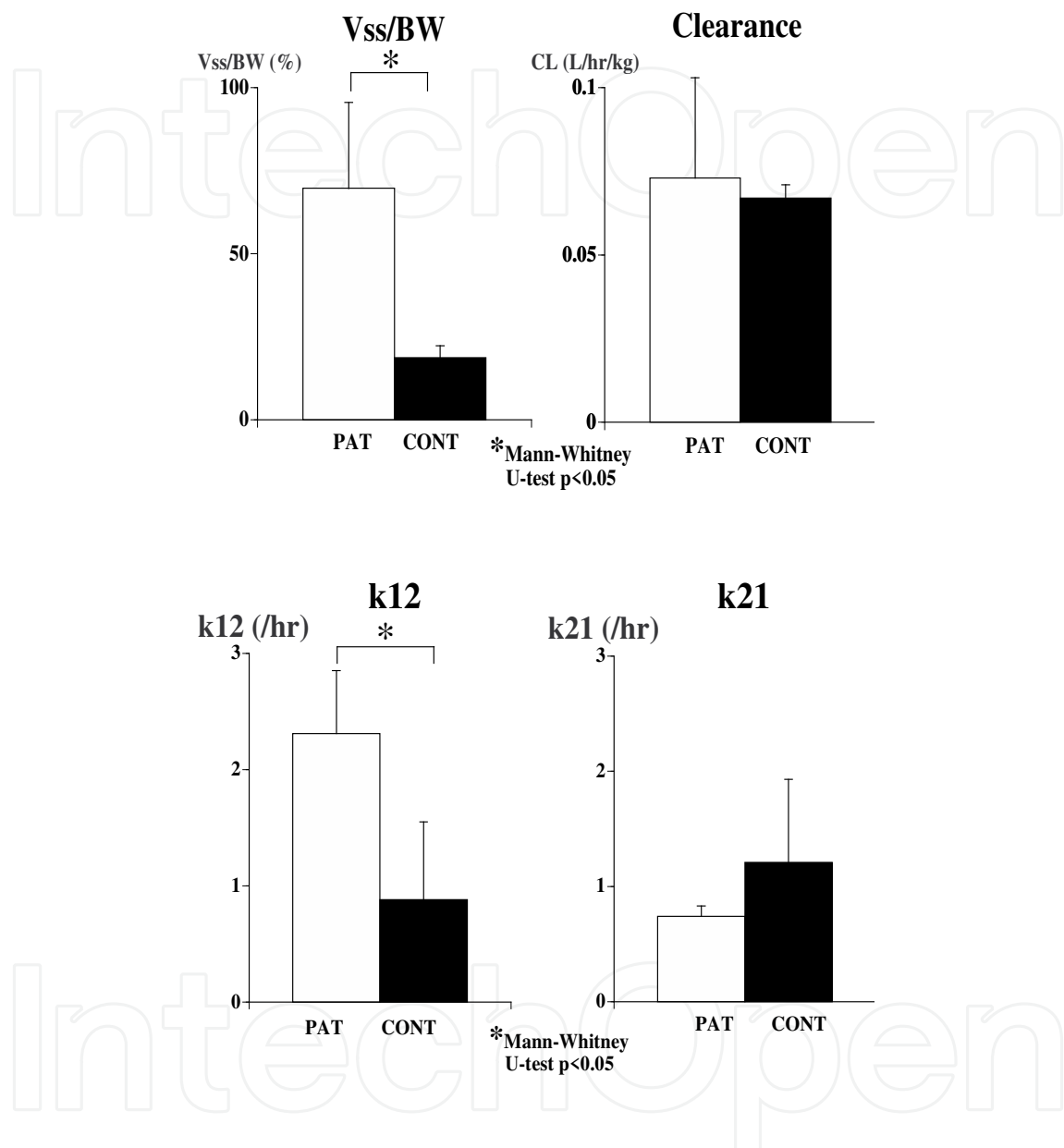


Figure 1. Vss/BW (the percentage of the distribution volume to 4 body weight) and the clearance between the groups

Figure 1A depicts the comparisons of Vss/BW (the percentage of the distribution volume to body weight) and the clearance between the groups. Remarkable inflation was found in Vss/Bw of the patient group, but there were no significant differences in the clearance between the two groups. Figure 1B shows the comparisons of the elimination constants of the groups. $k_{1/2}$ in the patients group is remarkably higher than that in the control group, but k_{21} did not differ between the two groups.

3.1. Serum concentration changes of ABK in critically ill patients

There are several reports demonstrating the distribution volume inflation of aminoglycoside in sepsis patients, indicating the importance of increasing the antibiotic dose in such conditions [4, 5]. However, there has been limited information regarding the relationship between CCR and serum concentration of the agent in critically ill patients with increased distribution volume of aminoglycoside. It is generally known that adjusting the aminoglycoside dosage according to CCR is crucial for preventing untoward effects in patients with chronic renal dysfunction [7]. Furthermore, such antibiotic adjustment has been done even in patients with acute renal dysfunction by the conventional regulations [7]. However in chronic renal failure patients, the distribution volume of ABK does not elevate in contrast to that of those with acute renal failure [8, 9, 10].

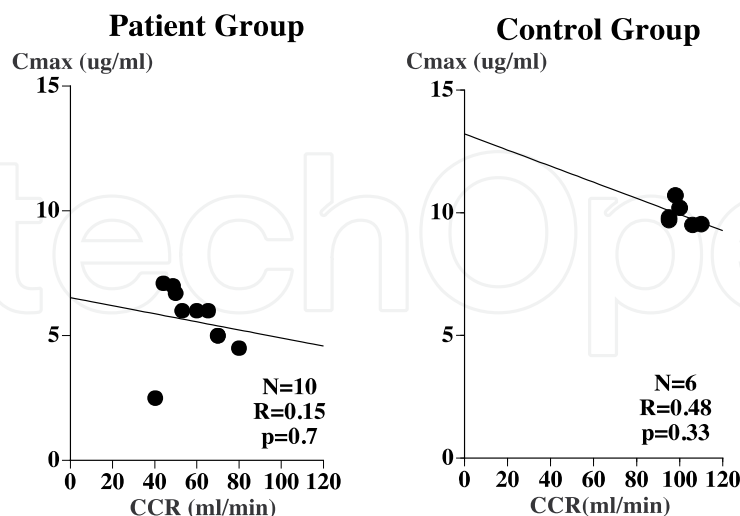
The current results showed that in critical patients with acutely decreased CCR, an ABK dose for normal CCR volunteers did not achieve effective levels of the agent. Moreover, pharmacokinetic analysis revealed remarkable increases both in V_d/Bw and $k_{1/2}$, but not in k_{21} as compared to the control. Aggressive fluid resuscitation for septic patients causes an inflation of the distribution volume for aminoglycosides [11]. Hypoalbuminemia may cause a shift of body water from the intravascular to the extravascular space [12]. Actually, this study showed a positive daily water balance as well as hypoalbuminemia in the patient group (data not shown). Thus, it is probable that the decreased C_{max} presented in this study is resulting from 1) augmented distribution volume, possibly resulting from edema, and 2) enhanced drug distribution from central to peripheral compartments.

3.2. Pharmacokinetic differences between acute and chronic renal dysfunction

In this study, we have shown V_d increment as well as transfer rate constant enhancement in critically ill patients with lowered renal function. However, chronic renal failure patients have normal distribution volume of ABK [8, 9, 10] as well as other aminoglycosides [13]. The CL of ABK correlates significantly with CCR in patients with chronic renal failure [8]. However, in the patients of this study, there were no correlations between the two parameters, as shown in Figure 2B. The pharmacokinetic condition differs greatly between acute and chronic renal dysfunctions. Thus, the CL of ABK did not estimate according to CCR in an acutely lowered renal dysfunction. We therefore need to reconsider dosing for aminoglycoside based on CCR in patients with acute renal dysfunction, who have augmented distribution volume and/or elevated vascular permeability. The present results also indicate that in critically ill patients with reduced renal function, the requiring dosage of ABK for obtaining an effective level will be higher than the recommended dose for subjects with intact renal function. Thus, in critically ill patients receiving ABK, therapeutic drug monitoring is very important, not only for avoiding the side effects, but also for obtaining adequate effects from the agent.

Figure 2A demonstrates the correlation between C_{max} and CCR in each group. Figure 2B shows the correlations of the clearance and CCR in each group. Note that although there was no significant correlation between C_{max} and CCR in either group (Figure 2A), a significant correlation between clearance and CCR was observed only in the control group (Figure 2B).

C_{max} and CCR



Clearance and CCR

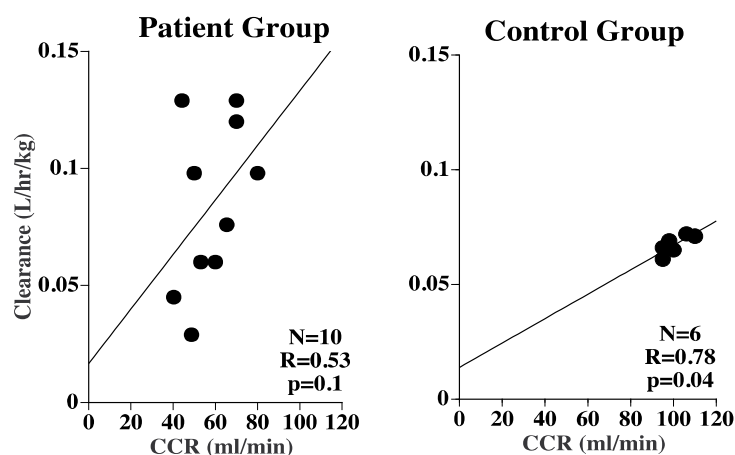


Figure 2. ABK C_{max} and CCR; Drug Clearance and CCR

4. Clinical applications

Once-daily dosing is now widely used in aminoglycoside administration [14]. This method may be reasonable for obtaining an effective level of aminoglycoside, but a concern remains as to whether the concentration can be maintained below the toxic level of the agent. It has been reported that a therapeutic drug monitoring group receiving significantly greater doses of aminoglycosides than a once-daily group experience a significantly lower incidence of nephrotoxicity [15]. This recent report suggests the importance of therapeutic drug monitoring during the administration of aminoglycosides in each case. In our previous study, remarkable changes in the body fluid condition or drug pharmacokinetics were found in critically ill patients. Thus, we need to perform a pharmacokinetic analysis to estimate the appropriate

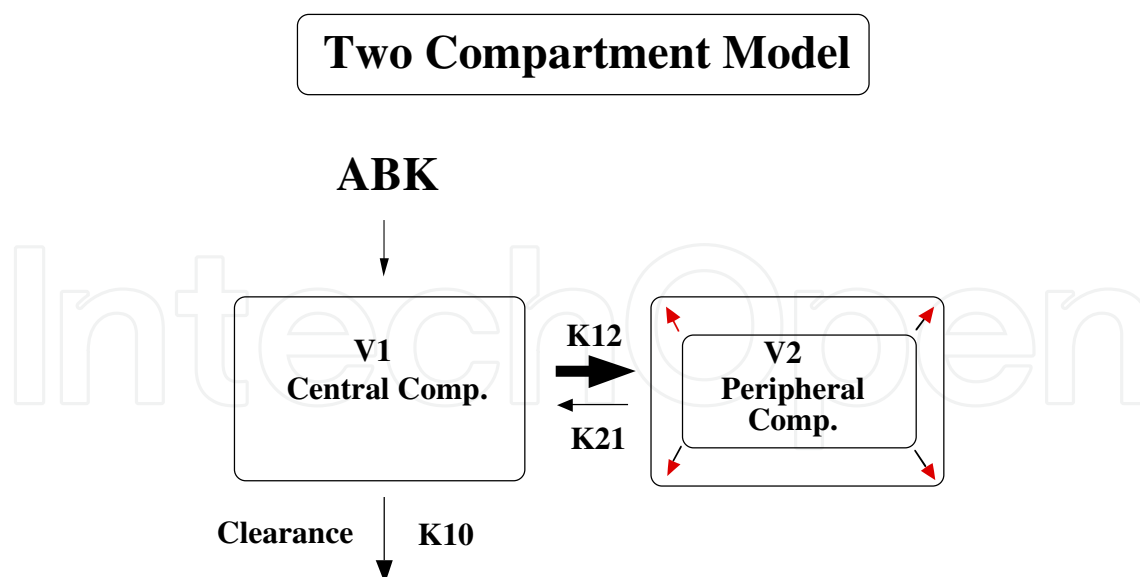


Figure 3. A possible mechanism for failure to obtain an effective level of ABK in critically ill patients. Note that there is an augmentation of the distribution volume (V2) as well as an increase in the elimination rate constant ($k_{1/2}$) of moving from the central to peripheral compartments.

dosage for administration of aminoglycosides, especially in critically ill patients with lowered renal function.

5. Other antibiotics (vancomycin, daptomycin and barbapenums)

5.1. Vancomycin

Recent study using a one-compartment model reported that, in septic patients receiving renal replacement therapy (RRT), mean vancomycin clearance (CL) and V_d were 2.9 L/h, 0.8 L/kg, respectively. Normal ranges of CL and V_d are 9.1 L/h, 0.4 to 1 L/kg [16]. However, no covariates were found to explain changing these parameters. Furthermore, CL did not correlate with RRT, which might be due to the multiple confounders known to influence antibiotic dosing in this setting. These data indicate the challenges of explaining pharmacokinetics in critically ill patients receiving RRT and emphasize a need for therapeutic drug monitoring in this setting [17].

Dosing of vancomycin (VAN) according to glomerular filtration rate (GFR) is an issue in critically ill patients. Recent paper shows very interesting findings as follows: seventy-eight adult patients admitted in intensive care unit received a 15 mg/kg loading dose of VAN followed by a continuous infusion at the rate of 30 mg/kg/day. Serum concentrations were measured 48 hours later and the dose was adjusted to obtain a target concentration ranging from 20 to 25 mg/l. GFR was estimated by measured creatinine clearance (CLCR), Cockcroft, Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. The first dosage needed to be increased in 51% of all patients and

in 84% of trauma patients, but decreased in 17% of patients. The closest relationship between clearances of VAN was found in CKD-EPI to GFR, but rather poor with the Cockcroft or Modification of Diet in renal Disease equation [18]. Although these findings indicate a caution on the VAN dosing using the latter two, this paper may show changes in distribution volume or vascular permeability of the agent in critically ill patients.

5.2. Daptomycin

Daptomycin is bactericidal against gram-positive bacteria, with peak-dependent effect but trough-dependent toxicity, but recommended dosing during continuous veno-venous hemodiafiltration (CVVHDF) remains unclear.

A study reported that in nine critically ill patients, undergoing CVVHDF due to acute renal failure and antimicrobial treatment, a pharmacokinetic analysis was done using an open two-compartment model. The total clearance was 6.1 ± 4.9 mL/min, and the elimination half-life was 17.8 ± 9.7 h (9 hours in normal subjects: [19]). The unbound fraction was $16 \pm 4.5\%$ (protein binding: mean amount bound, 91.7%, volume of distribution of 0.1 L/kg, [20]). Accumulation occurred if daptomycin was given every 24 h. Simulation of 8 mg/kg daptomycin given every 48 h resulted in adequate levels without accumulation. So, the authors of this study recommend 8 mg/kg daptomycin every 48 h in patients on CVVHDF and therapeutic drug monitoring (TDM) [21].

In a prospective study, the pharmacokinetics (PK) of daptomycin after initial bolus (8 mg/kg of body weight) and multiple intravenous doses (4 mg/kg body weight) at a stable state were determined for serum concentrations in critical patients treated with continuous hemodialysis (CVVHD). Subjects with normal renal function received one dose of 4 mg/kg body weight of daptomycin. Approximately 40% of the daptomycin dose administered was eliminated by CVVHD, so that, plasma half-lives of the agent in patients were 2 - 3 times longer as compared to normal controls. The dosing method of 4 mg/kg body weight of daptomycin given to patients with CVVHD every 48 h could not achieve effective plasma levels of daptomycin. Doses of more than and equal to 4 mg/kg every 24 h are necessary in CVVHD patients to assure plasma daptomycin levels [21]. These two studies show heterogeneity among critical patients treated with CVVHD or CVVHDF and also indicate an importance of TDM in each patient.

5.3. Carbapenem (doripenem; meropenem)

Doripenem is a carbapenem with limited data for dosing during CHDF in critically ill patients. A recent study determined the pharmacokinetics of doripenem in twelve septic adult patients with acute kidney injury (AKI) undergoing CHDF using a two-compartment model. The patients received 500 mg of intravenous doripenem every 8 h for 60 min. The median blood, dialysate and replacement fluid rates were 200, 1000 and 1000 mL/h, respectively. The mean value for total doripenem clearance was 4.46 L/h (normal range: $\frac{1}{2}$ to 16 L/h, [22]) and volume of distribution was 0.63 L/kg BW (normal range: 0.23 to 0.35 L/kg BW, [22]). Doripenem elimination by CHDF depended on the rate filtration and contributed from 30% to 37% of total clearance. An intravenous dose of 500 mg every 8 h obtained an MIC up to 4 mg/L, which seems enough in PK/PD analyses for all patients. A dose of 500 mg intravenously every 8 h was appropriate for our CVVHDF settings for infections caused by susceptible bacteria [23].

A recent randomized crossover study examined whether in ten critically ill patients, a prolonged 3-hour infusion of meropenem 500mg achieves an equivalent proportion of time above the MIC (%TMIC) to that of meropenem 1000mg given over 30 minutes. Meropenem was administered as a 1000mg, 30-minute infusion or as a 500mg, 3-hour infusion. Serial plasma concentrations for each dosing were determined, thereby comparing %TMIC at different MICs (the percentage of time above its MIC). For low MICs (≤ 2 mg/L), both regimens attained a %TMIC $>40\%$ in all patients. For an MIC of 4mg/L, this target was attained in all but one patient, but with an MIC of 8mg/L, three patients in each group had a %TMIC $<40\%$. There was significant variability in the pharmacokinetic and hence the pharmacokinetic-pharmacodynamic parameters between individuals. Several patients had elevated creatinine clearances and, with both regimens, their target attainment was poor. Meropenem at 1000mg over 30 minutes achieved a similar %TMIC to meropenem at 500mg given over 3 hours. Meropenem pharmacokinetics was highly variable from individual to individual [24].

6. Biological preparations

6.1. Antithrombin (AT) agent

6.1.1. *Summary of AT*

Decreased serum albumin levels suggest heightened vascular permeability in critically ill patients. In such a situation, plasma antithrombin (AT) may also decrease due to the leakage because albumin's molecular weight of 63,000 is similar to AT 56,000. But another mechanism of decreasing AT during DIC could be AT consumption, which could be estimated by the levels of plasma thrombin-antithrombin complex (TAT). So, we measured serum albumin levels and plasma TAT in patients with DIC before and after AT administration. The levels of serum albumin prior to AT administration correlated with pre- and post-administered AT activity, but not with TAT levels (Figure 1 (AT)). With no correlations of TAT levels, the trough levels of AT activity on the third day increased significantly. In patients with serum levels of albumin less than 2.5 g/dl, the trough levels of AT activity on the third day were significantly lower than those showing higher levels of serum albumin. The half-life duration of AT preparation in the distribution phase in the acute patients was shortened to less than 1/3 of the value reported in congenital AT deficiency, suggesting increased vascular permeability in the acute patients. The distribution volume of the agent increased remarkably compared to the previous control. Therefore, we need to pay attention to the characteristic PK profiles of increased vascular permeability as well as distribution volume observed in critical patients even on the administration of AT preparation, a high molecular weight agent.

6.1.2. *Background of AT*

Antithrombin III (AT) has anti-coagulatory as well as anti-inflammatory effects [25, 26]. According to subgroup analyses of the Kybersept study data [27, 28], prognosis in septic patients with disseminated intravascular coagulation (DIC) might be improved with AT administration.

Plasma thrombin-antithrombin complex (TAT) is a marker of intravascular thrombin formation, reflecting enhancement of intravascular coagulation [29]. In vitro thrombin application itself increases the permeability of endothelial cell monolayer [30]; however, it is still unknown whether AT levels after AT administration would change depending on TAT levels in patients with DIC.

On the other hand, albumin leakage from the capillaries is a more important mechanism for the decrease in serum albumin levels than its depressed synthesis during sepsis, where vascular permeability is enhanced [31, 32, 33]. Since the molecular weight of AT is similar to albumin, it is likely to expect that in critical conditions including sepsis, not only albumin but also AT would be permeable through the capillaries. We analyzed pharmacokinetic (PK) properties on AT preparation in order to define its PK characteristics in critically ill patients, because PK information for AT in such patients was not enough. The present results suggest that crucial mechanisms for AT reduction in critically ill patients with DIC might be a reduced synthesis and/or leakage of AT to extravascular space.

6.2. Correlations among AT activity, TAT and albumin levels

Figures of AT 4A and 4B show serum albumin levels prior to AT application correlated with plasma AT activities ($r_s=0.72$, $p=0.003$), but not with TATs ($r_s=0.38$, $p=0.1$). The pre-administered serum albumin values also correlated with plasma AT trough activity on the third day after the initiation of AT preparation ($r_s=0.76$, $p=0.001$).

As shown in Figures 4A and B, serum albumin levels before AT administration moderately correlated with serum AT levels ($r_s=0.72$, $p=0.003$), but TAT did not. The pre-administered serum albumin levels were also significantly correlated with AT trough activity on the third day after the treatment ($r_s=0.76$, $p=0.001$). Pre-TAT, TAT levels before AT administration; Pre-AT, AT activities before AT administration; Pre-albumin, serum albumin levels before AT administration; Post-AT, AT trough levels on the third day after AT administration.

As shown in Figures of AT 5A and B, the levels of AT trough activity on the third day elevated significantly in patients irrespective of TAT levels $15 \mu\text{g/l}$, a level of which was moderately elevated (normal level $< 4 \mu\text{g/l}$). However, AT trough levels on the third day in patients with serum albumin levels $\leq 2.5 \text{ g/dl}$ were significantly lower than those with such levels higher than and equal to 2.5 g/dl .

As demonstrated in Figure 5A, AT trough levels on the third day increased significantly regardless of TAT levels of $15 \mu\text{g/l}$ (normal level $< 4 \mu\text{g/l}$). As shown in Figure 5B, in patients with serum albumin levels less than and equal to 2.5 g/dl , AT trough levels on the third day were significantly lower than those more than and equal to 2.5 g/dl .

6.3. PK analysis for AT

As demonstrated in Figure 6 of AT, AT activity and antigen levels correlated well ($r_s=0.91$, $p=0.0001$).

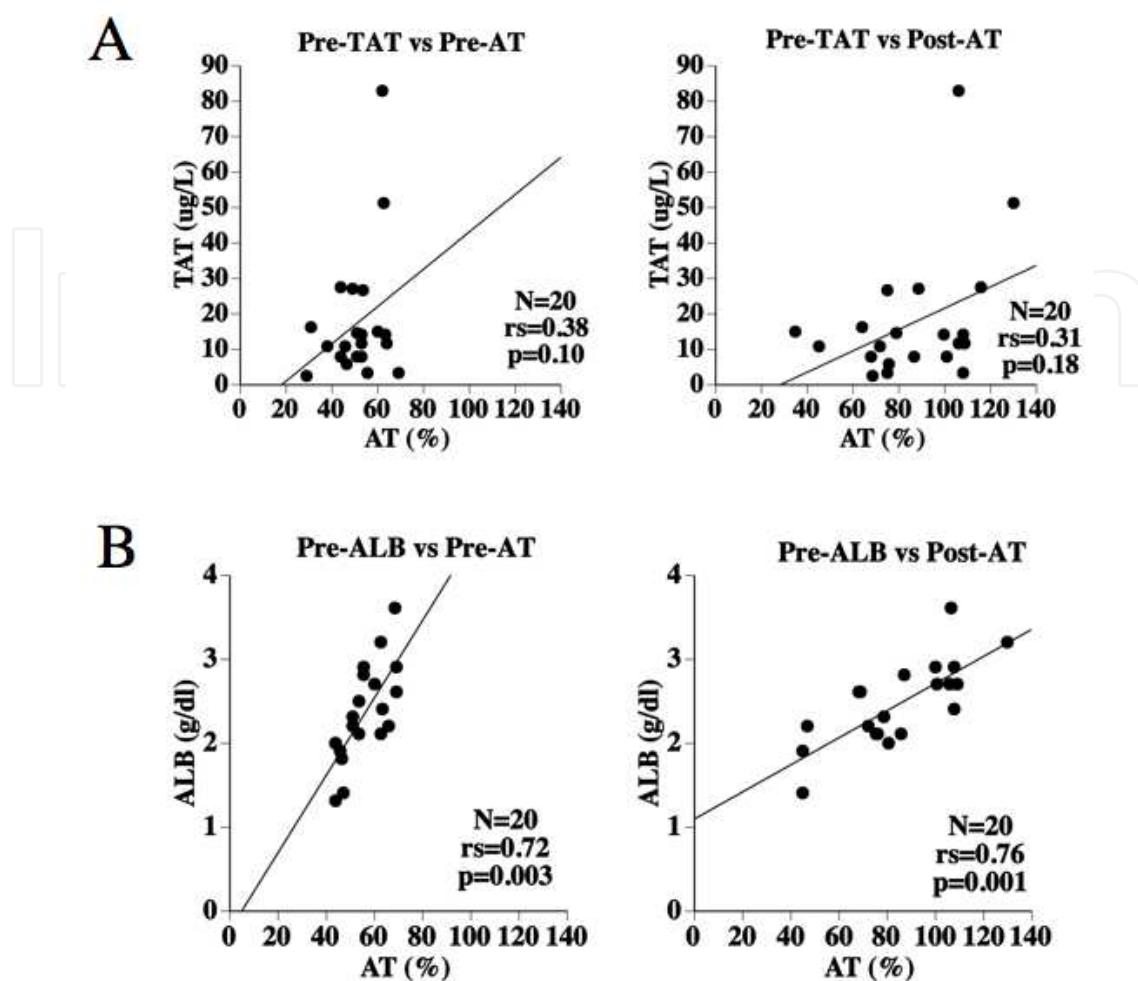


Figure 4. Panel A shows the correlations between pre-TAT and pre-AT levels (left), and post-AT levels (right). Panel B demonstrates the correlations between pre-albumin and pre-AT (left), and post-AT levels (right).

As shown in Figure 7A, the half-life of the distribution phase ($\alpha_{1/2}$) in acute patients (7.0 ± 2 hours) was markedly shortened as compared to that previously reported in patients with congenital AT deficiency (26.2 ± 1.5 hours). This result may suggest increased vascular permeability. However, the half-lives of the elimination phase ($\beta_{1/2}$) in both groups were not different (congenital: 60 ± 22 versus acute: 62 ± 7 hours).

As shown in Figure 7A (left), the half-life of the distribution phase ($\alpha_{1/2}$) in acute patients (7 ± 2 hours, $N=10$) was remarkably shortened as compared to the value of which was previously reported in patients with congenital AT deficiency (26.2 ± 1.5 hours, $N=11$). However, as demonstrated in Figure 7A (right), the half-lives of the elimination phase ($\beta_{1/2}$) in both groups did not differ (congenital: 60 ± 22 versus acute: 62 ± 7 hours). As demonstrated in Figure 7B, the distribution volume of the agent in the acute disease group inflated significantly to 6.9 ± 3.3 L as compared to the previous control of 2.3 ± 0.4 L. Figure 7B demonstrated that the distribution volume of the agent in the acute group increased remarkably to 6.9 ± 3.3 L from the previous control of 2.3 ± 0.4 L.

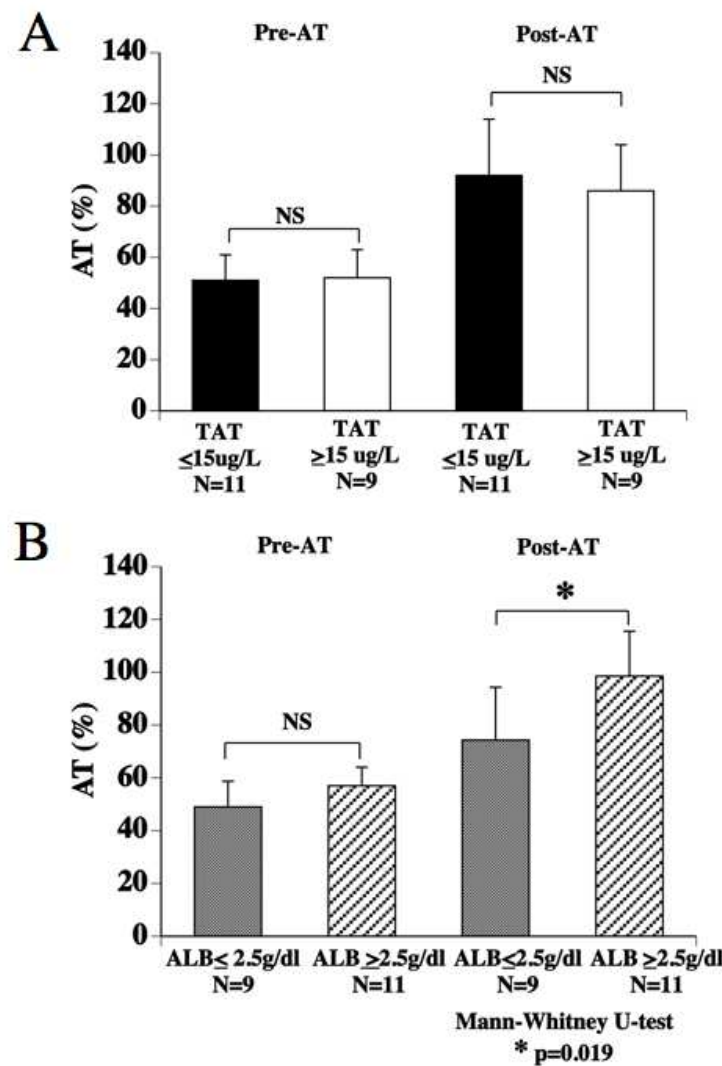


Figure 5. Comparisons of AT levels depending on TAT or Serum Albumin level in critically-ill patients

6.4. Relations of AT activity and TAT or albumin levels

TAT is a sensitive marker of thrombin production in the circulating blood, suggesting an augmented intravascular coagulation [34]. Intravascular production of thrombin may cause an enhanced vascular permeability [30]. Thus, it is likely that increased TAT levels could estimate AT leakage resulting from heightened vascular permeability. However, in this study, we found no correlations between TAT and AT activity in the pre-administration phase in critical patients with DIC. Furthermore, TAT is believed to be uncorrelated with AT activity because the total amount of AT in the body is so enormous that AT levels would not decrease even after remarkable TAT production [35]. Therefore, the present results confirm the data of the previous paper [35].

It was unknown whether AT activity after AT preparation would change depending on the levels of TAT if vascular permeability was enhanced. If TAT is a potential indicator of showing increased vascular permeability, TAT levels before AT administration would be well corre-

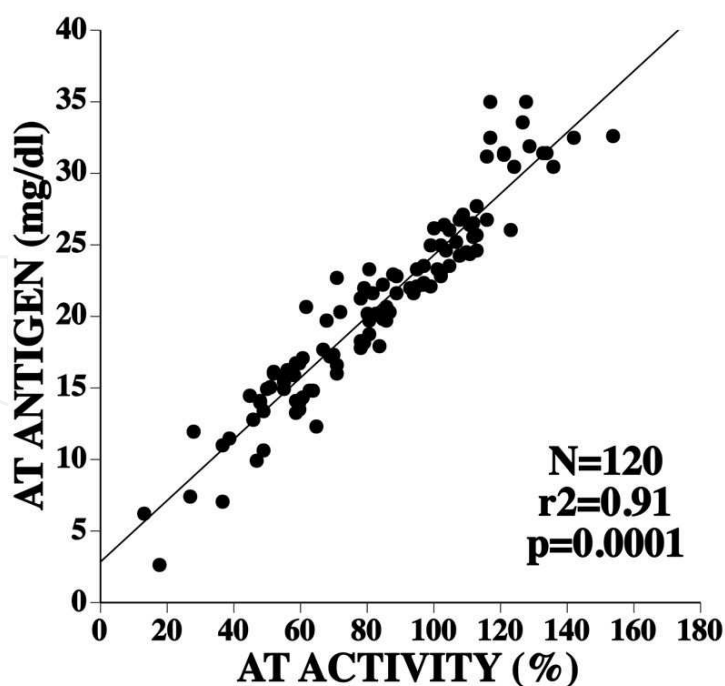


Figure 6. Correlations between AT activity and antigen are shown. A good correlation is obtained between the two parameters ($r_s=0.91$, $p=0.0001$).

lated with AT activity after the administration of AT preparation. But, we demonstrated in this study that TAT levels before AT administration are not correlated even with post-administered AT activities. Therefore, it is possible that high TAT levels does not mean increased vascular permeability in clinical settings. However, TAT has a short half-life time (approximately 7 minutes) in the circulating blood [36], whereas AT has a much longer half-life period: approximately 24 hours in congenital AT deficiency in a non-acute state [37] as well as in normal subjects [38], and even in the acute state as presented in this study approximately 7 hours. So, we might be able to speculate that this difference in half-life time between TAT and AT activity is an explanation for the low correlation co-efficient as clarified in this study.

Serum albumin levels decreased due to its reduced synthesis and/or enhanced consumption during sepsis [31, 32, 33], frequently involving DIC. Albumin leakage from the capillaries is a factor more crucial for albumin reduction during sepsis [31]. Because the molecular weight of AT (56,000) is smaller than that of albumin (63,000), it is likely that during sepsis, albumin and AT could pass through the capillaries into the extravascular space. In the current study, AT levels altered with regard to serum albumin levels. Further, when the serum albumin level was lower than 2.5 g/dl, AT activities after administration was significantly lower as compared to those when the serum albumin level was over 2.5 g/dl. Therefore, it is possible that the serum albumin level could be a reliable index for estimating changes in the post-administration AT levels in critical patients with DIC. Furthermore, this study supports a previous paper [35] that in septic patients with DIC, AT could be decreased by enhanced vascular permeability rather than its consumption.

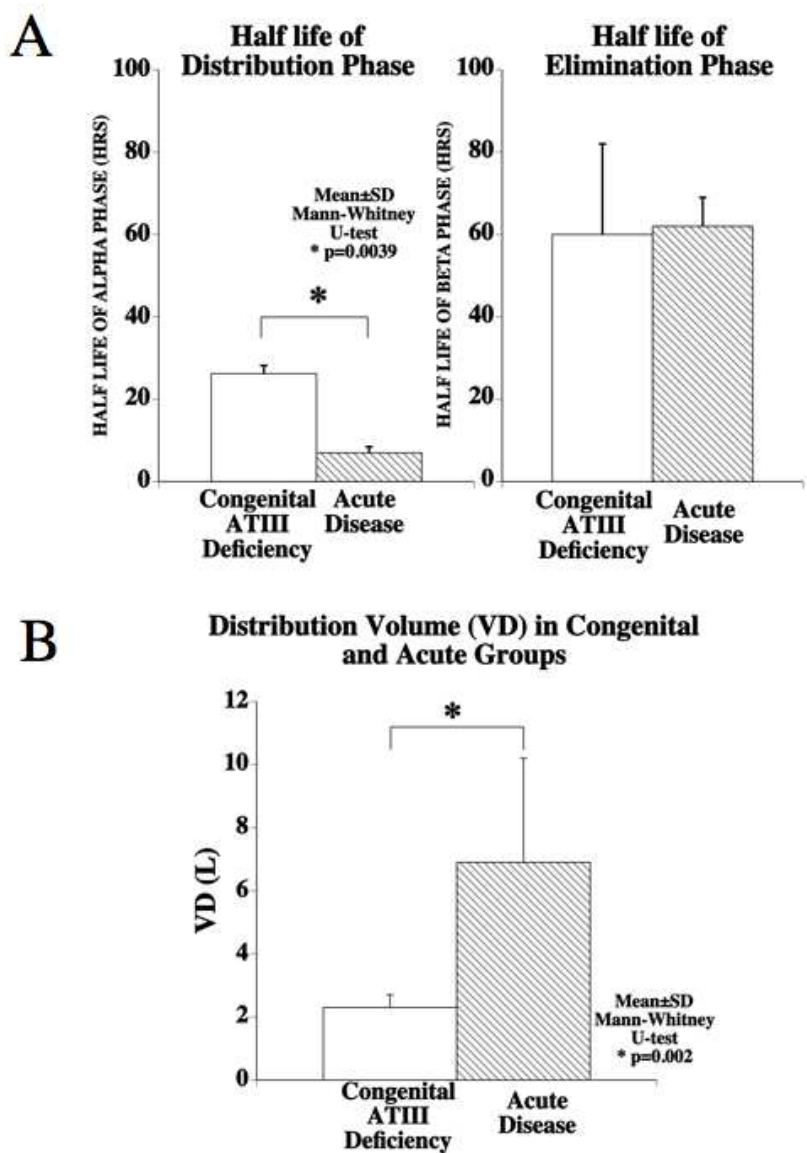


Figure 7. A: Half life of AT (elimination and distribution phases) in each condition; B: Comparison of distribution volume (VD) between congenital AT deficiency and acute disease

6.5. Pharmacokinetics of AT agent in critical patients

There are reports describing the pharmacokinetic analysis of AT agent in critical patients [39, 40]. However, a previous paper included several limitations: for example, the selection of a one-compartment model for AT agent in sepsis patients [40]. It is well known that AT distributes to the intra-vascular as well as extra-vascular spaces [41], which obliges us to choose a two-compartment model for this study. Furthermore, we found that changes in AT activity showed a biphasic decay curve after AT administration (Figure 6).

We have demonstrated clearly in this study that the half-life of the distribution phase in the patient group was shortened remarkably as compared to that previously reported in congenital AT deficiency, suggesting increased vascular permeability in the acute patients here. Further-

more, the distribution volume in the patient group was inflated much more than that of the previous controls. We have shown for the first time that in critical patients with DIC, changes in AT can be predicted by serum albumin levels before AT administration, but not by TAT. These findings might be explained, at least in part, by the shortened AT half-life of the distribution phase and increased distribution volume observed in the critical patients in this study.

6.6. Limitations of AT study

As a control, we referred data from a previous paper describing AT pharmacokinetic analysis in congenital AT deficiency in a non-acute state [37], in which two-compartment analysis was used same way as our current study. It is likely that this congenital disease in non-acute state was not complicated by either an increase in vascular permeability or distribution volume [39]. We therefore selected the previously published data as a control for this study. However, further research is required to define any age-dependent changes in the PK profile of AT preparation because there was a significant difference in age between acute disease and congenital groups.

This study has several limitations in the variety of the diseases as well as number of patients, but all patients were complicated with DIC. Furthermore, we have found discrepancies between AT and TAT, and vascular permeability with increased distribution volume in the patients of this study. However, we need to clarify each pathological profile in critically ill patients with different pathology in the future.

7. Conclusions

We described in this chapter that in critically ill patients even with low CCR, the ABK dose for normal CCR subjects does not elevate its serum concentration to effective levels because of augmented distribution volume and increased vascular permeability. Furthermore, we reported in critical patients with DIC, shortened elimination half-life and increased distribution volume AT, a preparation of large molecular weight. From the view of pharmacokinetic profile, these findings presented here should be considered on the administration of not only antibiotics but also biological agents to the critically ill patients.

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