Pharmacokinetics, Safety, and Tolerability of Nacubactam after Single Co-administration with β-Lactams in Japanese Healthy Subjects

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Abstract

Background: Increase of carbapenemase-producing Enterobacterales (CPE) is one of serious public health concerns and new therapeutic options are urgently needed to treat patients with CPE infections in such as complicated urinary tract infection (cUTI), complicated intra-abdominal infections (cIAI) and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP).
Nacubactam (NAC) is a novel DBO(diazabicyclooctane)-type β-lactamase inhibitor with a dual mode of action: a) Inhibition of serine β-lactamases (Class A, C and some D), resulting in protection of the partner β-lactam; b) Inhibition of penicillin binding protein 2 (PBP2) of Enterobacterales, resulting in antibacterial activity as well as enhancing the activity of β-lactam antibiotics. Nacubactam is being developed as a combination therapy with the β-lactams as a new therapeutic option for the treatment of infections caused by CPE.
Methods: A single administration of NAC with concomitant β-lactams in Japanese healthy subjects was conducted to assess pharmacokinetics (PK), safety, and tolerability of NAC in co-administration with cefepime (FEP), aztreonam (ATM), meropenem (MEM), or piperacillin (PIP).
The administration period included Period I, Period II, and Period III where NAC alone, concomitant drug alone, NAC and concomitant drug were administered by 1hour-IV infusion in each period. The dose of each drug tested was 2 g of NAC, FEP, ATM, MEM and 4 g of PIP and 8 subjects were administered in each cohort (32 subjects in total).
Results: Plasma NAC concentrations and NAC urinary excretion rate after co-administration with each concomitant drug were similar to those of administration of NAC alone. The PK parameter of NAC showed the similar value both after administration of NAC alone and after concomitant administration with each concomitant drug. Based on these findings, it was confirmed that co-administration of NAC with each β-lactam (FEP, ATM, MEM or PIP) did not affect the PK of NAC.
Plasma concentrations and urinary excretion rate of FEP, ATM, MEM or PIP after co-administration of each concomitant drug with NAC were similar to those of administration of each concomitant drug alone. The PK parameter of each β-lactam tested showed the similar value both after administration of β-lactam alone and after concomitant administration with NAC. Based on these finding, it was confirmed that co-administration of each concomitant drug with NAC did not affect the PK of FEP, ATM, MEM and PIP.
As for the safety, there was no serious adverse event (SAE), all of treatment-emergent adverse events (TEAEs) reported were mild in severity and judged to be “not related”.
Conclusion: It was confirmed that single co-administration of NAC with each β-lactam (FEP, ATM, MEM, or PIP) did not affect the both PKs of NAC and β-lactams, and was safe and well-tolerated in Japanese healthy subjects.

Methods

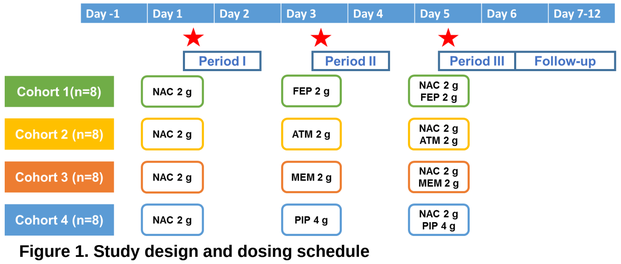


Figure 1. Study design and dosing schedule

Results

Table 1. Demographics and baseline characteristics of each cohort

Cohort	Age (year)	Height (cm)	Weight (kg)	BMI (kg/m^2)
1	24.6 ± 6.7	170.0 ± 2.5	59.7 ± 6.9	20.6 ± 2.0
2	23.0 ± 5.0	169.4 ± 6.8	62.9 ± 6.1	22.0 ± 2.6
3	22.5 ± 3.1	170.9 ± 6.0	60.6 ± 6.8	20.6 ± 1.5
4	26.6 ± 5.4	170.4 ± 6.4	60.7 ± 9.9	20.8 ± 2.3

Data are presented as mean ±standard deviation

Table 2. Comparison of NAC PK parameter and 90% confidence interval

Cohort 1	NAC alone	NAC with FEP	difference	90% confidence interval lower	upper
C_{max}	135.9 ± 12.4	123.8 ± 10.7	0.91	0.86	0.96
$AUC_{0\text{-}24}$	288.7 ± 22.5	280.2 ± 31.4	0.97	0.92	1.02
$AUC_{0\text{-}\infty}$	288.8 ± 22.5	280.3 ± 31.4	0.97	0.92	1.02
$t_{1/2}$	2.5 ± 0.2	2.5 ± 0.1	1.00	0.93	1.06
Cumulative urinary drug excretion rate	88.4 ± 3.2	87.5 ± 5.2	0.99	0.95	1.03

Cohort 2	NAC alone	NAC with ATM	difference	90% confidence interval lower	upper
C_{max}	129.0 ± 14.8	126.4 ± 10.4	0.99	0.94	1.03
$AUC_{0\text{-}24}$	302.6 ± 35.7	288.2 ± 32.5	0.96	0.92	0.99
$AUC_{0\text{-}\infty}$	302.8 ± 35.7	288.3 ± 32.6	0.95	0.92	0.99
$t_{1/2}$	2.4 ± 1.0	2.5 ± 0.1	1.06	1.02	1.11
Cumulative urinary drug excretion rate	89.1 ± 1.8	89.3 ± 2.9	1.00	0.97	1.03

Cohort 3	NAC alone	NAC with MEM	difference	90% confidence interval lower	upper
C_{max}	129.3 ± 20.9	126.6 ± 12.3	0.99	0.92	1.05
$AUC_{0\text{-}24}$	284.0 ± 42.1	292.3 ± 30.0	1.04	0.99	1.08
$AUC_{0\text{-}\infty}$	284.1 ± 42.1	292.4 ± 30.0	1.04	0.99	1.08
$t_{1/2}$	2.5 ± 0.1	2.5 ± 0.1	0.99	0.96	1.01
Cumulative urinary drug excretion rate	85.9 ± 11.3	90.4 ± 1.7	1.07	0.96	1.17

Cohort 4	NAC alone	NAC with PIP	difference	90% confidence interval lower	upper
C_{max}	118.6 ± 18.9	131.5 ± 15.5	1.12	1.05	1.18
$AUC_{0\text{-}24}$	266.6 ± 39.4	319.4 ± 34.1	1.20	1.16	1.24
$AUC_{0\text{-}\infty}$	266.5 ± 39.7	319.5 ± 34.1	1.21	1.16	1.25
$t_{1/2}$	2.3 ± 0.2	2.3 ± 0.1	1.03	0.94	1.12
Cumulative urinary drug excretion rate	87.2 ± 3.5	89.2 ± 6.1	1.02	0.99	1.05

PK parameter data are presented as mean ±standard deviation

Table 3. Comparison of concomitant drug PK parameter and 90% confidence interval

Cohort 1	FEP alone	FEP with NAC	difference	90% confidence interval lower	upper
C_{max}	123.5 ± 8.7	124.4 ± 9.2	1.01	0.99	1.03
$AUC_{0\text{-}24}$	311.7 ± 17.8	312.7 ± 27.8	1.00	0.97	1.03
$AUC_{0\text{-}\infty}$	311.9 ± 17.8	312.9 ± 27.8	1.00	0.97	1.03
$t_{1/2}$	2.5 ± 0.1	2.5 ± 0.1	1.00	0.98	1.02
Cumulative urinary drug excretion rate	93.7 ± 5.6	92.3 ± 5.0	0.99	0.93	1.04

Cohort 2	ATM alone	ATM with NAC	difference	90% confidence interval lower	upper
C_{max}	175.5 ± 15.6	171.6 ± 15.8	0.98	0.92	1.04
$AUC_{0\text{-}24}$	486.9 ± 49.0	480.8 ± 43.7	0.99	0.97	1.00
$AUC_{0\text{-}\infty}$	487.2 ± 49.1	481.1 ± 43.8	0.99	0.97	1.00
$t_{1/2}$	2.2 ± 0.1	2.3 ± 0.2	1.00	0.98	1.03
Cumulative urinary drug excretion rate	82.4 ± 5.8	82.3 ± 3.6	1.00	0.96	1.04

Table 3(cont.). Comparison of concomitant drug PK parameter and 90% confidence interval

Cohort 3	MEM alone	MEM with NAC	difference	90% confidence interval lower	upper
C_{max}	101.0 ± 12.6	107.4 ± 12.5	1.07	1.02	1.11
$AUC_{0\text{-}24}$	183.6 ± 21.9	186.9 ± 22.5	1.02	0.99	1.05
$AUC_{0\text{-}\infty}$	183.3 ± 21.8	186.6 ± 22.5	1.02	0.99	1.05
$t_{1/2}$	1.2 ± 0.1	1.3 ± 0.2	0.91	0.82	0.99
Cumulative urinary drug excretion rate	59.6 ± 5.4	60.3 ± 4.8	1.01	0.96	1.06

Cohort 4	PIP alone	PIP with NAC	difference	90% confidence interval lower	upper
C_{max}	239.9 ± 29.8	247.5 ± 38.7	1.03	0.97	1.09
$AUC_{0\text{-}24}$	400.6 ± 59.5	412.1 ± 75.6	1.03	0.98	1.08
$AUC_{0\text{-}\infty}$	400.3 ± 59.6	411.7 ± 75.7	1.03	0.98	1.08
$t_{1/2}$	1.5 ± 0.5	1.5 ± 0.6	1.01	0.76	1.27
Cumulative urinary drug excretion rate	60.5 ± 2.1	58.9 ± 3.8	0.97	0.92	1.03

PK parameter data are presented as mean ±standard deviation

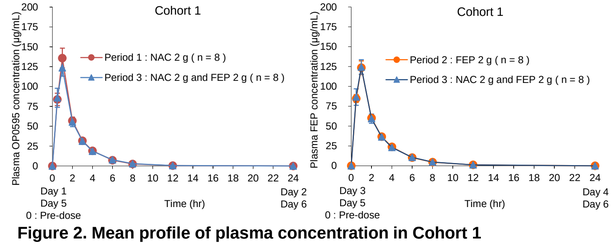


Figure 2. Mean profile of plasma concentration in Cohort 1

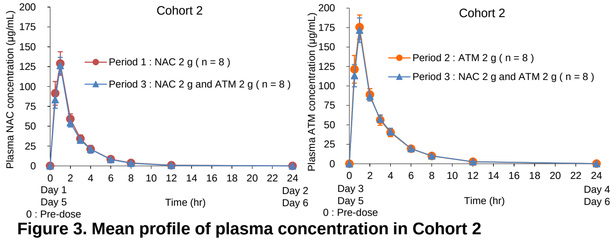


Figure 3. Mean profile of plasma concentration in Cohort 2

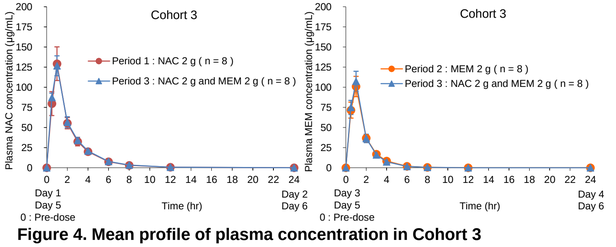
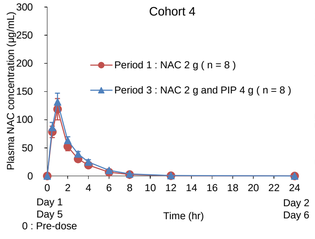


Figure 4. Mean profile of plasma concentration in Cohort 3



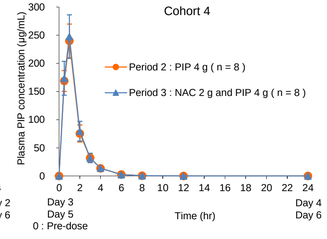


Figure 5. Mean profile of plasma concentration in Cohort 4

Table 4. Adverse events

Cohort	Period	Subject ID	MedDRA Ver.22.0 PT	Severity	Outcome	Relationship
2	Follow-up	203	Headache	Mild	Recovered	Not related
			Feeling hot	Mild	Recovered	Not related
		205	Blood creatine phosphokinase increased	Mild	Recovered	Not related
		206	Blood creatine phosphokinase increased	Mild	Recovered	Not related
3	Follow-up	307	Blood bilirubin increased	Mild	Recovered	Not related

There were no SAEs or TEAEs leading to discontinuation of the study drug. With regard to the number of subjects with TEAEs (incidence rate) and the number of events, 3 of 8 subjects (37.5%) experienced 4 events (headache, feeling hot in 1 subject and blood creatine phosphokinase increased each in 2 subjects) in cohort 2, and 1 of 8 subjects (12.5%) experienced 1 event (blood bilirubin increased) in cohort 3. All of these TEAEs were mild in severity, and the subjects recovered without treatment. Since the onset of events was in the follow-up period, the causality with the study drug was judged to be "not related". No TEAEs were reported in cohort 1 and cohort 4.

Conclusions

- The concomitant administration of NAC with each β-lactam (FEP, ATM, MEM, or PIP) did not affect the PK of NAC.
- The concomitant administration of each concomitant drug with NAC did not affect the PK of FEP, ATM, MEM and PIP.
- The safety and tolerability after concomitant administration of NAC with FEP, ATM, MEM or PIP were confirmed.

Acknowledgment

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This clinical study was approved by the institutional review board by Hakata Clinic .