Toxic Encephalopathy

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กลุ่มงานอุบัติเหตุฉุกเฉินและนิติเวช

โรงพยาบาลกาฬสินธุ์

Agenda


Introduction
Timeline
Toxic encephalopathy
Summary
Pitfall

Introduction

Case ผู้ป่วยชายอายุ 59 ปี

Underlying: DM type 2, Hypertension, IHD, CKD stage 4

Refer จาก รพช. ด้วยเรื่อง ซึม พูดลำบาก 1 วันก่อน มา รพ.

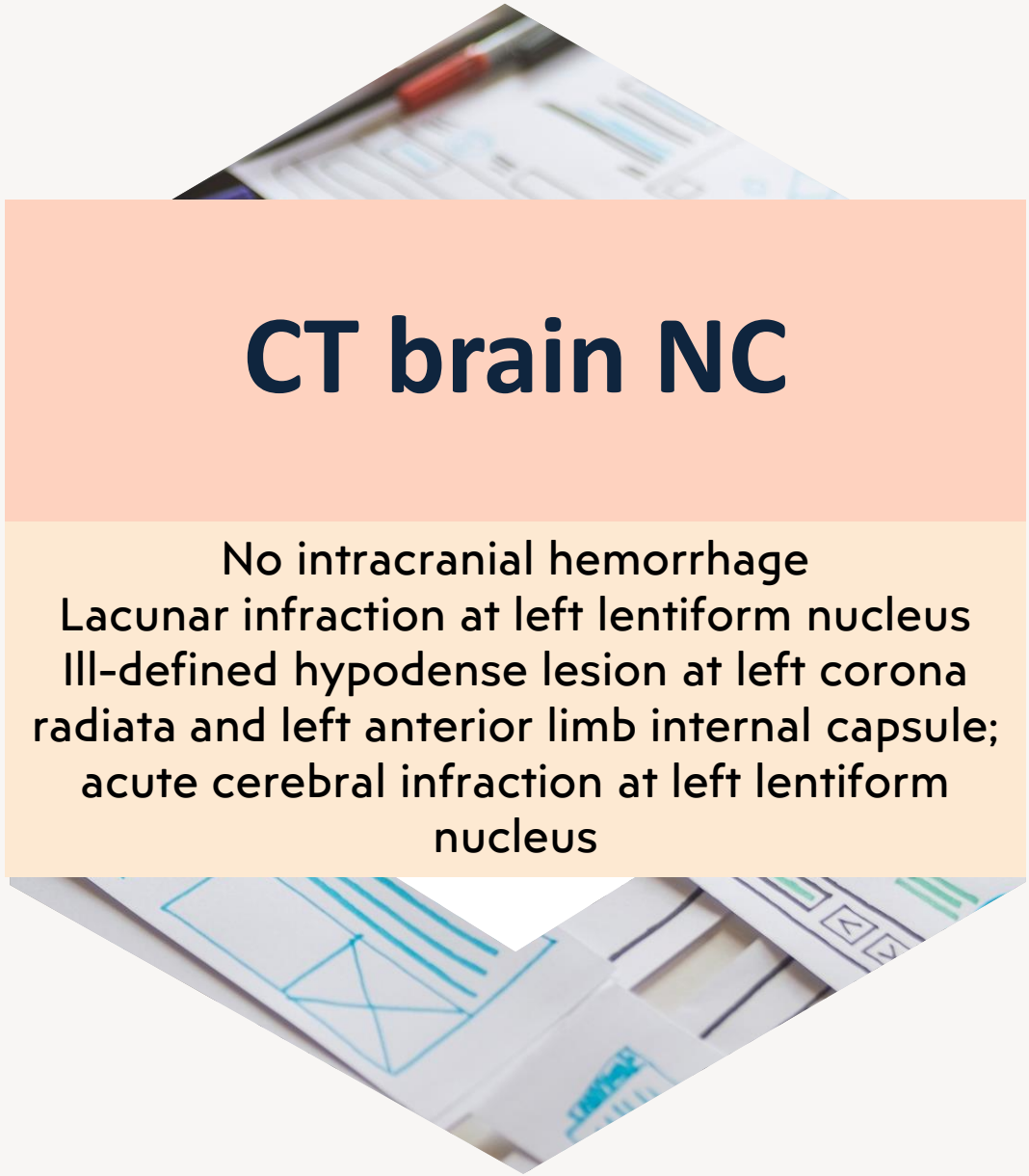
History : last well seen 15/1/67 (09.30น.) ยังพอพูดคุยได้ ทำตามสั่งได้ แต่ดูช้าลง motor gr IV all หลับทั้งวัน

16/1/67 (06.30น.) ญาติพบว่า ผู้ป่วยซึมลง พูดลำบาก น้ำลายไหลจากมุมปาก ไม่มีไข้ ไม่มีอาการชักเกร็ง ปฏิเสธประวัติ Trauma

Introduction

At รพช.
Physical examination: BP 144/80 mmHg, PR 70/min, DTX 117 mg%
E3V3M5 pupil 2mm
Lab: (11/1/67) BUN/Cr 40/2.61 → (15/1/67) BUN/Cr 61/6.16
ยาเดิม: Ceftriaxone, Clindamycin, paracetamol, Gabapentin, lercanidipine, SDM, omeprazole, acyclovir
At ER รพ.กาฬสินธุ์
BT 37.4c, PR 74/min, RR 20/min, BP 135/84 mmHg, slow response and looked drowsy
Neuro sign: E3V4M6 pupil 2 mm, motor gr III all

- Initial management : alteration of consciousness
- W/U lab
- CT brain NC



CT brain NC

No intracranial hemorrhage
Lacunar infraction at left lentiform nucleus
Ill-defined hypodense lesion at left corona radiata and left anterior limb internal capsule; acute cerebral infraction at left lentiform nucleus

BUN	65.57
Cr	6.52
Na	128.7
K	3.47
Cl	102.2
HCO3	11.21

VBG: pH 7.19, pCO2 37, pO2 67, HCO3 14.1

Patient with acute encephalopathy

Timeline

28/12/67

Hx เหยียบตะปู มีแผลหนองบวม
Refer มา admit: NF Rt foot

9/1/67

Revisit: infected wound

ATB:
ceftazidime+clidamycin

9/1/67

Tx: Acyclovir cream
+ set OR for DB

10/1/67

Acyclovir(200) 4*5
for 7 day

11/1/67

Refer back รพช

Timeline

15/1/67

Pt. altered metal status

16/1/67

Refer back kalasin

17/1/67

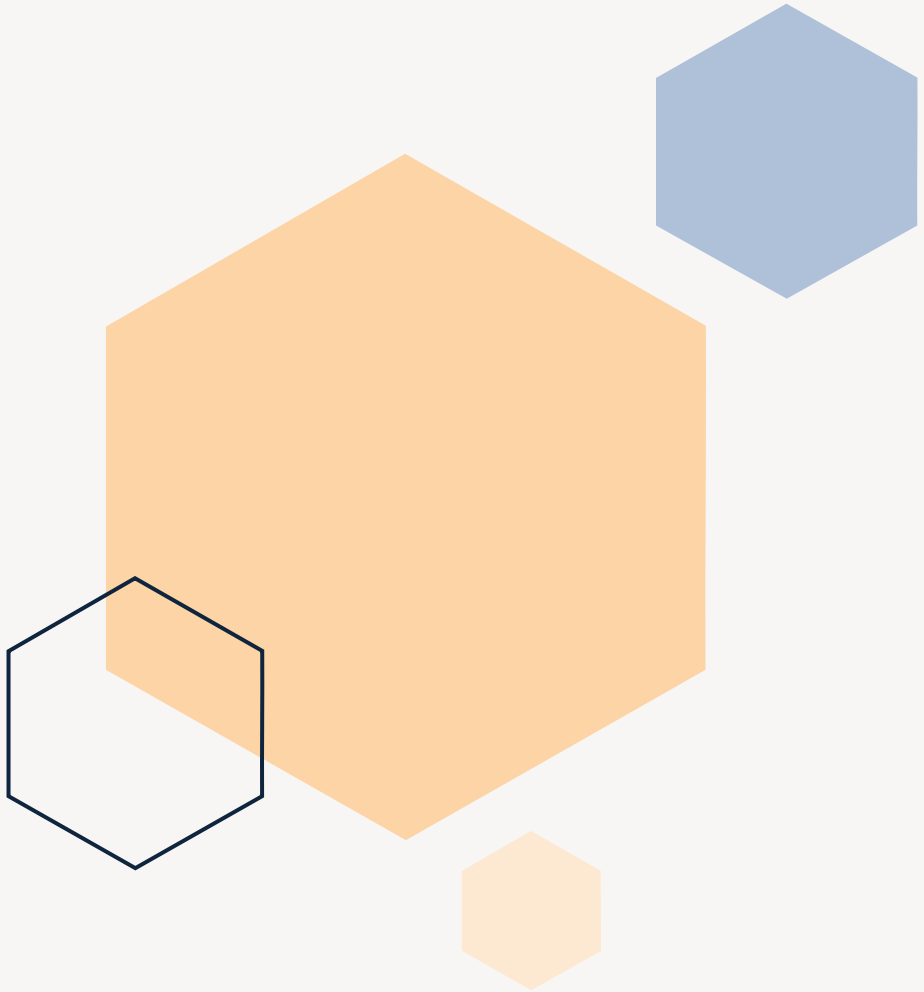
Repeat CT brain
LP: CSF normal

18/1/67

Consult toxico → suggest HD

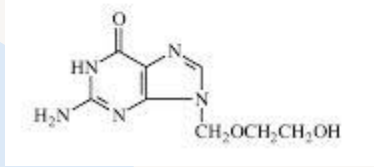
19/1/67

Clinical improve



Acyclovir-Association Encephalopathy

Acyclovir



Indication

- Herpes simplex
- Herpes zoster
- Varicella; chickenpox
- กลไล : Acyclovir → acyclovir monophosphate by thymidine kinase → triphosphate : inhibition of viral DNA replication

รูปแบบของยา acyclovir

- ยาเม็ด ขนาด 200 mg, 400 mg, 800mg
- Suspension 200 mg/5ml
- Cream
- IV 250 mg, 500 mg
- Ophthalmic ointment

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Pharmacokinetic

Distribution	Metabolism	Excretion	Elimination
➢ Protein binding: 9-33% ➢ Vd: (adult) 48 L/m2	➢ 9-carboxymethyoxythylguanine	➢ Renal: 62-91% unchanged ➢ Fecal: 2% ➢ Dialyzable: Yes (hemodialysis), No (peritoneal dialysis) ➢ Other extracorporeal: No	➢ Adults: 2.5 – 3.5 hr ➢ Anuric adults: 19.5 hr ➢ Pediatrics: 2.36 3.8 hr

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ขนาดการใช้ยา acyclovir

Indication	Route	Usually recommended dosage
Herpes simplex Immunocompetent patients	Oral	- 400 mg วันละ 3 ครั้ง หรือ 200 mg วันละ 5 ครั้ง เป็นเวลา 7-10 วัน - Recurrent 400 mg วันละ 3 ครั้ง เป็นเวลา 5 วัน หรือ 800 mg วันละ 2 ครั้ง เป็นเวลา 5 วัน
Herpes simplex Immunocompromised patients	Oral	- 400 mg วันละ 3 ครั้ง เป็นเวลานาน 5-7 วัน - severe (IV) 5-10 mg/kg q 8 ชั่วโมง เป็นเวลา 2-7 วัน - CNS infection (IV) - Encephalitis: 10 mg/kg q 8 ชั่วโมง เป็นเวลา 14-21 วัน - Meningitis: 10 mg/kg q 8 ชั่วโมง เป็นเวลา 10-14 วัน

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ขนาดการใช้ยา acyclovir

Indication	Route	Usually recommended dosage
Herpes zoster Immunocompetent patients	oral	- 800 mg วันละ 5 ครั้ง เป็นเวลา 7-10 วัน
Herpes zoster Immunocompromised patients	oral	- 800 mg วันละ 5 ครั้ง เป็นเวลานาน 7-10 วัน CNS infection (IV) - Encephalitis: 10-15 mg/kg q 8 ชั่วโมง เป็นเวลา 10-14 วัน

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Dose adjustments: Renal impairment

Route	CrCl	Dose adjustment
Oral: 800 mg 5 time/day	- CrCl >25 ml/min/1.73m2 - CrCl 10-25 ml/min/1.73m2 - CrCl <10 ml/min/1.73m2	- No adjustment - 800 mg q 8 hr - 800 mg q 12 hr
Oral: 200 mg 5 time/day or 400 mg q 12 hr	- CrCl > 10 ml/min/1.73m2 - CrCl < 10 ml/min/1.73m2	- No adjustment - 200 mg q 12 hr
IV	- CrCl > 50 ml/min/1.73m2 - CrCl 25-50 ml/min/1.73m2 - CrCl 10-25 ml/min/1.73m2 - CrCl < 10 ml/min/1.73m2	- No adjustment - Extend interval q 12 hr - Extend interval q 24 hr - Administer 50% of usual dose q 24 hr

- Hepatic impairment: No specific recommendations are available.
- Geriatric: Adjustment may be necessary in geriatric patients with underlying renal impairment; use caution with dose selection.
- Hemodialysis: Adjust the dosing schedule so that an additional dose is administered after each dialysis session.
- Peritoneal dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.
- Obesity: Use ideal body weight to calculate adult dose.

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Toxicity of Acyclovir

Acyclovir toxicity

Neurotoxicity	Nephrotoxicity
❖ Altered mental status ❖ Stupor/ confuse/ coma ❖ Hallucinations/ psychosis ❖ Myoclonus/ tremor/ ataxia/ nystagmus/ dysarthria ❖ Agitation ❖ Seizure	❖ At high concentration, acyclovir precipitates as crystal in the urine → nephropathy

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Acyclovir-associated encephalopathy and varicella zoster virus encephalitis

Table 3

Differences between acyclovir-associated encephalopathy and varicella zoster virus encephalitis.

	ACV-associated encephalopathy	VZV encephalitis
Risk factors	ACV Elderly NSAIDs	Immunocompromised Cranial nerve dermatome Presence of cutaneous dissemination
Symptoms	Rarely meningismus· fever·headache	Meningismus· fever·headache
Cerebrospinal fluid	Normal	Lymphocyte domination
Imaging studies	Normal	Abnormal (50%)
Treatment	ACV discontinued Dialysis	ACV
Prognosis	Improve (within 48–72 h)	Mortality 0%–25% (Normal immunity)

ACV = acyclovir, VZV = varicella-zoster virus.
This table is an original table adapted from the following literature:
Kaewpoowat et al Infection. 2016; 44:337-45
Dworkin et al Clin Infect Dis. 2007;44 Suppl 1: S1-26.
Kenzaka et al. Medicine (2021) 100:21

Diagnosis

- Gold standard of diagnosis in encephalitis : CSF, PCR
- CSF analysis is helpful for the diagnosis of herpes encephalitis
- Electroencephalography: nonspecific investigation for encephalitis
- CT brain/ MRI

- **In acyclovir-induced neurotoxicity, the most common presentation is also cognitive and motor disturbance**
- **Symptoms usually occur within 24-72 hours after treatment initiation**

Acute kidney injury and acyclovir-associated encephalopathy after administration of valacyclovir in an elderly person with normal renal function

A case report and literature review

Abstract

Introduction: Acyclovir (ACV)-associated encephalopathy is related to an increase in plasma levels of 9-carboxymethoxymethylguanine, an ACV metabolite, and is often reported in patients with renal dysfunction. We report a case of ACV-associated encephalopathy with rapid progression of renal dysfunction after oral administration of valacyclovir (VACV) and review literature of previous ACV-associated encephalopathy cases.

Patient concerns: An 88-year-old man was diagnosed with herpes zoster. VACV (3000 mg/day) treatment was initiated. Serum creatinine (Cr) level was 0.80 mg/dL. However, irritability, memory impairment, and decreased responsiveness occurred after 3 days. The Cr level was 6.76 mg/dL on admission.

Diagnosis: He was diagnosed with ACV-associated encephalopathy with acute kidney injury.

Interventions: VACV was discontinued, hemodialysis was initiated on the day of admission, and then the signs and symptoms improved approximately 72 hours after the admission.

Conclusion: Worsening of renal function and encephalopathy should be a focus when using VACV or ACV, regardless of age and original renal function. Acute kidney injury and ACV-associated encephalopathy may particularly occur in the elderly even when renal function is normal. Therefore, regular monitoring of renal function and consciousness is necessary during VACV treatment.

Abbreviations: ACV = acyclovir, VACV = valacyclovir.

Keywords: acute kidney injury, acyclovir neurotoxicity, case report, herpes zoster, valacyclovir

Kenzaka et al. Medicine (2021) 100:21

Acute kidney injury and acyclovir-associated encephalopathy after administration of valacyclovir in an elderly person with normal renal function

- **ACV-associated encephalopathy is commonly observed in patients with impaired renal function but may develop even when renal function is normal**
- **Two mechanisms of ACV-induced acute kidney injury exist**
  - Dehydration and the use of nonsteroidal anti-inflammatory drugs, as well as tubular obstruction due to ACV itself
  - Direct mechanism of ACV aldehyde
- The serum ACV level increases due to dysuria when renal dysfunction occurs, which further exacerbates renal dysfunction and causes ACV-associated encephalopathy
  - Elderly people are prone to dehydration and potentially impaired renal function

Kenzaka et al. Medicine (2021) 100:21

Toxic Encephalopathy

Antineoplastic agents	Immune modulation therapy	Antimicrobial agents	Antiviral/ Antifungal agents	Miscellaneous
• Cytarabine • MTX, 5-FU • Ifosfamide • Cisplatin • Capecitabine • Tamoxifen • Rituximab	• Levamisole • Interleukin-2 • Interferon • Ciclosporin • Tacrolimus	• Penicillin • Cephalosporins • Aminoglycosides • Isoniazid • Rifampin • Metronidazole	• Acyclovir • Ganciclovir • Amphotericin B	• Benzodiazepines • Antiepileptic agents (valproic acid) • Nacrotics • Anesthetic agents

Tali Siegal, Netta Levin, in Handbook of Clinical Neurology, 2012

Treatment

- Supportive care
  - พิจารณาหยุดยาที่เป็นสาเหตุ
  - Nausea and vomiting treat with antiemetics
  - Massive overdose: hydration and monitor renal function
- Decontamination: activated charcoal
- Airway management
- Antidote: None
- Monitoring: renal function/ urine output (IV or massive oral overdose)
- Enhanced elimination: Acyclovir and famciclovir (low protein binding, Vd) → Hemodialysis

สิ่งที่ได้เรียนรู้จากกรณีศึกษา

- การปรับขนาดยาตาม CrCl
- ระบบการติดตามและการเฝ้าระวังการใช้ยา
- ขาดการตระหนักถึงอาการ Acyclovir-induced neurotoxicity

Summary

- Acyclovir-induced neurotoxicity is a self-limiting, dose dependent phenomenon which is more common in the elderly, in patients with renal failure
    - They are particularly at risk and the dosing frequency of acyclovir must be adjusted
- Acyclovir toxicity presenting with neurologic symptoms in patients with adequate kidney function****
- Should acyclovir-induced toxicity being diagnosed, cessation of causating drug – acyclovir and hemodialysis is the most effective treatment

****Jay Patel, Brendan Hayes, Laura Bauler, Joshua Mastenbrook

Thank you

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