Pancytopenia related to colchicine drug interactions in a patient with Chronic kidney disease

Speaker: 江芳俞 藥師

- 65 y/o. Female.
- Admission date: 2012-01-23

- Chief complaint
  - Dizziness, nausea, low legs edema for many days. Water diarrhea and poor appetite for more than one month.

- Past history
  - 1.Brain stem infarction with left hemiplegia on 99-11-23.
  - 2.Diabetes Mellitus with Insulin control
  - 3.Hypertension.
  - 4.Gouty arthritis.
  - 5.Right shoulder contusion
  - 6.Chronic kidney disease stage 4-5
  - 7.Cataract s/p op, OU
  - Allergic to 麻醉藥

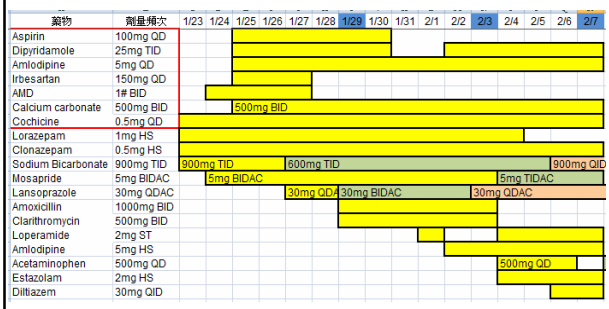
- Present Illness
  - This time, she suffered from dizzness, nausea, low legs edema for many days, water diarrhea and poor intake for more one month, ever visited to our ER and ◎◎hospital (BUN: 96, Cr: 8.7, Hb:6.7, Hct:20.3). But her symptoms got worse, so visited to our MER again. At ER, the blood laboratory measure BUN: 94, Cr:8.4, Glucose AC: 308, Na: 134.3, K:4.5, AST:41, CPK:333, Hb:7.0, WBC: 6200, NE: 91%. Under the impression of Acute on chronic kidney disease. She was admitted to our ward for further evaluation and treatment.

- Imp
  - 1# Acute on chronic kidney disease, suspect volume depletion
  - 2# Anemia due to #1, suspect GI bleeding
  - 3# Brain stem infarction with left hemiparesis on 99-11-23.
  - 4# T2DM with polyneuropathy.
  - 5# Hypertension
  - 6# Gouty arthritis.

- Management
  - Add Sodium bicarbonate 3#(900mg) tid
  - IVF hydartion with N/S 1000ML QD
  - Give PRBC 1U X 4 days (1/23~1/26) s/p Rasitol 1amp
  - Hold Persantin 1# tid, Bokey 1# qd
  - Keep Insulatart 19u qdac

Progression note

1/24	Sore throat. GI consult: GERD-> mopride, AMD
1/27	PES: stomach: hypereemia in the antrum and a 0.3 cm H3 ulcer at angle, biopsy.-> takepron
1/29	HP infection s/p triple therapy. Add amoxicillin, klarith
1/30	Renal echo: bilateral small kidneys and renal cyst, possible chronic nature
1/31	CC: diarrhea 4~5times/d
2/3	DC amoxicillin, klarith.
2/4	Diarrhea 4 times-> ufunin. N/V->norvomin.
2/6	Dyspnea(RR:18->25). CXR: 疑似肺部積水. EKG: AF -> add herbesser, rasitol 4amp q6h Consult GI: triple therapy side effect(抗生素腹瀉，腹部不適，嘴巴苦味), suggest complete 7 days course, and prescribe mild antidiarrhoeal agent. Check UBT 1 month later.



檢驗項目	標準值	1/23	1/25	1/30	2/5	2/6	2/7	2/8	2/9	2/10	2/11	2/13	2/14	2/16	2/18	2/20
BUN	8~20	94	89	69	80	93	113					83				
eGFR		4.8	5.4	6.9	6.1	5.9	4.8					13.6				
Cr		8.4	7.6	6.1	6.8	7	8.4					3.4				
WBC	4.5~11	6.2				1.4	0.7->0.3	0.3	0.2	0.3	0.4	8.2	***27.4***	***22.7***	***17.6***	***16.6***
RBC	4.2~5.4	2.07				3.02	2.59		2.51	3.14	3.59	3.76	3.44	3.04	3.28	4.03
Hgb	12~16	7				9.5	8.3		7.8	9.6	11.2	11.3	10.3	9.2	10.2	12.5
Plt	150~400	132				31	10	7	84	15	32	5	83	7	31	6
Basophil	0.2~2	0				0	0	0	0	0	0	0	0	0	0	0
Eosinophil	0.2~7.3	0				0	0	0	0	0	0	0	0	0	0	0
Monocyte	2.7~7.6	2				6	6->5	1	0	1	***12***	8	3	0	1	6
Lymphocyte	21.3~50.2	7				22	24->18	22	18	23	28	6	2	3	8	7
Neutrophil	38.3~71.7	***91***				72	68->11	3	20	1	3	26	32	59	***91***	***78***
Band	0~5						2->8	3			4	***45***	***63***	***38***		***9***

Searching for offending drugs

1. 入院時white count 正常
   WBC: 6.2(1/23)-> 1.4 (2/6)
   Plt: 132(1/23)-> 31 (2/6)
2. 搜尋1/23~2/6間所有使用藥物其不良反應型態 (工具: up to date, micromedex)
3. 符合Leukopenia, diarrhea 者: amoxicillin, colchicine
4. 文獻搜索結果: colchicine 的案例數量遠大於 amoxicillin
5. 2/7 DC colchicine, amoxicillin, clarithromycin
6. 2/8~10 give granocyte, PRBC * 3d

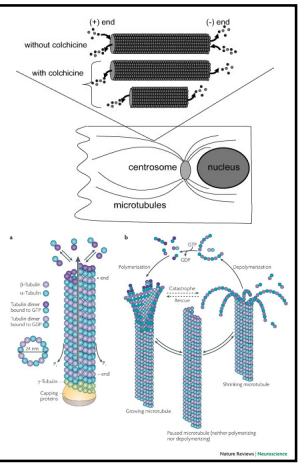
2/7	CC: diarrhea several times. On o2 mask 35% 10L/min. HR irregular 120->80. Leucopenia, neutropenia. No fever. Consult infection : Maxipime 2g qd, G-CSF 5meq/kg qd Consult oncology: Drug induced. If fever, treated as febrile neutropenia. If no fever, just f/u CBC/DC every 3-5 days. Consult ENT: sore throat。多喝水，太乾發炎。 17: 13 E1V1M1. Transfer to ICU. 17: 30 E4VeM4. Emergent HD for lung edema 2.5hr.
2/8	06:43 E1V1M1, asystole, after cardiac message 2mins, gain pulse. BNP 1920. 08: 00 fever. 12: 00 asystole. Left femerol sheath on temporary pacemaker.
2/9	Pancytopenia. Tachycardia-bradycardia syndrome. Maxipime (day3) + U-vanco q5d (2/08, day1).
2/11	Urine culture: Candida. Diarhea
2/13	Coloscopy: No organic lesion in the large bowel, note likely ufunin-induced aggravation of colitis. More likely functional. 16: 16 E3VeM6->E1VeM1~2

2/14	Brain CT:No evidence of mass lesions within the brain parenchymas
2/16	Sepsis and septic shock. Mepem (day2), Diflucan (day2) and Tygacil (day3).
2/17	右上臂淤青10*10 cm. 尾骶骨水泡傷口1.5*1.5 cm. Oral, anal ulcer. Consult dermatology: herpes.
2/20	B/C: prevotella loescheii *2. (2/11 sampling)
2/21	Deep coma. DDT.

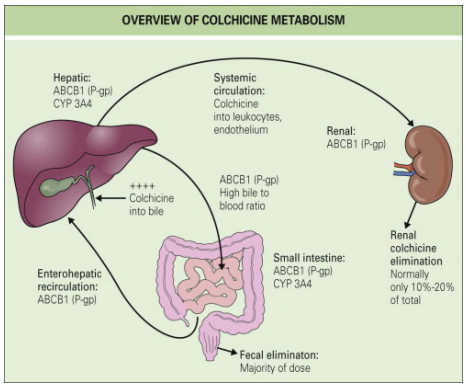
COLCHICINE DRUG INFORMATION

- **Use**
  - **Prevention and treatment of acute gout flares;**
  - **treatment of familial Mediterranean fever (FMF)**
  - **Unlabeled: Primary biliary cirrhosis; pericarditis**

- Mechanism: Disrupts cytoskeletal functions by inhibiting β-tubulin polymerization into microtubules, preventing activation, degranulation, and migration of neutrophils associated with mediating some gout symptoms.



- Readily bioavailable via uptake in the jejunum and ileum,
- The lipophilic nature of colchicine allows it to be absorbed readily by multiple cell types and to bind to its primary target, tubulin, serving as a reservoir of the drug
- Biliary excretion and through the stool: **predominantly**. Extrusion from cells (including enteric lining cells) into the GI tract mediated by the multidrug resistance transporter molecule ABCB1 (also known as ATP-binding cassette subfamily B member 1, MDR1, PGY1. P-glycoprotein, CD243).
- Enteric and hepatic cytochrome P450 3A4 metabolism: 5to 20%, catalyzes demethylation of colchicine to inactive metabolites.
- Renal elimination: 10 to 20% of drug disposition



Gout 用法用量

U.S. labeling:

- Flare treatment

➢ Initial: 1.2 mg at the first sign of flare, followed in 1 hour with a single dose of 0.6 mg (maximum: 1.8 mg within 1 hour).

- Prophylaxis

➢ 0.6 mg once or twice daily; maximum: 1.2 mg/day

CKD AND COLCHICINE

Gouty arthritis is rarely an isolated condition.

- In a review of a Veterans Affairs medical database,
  - ➢ no comorbidities except gouty arthritis: 2%
  - ➢ H/T: 89%,
  - ➢ Hyperlipidemia: 63% ,
  - ➢ CKD: 47%,
  - ➢ CAD: 37%,
  - ➢ DM: 29%
- Perhaps the most challenging comorbidity associated with the management of gouty arthritis is CKD, wherein many of the drugs commonly used for the treatment of gouty arthritis (eg, NSAIDs and colchicine) may have limited utility because of potential safety concerns

- 41% (119/293) of patients were treated with colchicine despite having 1 or more absolute or relative contraindication to the drug (Keenan, 2011)
- 60% (30/50) of patients treated with colchicine for acute gouty arthritis had at least 1 risk factor for colchicine toxicity (ie, age 75 years, statin use, renal transplant, hemodialysis, or renal impairment)(Ly J, 2007)

Dosage adjustment

- *Gout prophylaxis:*

✓ Clcr 30-80 mL/minute: Dosage adjustment not required
✓ Clcr <30 mL/minute:
Initial dose: 0.3 mg/day; use caution if dose titrated
✓ Dialysis: 0.3 mg twice weekly
✓ Monitor closely for adverse effects.

- *Another dose adjusting regimen for Gout prophylaxis:*

✓ Clcr > 50 mL/min: 0.6 mg BID
✓ Clcr 35~49 mL/min: 0.6 mg QD
✓ Clcr 10~34 mL/min: 0.6 mg every 2 ~ 3 days
✓ Clcr < 10 mL/min, hemodialysis, severe hepatobiliary dysfunction: avoid

Ref: Terkeltaub RA. Clinical practice. Gout. N Engl J Med 2003;349: 1647-55.

Dosage adjustment

Gout flare treatment:

✓ Clcr 30-80 mL/minute: Dosage adjustment not required
✓ Clcr <30 mL/minute: Dosage reduction not required but may be considered; treatment course should not be repeated more frequently than every 14 days. For these patients, requiring repeated courses, consideration should be given to alternate therapy.
✓ Dialysis: (原來的1/2劑量) 0.6 mg as a single dose; treatment course should not be repeated more frequently than every 14 days.
✓ Not removed by dialysis. Hemodialysis: Avoid chronic use of colchicine.

Ref: Colcrys (cochicine USP) tablets [prescribing information]. Philadelphia, PA: AR Scientific; 2010.

Dosage adjustment

Geriatric

- CKD is often not recognized in elderly patients because laboratory tests may indicate that Cr levels are normal despite significant underlying renal impairment.

➢ Reduce prophylactic daily dose by 50% in individuals >70 years (Terkeltaub, 2009)
➢ Avoid when eGFR<30 (Hamburger M, 2011)

Alternative drug choice

For treatment of acute flares

Drug	In Stage 1-2 CKD	In Stage 3-5 CKD	Caution with Other Comorbidities
NSAIDs	Relatively contraindicated; if used, suggest indomethacin 50 mg tid until pain is tolerable and for no longer than 1 wk	Can be used with caution in patients with stage 3 CKD with careful monitoring of creatinine levels. Generally not recommended in stage 4 or 5 CKD	Can worsen hypertension or result in new onset of hypertension; should not be used with ACE inhibitors and diuretics
Corticosteroids	**Preferred** treatment for acute attacks; dosage varies for individual patients (eg, 4-48 mg/d methylprednisolone)	Use with caution; risk of side effects may be increased in patients with impaired renal function	Use with caution in CHF, hypertension, and hyperglycemia

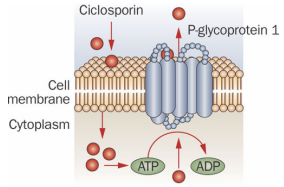
DRUG-DRUG INTERACTION OF COLCHINE

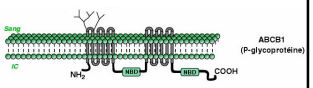
- Between 2004 and 2011, a total of 2655 adverse event reports involving colchicine interactions with other drugs were found in the FAERS(the FDA adverse event reporting system) database
  - 718 reported a death (27.0%),
  - 762 reported a hospitalization (28.7%),
  - 78 referred to life-threatening events (2.9%),
  - 56 reported disability (2.1%).
- Pancytopenia, renal failure, vomiting, drug toxicity, and diarrhea were the most common reported events.
- All reports involving colchicine as the primary suspect drug were 4717 , of which 527 reported a death (11.2%).
- When combined with certain other drugs, evidence suggests that colchicine may be associated with a relatively high death rate

VALUE IN HEALTH 16 (2013) A1 -A2 9 8

p-glycoprotein

- A product of multidrug resistance gene MDR1 and a member of family of ATP-binding cassette (ABC) drug efflux proteins
- Hydrolyze ATP and provide the energy necessary to efflux drugs from cell to lumen.
- Extensively exist: blood-brain barrier, blood–spinal cord barrier, heart, lungs, pancreas, Intestines, biliary epithelial cells , proximal renal tubules, placenta





P-gp inhibitors

- Inhibitor
  - Lopinavir and ritonavir
  - Erythromycin, azithromycin, clarithromycin, ketoconazole, itraconazole
  - Captopril, carvedilol, felodipine, diltiazem, verapamil
  - Amiodarone, dronedarone, quinidine,
  - Cyclosporine, conivaptan, quercetin,ranolazine
- Inducer
  - Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir

CYP3A inhibitors

Strong Inhibitors; 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors; 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors ; 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
Boceprevir, **indinavir, lopinavir/ritonavir,** nelfinavir, ritonavir, saquinavir, telaprevir, **clarithromycin,** telithromycin, **itraconazole, ketoconazole,** posaconazole, voriconazole **conivaptan,** grapefruit juice, mibefradil, nefazodone,	Amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir, **erythromycin,** fluconazole, ciprofloxacin, aprepitant, **diltiazem, verapamil,** Grapefruit juice, imatinib	Alprazolam, **amiodarone,** amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, zileuton

Dosage adjustment

- Coadministration of strong CYP3A4 inhibitor :
- Coadministration of p-glycoprotein inhibitor :

Gout prophylaxis (原來的1/4劑量)
- ✓ If original dose is 0.6 mg twice daily, adjust dose to 0.3 mg once daily
- ✓ If original dose is 0.6 mg once daily, adjust dose to 0.3 mg every other day

Gout flare treatment (原來的1/2劑量)
- ✓ Initial: 0.6 mg, followed in 1 hour by a single dose of 0.3 mg; do not repeat for at least 3 days

- Coadministration of moderate CYP3A4 inhibitor:

Gout prophylaxis (原來的1/2劑量)
- ✓ If original dose is 0.6 mg twice daily, adjust dose to 0.3 mg twice daily or 0.6 mg once daily
- ✓ If original dose is 0.6 mg once daily, adjust dose to 0.3 mg once daily

Gout flare treatment (原來的劑量)
- ✓ 1.2 mg as a single dose; do not repeat for at least 3 days

Dosage adjustment

- Dosage adjustment also required in patients receiving CYP3A4 or P-gp inhibitors up to 14 days prior to initiation of colchicine
- Treatment of gout flare with colchicine is not recommended in patients receiving prophylactic colchicine and CYP3A4 inhibitors.
- Concurrent use of colchicine and P-gp or strong CYP3A4 inhibitors is contraindicated in renal impairment. Fatal toxicity has been reported. Use of colchicine to treat gout flares is not recommended in patients with renal impairment receiving prophylactic colchicine.

COLCHICINE INTOXICATION

Adverse Reactions

- >10%: Gastrointestinal: abdominal pain, cramping, nausea, vomiting (up to 26%), diarrhea (up to 23%)
- 1% to 10%: Respiratory: Pharyngolaryngeal pain (3%)

- <1% (Limited to important or life-threatening):
  - hepatotoxicity, ALT increased, AST increased,
  - CPK increased, muscle weakness, myalgia, myopathy, myotonia, rhabdomyolysis,
  - bone marrow suppression, aplastic anemia, granulocytopenia, leukopenia, thrombocytopenia, pancytopenia,
  - dermatosis, maculopapular rash, purpura, rash, hypersensitivity reaction,
  - alopecia, azoospermia, oligospermia, lactose intolerance, neuropathy, peripheral neuritis,

Prognostic factors after oral ingestion

- In a case series (150 cases),
  - <= 0.5 mg/kg: N/V , diarrhea (death have been reported)
  - 0.5 to 0.8 mg/kg: marrow aplasia and 10% mortality.
  - >0.8 mg/kg: death.

Bismuth C, et al. J Toxicol Clin Exp 1986; 6: 33-8

- reported fatalities from 7 to 60 mg
- toxic blood concentrations >5 μg/L
- prothrombin time (lowest in first 3 days)
- WBC (highest in first 3 days)
- onset of cardiogenic shock (within 72 hours)
- After DC of colchicine, leukopenia may last 2~5 days, leukocytosis may occur at 7th or 8th day, persist 2wks

Intoxication course

- The course of colchicine toxicity can be divided into three sequential and usually overlapping stages.
- ✓ First (0 ~ 24hrs): GI symptoms include diarrhea (bloody) , N/V , leading volume depletion and leukocytosis.
- ✓ Second(1~7 d): Multiorgan failure. Risk of sudden cardiac death, dysrhythmias ; confusion, coma, seizures; pancytopenia, renal failure, hepatic failure, sepsis, acute lung injury, electrolyte imbalances, rhabdomyolysis.
- ✓ Third(>7d): Recovery or death. Alopecia; myopathy, neuropathy, myoneuropathy, or rebound leukocytosis; death usually is caused by respiratory failure, intractable shock, dysrhythmias, and cardiovascular collapse

Ref: Simons RJ, Kingma DW: Fatal colchicine toxicity. Am J Med 1989; 86: 356-7

Management

- Aggressive early gastrointestinal decontamination (activated charcoal within 1~2 hrs)
  HD / HP not useful (large Vd, protein binding)
- Intensive supportive care
  - Fluid and electrolyte replacement
  - Ventilatory and vasopressor support
  - Blood and coagulation products
  - Antibiotic treatment
- Filgrastim (G-CSF) 5 μg/kg/day. Sargramostim.
- Immunotherapy with anti-colchicine antibodies (experimental; not available)

LITERATURE REVIEW

Leukopenia associated with long-term colchicine administration

Ashton E. Beggs, David J. Reeves, and Nancy S. Noel
Am J Health-Syst Pharm—Vol 69 Dec 15, 2012

年齡/性別	病史	併用藥物
85/M	Pseudogout CLL Osteoarthritis H/T	Acetaminophen 500~1000mg Q4~6HPRN Dexazosin 2mg HS Iron 150mg QD Omeprazole 20mg QD Testosterone 200iu/ month

Time	100/2	100/6	100/7	100/9	100/11	100/11	100/11 end	100/12	100/12	101/2
WBC	2.7	1.2	0.8	0.6	0.4	1.8	1.9	2	8.8	0.8
ANC	2.2	0.8	0.4	0.1	0.2	1.4	1.4	1.3	8.3	0.5

Colchicine 0.6mg QD 102/3
Colchicine 0.6mg QOD 102/8
Chemo pegfilgrastim
DC colchicine give filgrastim
Chemo pegfilgrastim
Restart colchicine

1. 起始用後一個月WBC就比之前少一半
2. DC colchicine 後兩個月數值恢復正常，期間有打CSF輔助
3. Rechallenge後兩個月內又開始 leukopenia
4. 使用低劑量
5. P't 肝功能正常，未提及腎功能

註:1. WBC, ANC 單位 10^3 cells/ μ L
2. CLL化療藥物: rituximab, bendamustine

Recurrent and fatal pancytopenia due to repeated colchicine self administration

年齡/性別	病史
57/F	Gout Long-term H/D Depression

Mathieu Demy, et al. European Journal of Internal Medicine 20 (2009) e116–e117

Fever, myalgia, diarrhea
Pancytopenia
-> recover on 4th day
→ 3 wks →
Alopecia
Pancytopenia
-> recover on 4th day
→ 1 momth →
Aplasia
Strptococcus sepsis

→ 1 yr →
Refractory shock
Died the next day
Colchicine serum level: 6 μ g/L

1. p't denied colchicine intake the whole time
2. Not dialysable
3. With DC of cochicine and proper supportive care, pancytopenia can recover within 4 days
4. 若有血中濃度資料，能更準確預測副作用類型及處置，但目前 colchicine 非常規 TDM 藥物

Cochicine-induced bone marrow aplasia in an elderly female with renal insufficiency

Chen-Sen Huang\ Jen-Pi Tsai , HOlllg-Rong Chang Acta Nephrologica Vol. 24, No. 1, 2010

年齡/性別	病史	併用藥物
78/F	Gout CVA H/T	Prednisolone 5mg/d ->20mg/d Colchicine 0.5mg/d -> 1.5mg/d Allopurinol 100mg/d Celebrex 200mg/d -> Diclofenac 50mg/d Cimetidine 600mg/d

- Change dose 7 days before admission. DC all drugs 2 days before admission.
- CC: general weakness, watery diarrhea and fresh blood stool

Time	D1	D6	D10	D19	D26
WBC (10^3/ μ L)	2.41	1.35	2.41	3.73	6.78
Hb (g/dL)	10.7	7.9	9.2	10	9.2
Plt (10^3/ μ L)	50	50	69	107	137

G-CSF 250 μ g D12
G-CSF 250 μ g D5
Cr/eGFR: 2.9/ 16.68
Cefazolin 1g Q12H for UTI
EPO 2000iu D 6,7,8
G-CSF 250g D8

1. 排除Allopurinol造成leukocytopenia 和 aplastic anemia，因爲沒有調劑量
2. DC colchicine 後 21天 WBC 才恢復正常，與renal dysfunction 和 drug interaction 相關?
3. EPO 效果不明顯

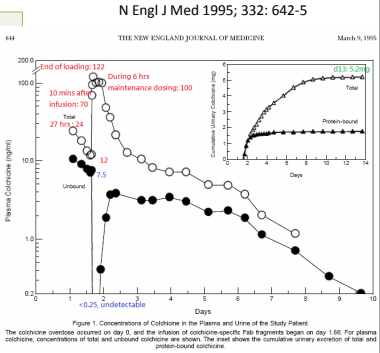
- EPO 和 GCSF 的劑量和使用時間仍待研究
  - ➢G-CSF 5 mcg/kg/d, DC when WBC> 10000/ μL
  - ➢In myelodysplastic syndrome
  - ✓The combination of G-CSF and EPO has synergistic effect
  - ✓G-CSF: initial 1 μ g/kg/d, plus EPO: 150 ~ 300 iu/kg/d
  - ✓EPO 60000~80000 iu/wk (Mundle et al, 2009)

Treatment of severe colchicine overdose with colchicine-specific Fab fragments.

N Engl J Med 1995; 332: 642-5

年齡/性別	併用藥物
25/F	Colchicine 60mg Phenobarbital 900mg Opium extract 750mg 27 hrs before admission In suicide attempt

1. 40 hrs afetr admission, give colchicine-specific Fab fragments 240mg for 1hr, then 240 mg infusion for 6 hrs
2. Rapid redistribution of colchicines from intracellular to plasma
3. Not available



Summary

- Colchicine toxicities happens in varied dosage range, even at theurapeutic dosage
- Risk factor: elderly, renal dysfunction, hepatic impairment, drug interaction, IV route, loading dose
- Most patients had gastrointestinal and neurological toxicities before or at onset of severe hematopoietic suppression
- G-CSF and EPO are used to treat pancytopenia, but the optimal dosage is yet to be determinated

Referances

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