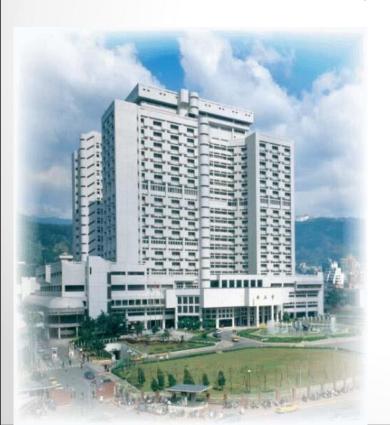
Indications and Stocking of Antidotal Therapy for Common Heavy Metal Poisonings



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Introduction

- Heavy metals may enter the body in food, water, or air, or through the skin.
- Heavy metal toxicity is an uncommon diagnosis. If unrecognized or inappropriately treated, heavy metal exposure can result in significant morbidity and mortality.

Introduction

- The antidotes of metal poisonings are chelation agents, such as British anti-Lewisite (dimercaprol, BAL), calcium disodium edetate (CaNa₂EDTA), dimercaptosuccinic acid (DMSA), 2,3-dimercaptopropanesulfonic acid (DMPS), which forms a complex with toxic heavy metals and leads to their removal.
- Chelators are of great importance in the treatment of metal poisonings, including arsenic, mercury, lead, copper, chromium, iron, thallium and other forms of toxic metal poisoning.

Common Metal Poisoning

- Lead (Pb)
- Mercury (Hg)
- Arsenic (As)
- Chromium (Cr)
- Iron (Fe)

Common Cause of Poisoning

- Intentional
- Folk or herbal Medicine
- Occupational and take-home exposure
- Environmental
- Accidental

Mineral drugs in Traditional Chinese Medicine

砒石,砒霜	Pishi, Pishuang	As_2O_3
雄黃	Xionguang, Realgar	As_2S_2
雌黄	Cihuang, Orpiment	As_2S_3
水銀	Shuiyin, Hydragyrum	Hg
升藥、紅粉	Shenyao, Hongfen	HgO
紅升丹	Hongshengdan	HgO/As ₂ S ₂
輕粉、粉霜	Quingfen, Calomel/Fen-shuang	Hg_2Cl_2
朱砂	Zhusha, Cinnabar	HgS
黄丹、密陀僧	Huangdan, Lithrage	PbO
紅丹,鉛丹	Hongdan, Qiandan	Pb ₃ O ₄

Inorganic Lead

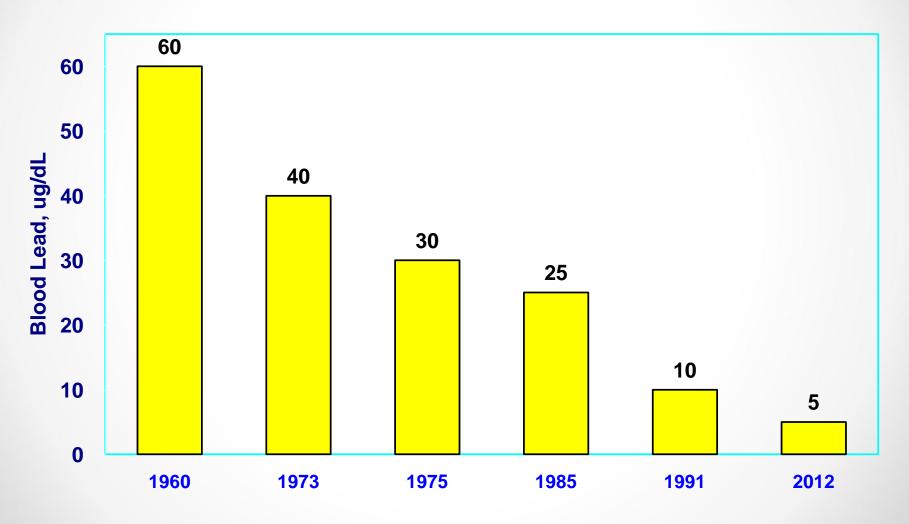
Acute effects

- Abdominal pain (lead colic)
- Encephalopathy
- Hemolysis
- Acute renal failure
- Elevation of liver enzyme

Chronic effects

- Fatigue and asthenia
- Arthralgias and myalgias
- Anemia
- Peripheral neuropathy (motor)
- Neurobehavior disturbances and chronic encephalopathy
- Gout and gouty nephropathy
- Chronic renal failure
- Hypertension
- Impaired fertility

CDC's Action Levels for Blood Lead in Children



Acceptable Blood lead level

Current suggestions in Taiwan

- References for general population: $< 5 \mu g/dl$
- Action level of child: 5 μg/dl
- Action level of adult: 10 μg/dl
- Legal limit of female worker: 30 µg/dl
- Legal limit of male worker: 40 µg/dl

從鉛水管的恐慌談鉛的風險溝通

Lead pipe problem

吳明玲醫師

衛生福利部暨臺北榮民總醫院臨床毒藥物諮詢中心

臺北榮民總醫院臨床毒物與職業醫學科

民國104年10月27日

http://www.pcc-vghtpe.tw/tc/index.asp

Management Recommendations: Adult Population

Blood lead level (µg/dL)	Management recommendations and requirements ^a for adults
< 5	No action needed
5–9	Discuss health risks
	Reduce exposure for pregnancy
10-19	Discuss health risks. Decrease exposure. Monitor BLL
	Remove from exposure for pregnancy, certain medical conditions, long-term risks
20-29	Remove from exposure if repeat BLL in 4 weeks remains ≥ 20 µg/dL
30–79	Remove from exposure. Prompt medical evaluation and consultation advised for BLL > 40 μ g/dL OSHA requirements may apply Chelation not indicated unless BLL > 50 μ g/dL with significant symptoms
≥ 80	Urgent medical evaluation and consultation indicated OSHA requirements may apply Chelation may be indicated if symptomatic and/or BLL ≥ 100 µg/dL

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Inorganic mercury poisoning

- Acute: corrosive and nephrotoxic.
- salivation, metallic taste, abdominal pain, bloody diarrhea
- proteinuria, and acute renal failure.
- fatal hypovolemic shock may result.
- aspiration: irritation, pulmonary edema, ARDS.

Arsenic Poisoning

Acute

- N/V, abdominal pain, diarrhea, dehydration, shock, QT prolonged, TDP, Liver & kidney damage, acute encephalopathy (seizure, delirium, coma)
 - → peripheral neuropathy, bone marrow depression, hair loss
- Industrial arsine gas : garlic odor, hemolytic anemia, AKI

Chronic

- peripheral neuropathy, bone marrow depression
- Hyperkeratosis, hyperpigmentation, Mee's line,
- Skin cancer, peripheral vasculopathy (black foot disease)

Chromium poisoning (Acute)

- Intensive GI irritation or ulceration and corrosion, epigastric pain, nausea, vomiting, diarrhea
- Hemorrhagic diathesis, intravascular hemolysis
- Toxic nephritis, renal failure, liver damage
- Circulatory collapse, peripheral vascular collapse, acute multisystem shock, coma, and even death, depending on the dose.

Iron Poisoning

Clinical course

- Phase I (0.5-2 h): Vomiting, hematemesis, abdominal pain, diarrhea, hematochezia, lethargy, shock, acidosis, and coagulopathy.
- Phase II (6-24h): apparent recovery and may contribute to a false sense of security.
- Phase III (2-12 h after phase I): profound shock, severe acidosis, CNS depression cyanosis, and fever.
- Phase IV (2 to 4 days): possible hepatotoxicity. Acute lung injury may also occur)
- Phase V (days to weeks): GI scarring and strictures.

Chelating agents

Chelator	Main indication	Other application
CaNa ₂ EDTA	Lead	manganese, cobalt
DMPS	mercury, arsenic, lead (chronic)	copper, chromium, cobalt
DMSA	lead, arsenic, mercury	
Prussian blue	thallium, radioactive	
	cesium	
	arsenic, mercury,	
Dimercaprol (BAL)	lead (in addition to	copper
	EDTA)	
D-Penicillamine	copper (Wilson disease)	lead, mercury rheumatoid arthritis, cystinuria
Deferoxamine	iron, aluminum	

Chelator Stocking

- Taiwan Poison Center established a chelator storage and distribution system for the response of the various metal poisoning accidents since 2001. The most life-saving chelators (EDTA, DMSA and DMPS) were chosen for the most common forms of heavy metal intoxication-lead, arsenic, or mercury.
- ✓ The clinical use of BAL is now limited due to its adverse effects and availability of safer chelators.
- ✓ Penicillamine and iron chelator are available in major hospitals because they have other applications.

Treatment of metal poisoning

- Removal of the patient from the source of exposure
- Prevention of the absorption of orally ingested metals
- Prevention of local corrosive action of metals on the mucous membranes
- Supportive care,
- Binding of the metals in body fluids (especially blood) and conversion to less toxic complexes

Metal poisoning through dermal route

Lead, Mercury, and Arsenic Poisoning Due to Topical Use of Traditional Chinese Medicines

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Lead poisoning through lead-containing patch

- 75/M, use 3-month herbal patch due to leg ulcer
- S/S: anorexia, N/V, BW loss, headache, dizziness, constipation and weakness for 2 months.
- Hb 7.1 g/dl, MCV 70 fl, ALT 82 U/L, AST 64 U/L, Na 128 mmol/L, K
 2.9 mmol/L; Panendoscopy: reflux esophagitis.
- Dx: Lead poisoning Tx: EDTA, DMSA

Lead content of herbal patch

516,898 ppm (52%)



Case 1: 75 /M, leg ulcer topical use for 3 months Blood Lead:225.7 µg/dL

250,000 ppm (25%)



Case 2: 56/F, breast cancer topical 1 bid for 1 year Blood Lead:199.0 µg/dL

Arsenic and mercury poisoning through anal use of herbo-metallic ointments

- 51/M, developed peri-anal gangrene and progressive limbs weakness after usage of herbo-metallic ointments for 2 weeks. The prescriptions was got from an unlicensed herbalist and used for his anal fistula.
- In the beginning of treatment, he had fever and anal pain.
- Day 8, 10: visit a TCM clinic due to dizziness, rash, skin itching, anorexia, herbal powder was given. He developed diarrhea which subsided after DC the powders (Hg 13.2 ppm, 12 ppm).
- Day 11: numbness over distant end of fingers and toes started
- Day 15: Worsening numbness and unstable gait appeared, high fever, severe anal pain, walking difficulties. The Fournier's gangrene was noted, so wound debridement and colostomy were performed.

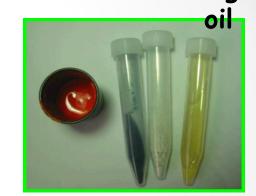
Lead, Mercury, and Arsenic Poisoning Due to Topical Use of Traditional Chinese Medicines

Wu ML, et al.. Am J Med 2013;126:451-4.

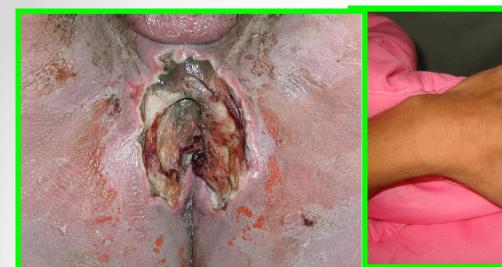
Herbal Suppository (for anal fistula)

- 8 kinds of materials prescribed, mixed as 5 medication
- A: indigo naturalis+musk+hong-dan(Pb₃O₄)
- B: Tung oil+hong-dan
- C : hong-dan+rice wine
- D : gypsum
- E : sulfanilamide ointment+mercurochrome
- Therapy course :
- 1st week: A+D qd, 2nd week: B qd, C prn if itchy(use everyday)

	Lead	Mercury	Arsenic
A:Blue powder	71.9	4.67	13.3
C:Orange ointment 1	166,700	24.5	
C:Orange ointment 2	12,200	16.5	_
D:White powder	_	_	-



C A D Tung







anal wound (Day1) after debridement

hand and lower limb atrophy (Day 26) EMG: severe axonal sensori-motor polyneuropathy









Day 26: Hyperkeratosis

Hair loss

Leg edema

Toxic epidermal necrolysis after dermal use of realgar-containing herbal ointment

- 24 y/o man visited a TCM clinic for atopic dermatitis. Multiple herbal prescriptions were used orally and topically for 18 days.
- Day 7: diminished appetite, dizziness, itching skin rash, and exfoliation
- Day 15: generalized edema, nausea, vomiting, diarrhea, vesicular formation and discharge with poor odor
- Day 16: fever and near-syncope 2-3 times per day.
- Day 18: visit TCM twice, syncope at clinic. He received some treatment and was sent back home.
- Midnight of day 18: whole body discomfort, visit ED.

Realgar-related death

- Diagnosis: toxic epidermal necrosis, complicated with soft tissue infection and sepsis
- ICU care, He died 2 days later
- Direct cause of death: Pseudomonas aeruginosa bacteremia with septic shock and multiple organ failure syndrome.
- Post-mortem blood arsenic level: 1225.4 ug/L.

Wu ML, Deng JF. Toxic epidermal necrosis after extensive dermal use of realgarcontaining (arsenic sulfide) herbal ointment. Clin Toxicol (phila) 2013:51:801-3.

中藥處方

- 當歸飲子(複方): 當歸、白芍、川芎、生地黄、白蒺藜、防風、荊芥、何首鳥、黃耆、甘草、生薑
- · 人參養榮湯(複方):人參、白术、黃耆、甘草、陳皮、肉桂、當歸、 熟地黃、五味子、茯苓、遠志、白芍、大棗、生薑
- · 溫經湯(複方): 吳茱萸、人參、桂枝、川芎、生薑、半夏、甘草、當歸、芍藥、阿膠、牡丹皮、麥冬
- 桂枝湯(複方): 桂枝、白芍、甘草、生薑、大棗
- 五苓散(複方):豬苓、澤瀉、白术、茯苓、桂枝
- 越婢加术湯(複方):麻黄、石膏、白术、生薑、甘草、大棗
- 蒲公英
- 地膚子

Arsenic content of herbal ointment

消炎止痛青

45,427 ppm

5,512 ppm



Skin cure and reactivation oint.: 8171 ppm



4,229 ppm

1.14 ppm Face





Mercury poisoning after using skin whitening cream

- 50 y/o F, topical use of skin cream for 1.5 month
- S/S: tingling pain, parethesia over face, aggravated headache, severe dry eye and eye itching
- PH: tension headache, goiter s/p subtotal thyroidectomy >10 years and follow-up thyroid function remain normal.

The product was claimed to be manufactured in China and sold in USA





urine Hg: 39.6, 87.2 ug/g creatinine

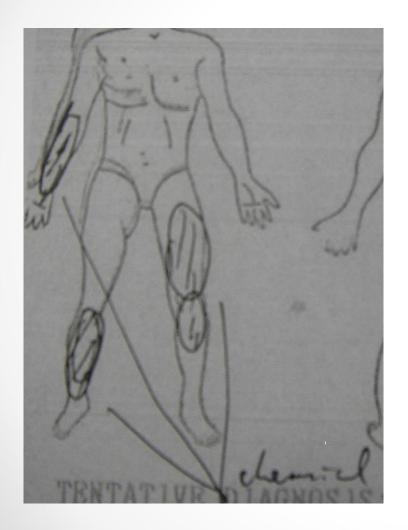
blood Hg: 33.46, 15.45 ug/L

Mercury: 26,992 ppm

Chromium poisoning

- 22 y/o M, worker, entering chromic acid-containing tank
- Chemical burn, 15%TBSA
- Urine chromium 88,208 μg/L
- Presentation: acute renal failure, acute pulmonary edema with respiratory failure, chrome ulcer, leucocytosis, anemia, thrombocytopenia, elevation of liver enzyme and CK.
- Treatment: mechanical ventilation, plasmapheresis, CVVH, hemodialysis, DMPS, N-acetylcystein.

Acute severe chromium poisoning after dermal exposure to hexavalent chromium. Lin CC, Wu ML, Yang CC, et al. J Chin Med Assoc 2009; 72:219-21.



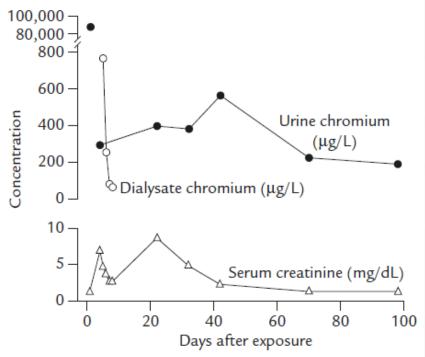
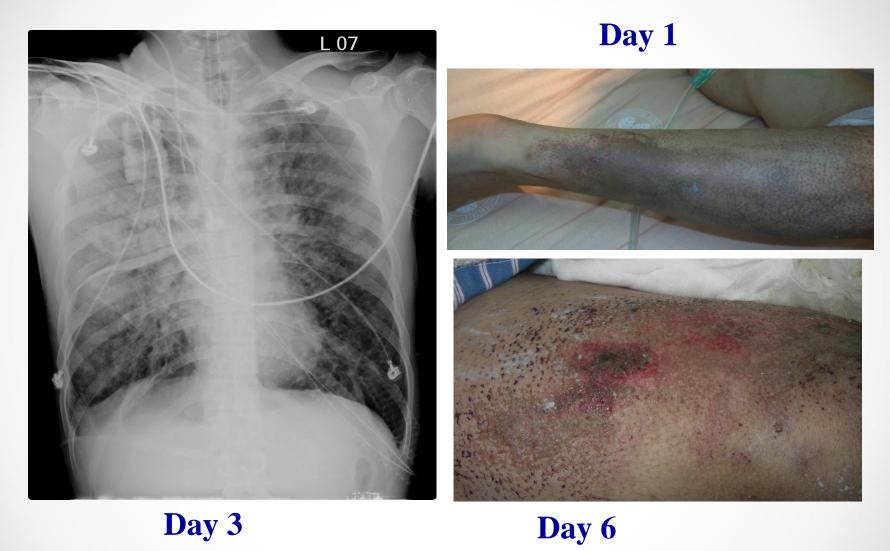


Figure 1. Sequential change in chromium and creatinine levels.



Lin CC, Wu ML, Yang CC, et al. Acute severe chromium poisoning after dermal exposure to hexavalent chromium. J Chin Med Assoc 2009; 72:219-21.

Metal poisoning through Inhalation

Cinnabar vapor inhalation (HgS)

- 73 y/o M, inhaled cinnabar for management of his insomnia. dizziness, general weakness, severe cough, and progressive dyspnea after 3hour exposure for 2 consecutive days
- → Acute respiratory distress syndrome
- On ETT day 7, Refer to our service day 9. Blood Hg 319 μg/L, Urine Hg 357 μg/L
- Treat with DMPS and NAC, died on day 19

Mercury Vapor Poisoning - 4 Cases Report

- A 43 y/o men heated mercury for gold electroplation at bedroom.
- All four family members exhibited symptoms of acute mercury vapor poisoning with weakness, fatigue, diarrhea, sore throat, anorexia, generalized soreness, cough and dyspnea.
- Two dogs and four pet mice died later

Initial Mercury Level

Day 4 (after DMPS use for 3 days)

- Father: 5396.1 (U), 326.7 (B)
- Mother: 2698.2 (U), 390.5 (B)
- Girl: 3026 (U), 141.3 (B)
- Boy: 2381.2 (U), 120.3 (B)

Unit: μg/L

Metal poisoning through oral route

Lead Poisoning - mineral herb

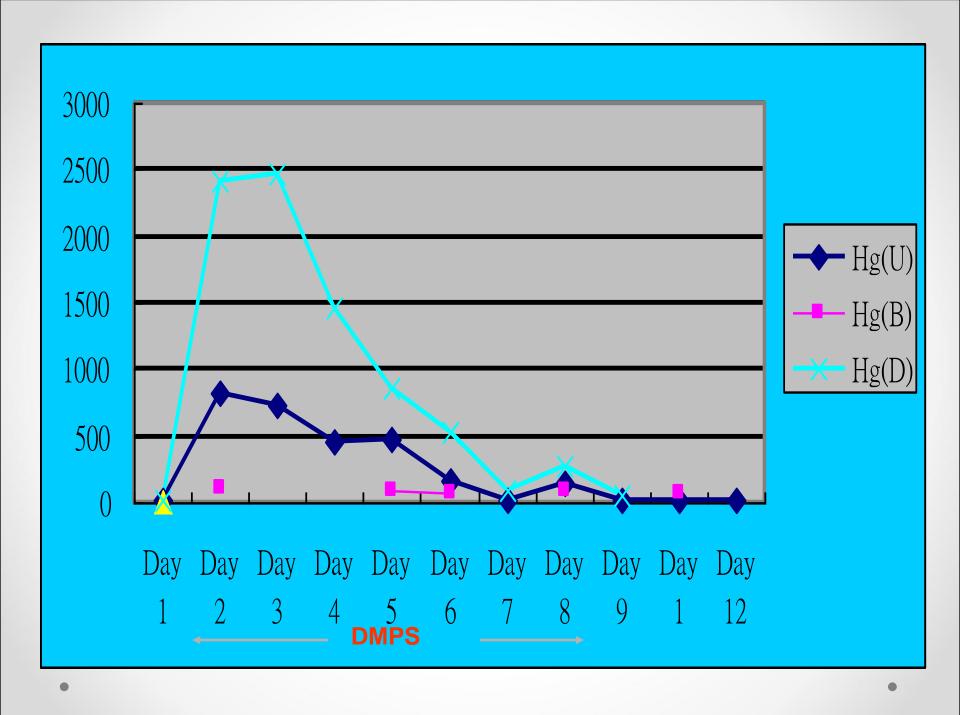
- 30 y/o M, one week use of herb drug (PbO) for management of urolithiasis.
- S/S: nausea, vomiting, abdomen fullness, acid regurgitation, weakness, anemia, elevation of liver enzyme.
- Blood lead 42 μg/dL
- Herbal powder: Pb 23750 ppm \ Hg 127 ppm
- DMPS therapy:250 mg IV q6h*2days , then 100 mg po q6h (June 20-July 1, total 12 day)





 $Hg(NO_3)_2$

- 20 y/o girl presented with GI upset (vomiting, sore throat, abdomen pain) after ingesting 150 ml insecticide (cypermethrin and tetramethrin) & unknown amount of mercury-containing chemical at 00:05 AM
- PE:oral ulcer, lip erosion, pinkish vomitus, epigastric tenderness



Realgar intoxication

- 59 y/o M
- Realgar 150 g in 5 days
- Drowsy
- Pancytopenia
- Acute hepatic, renal function impairment
- Progressive numbness, pain and weakness of distal four limbs→
 Severe sensorimotor polyneuropathy, axonal type, with active denervation

 As_2S_2



As: 635,573 ppm

Cd: 1028 ppm

Pb: 92.43 ppm

Hg:11.52 ppm

		Day 1		Day 2	Day 4	Day 6
	Urine (µg/g Cr)	Urine (µg/g Cr)	Blood (µg/L)	Blood (µg/L)	Urine (µg/g Cr)	Blood (µg/L)
As	7,714	20,141	135	171	1727	8.25
Hg		136	10.14	7.72	18.6	5.36



50/M Realgar ingestion 50 g?

S/S: Dizziness, severe

vomiting, hiccup and diarrhea

Reference level:

 $1-18 \mu g/L (blood)$

<120 µg/g creatinine (urine)

Iron Poisoning

- 1 y/o girl ingested 30 tablets of ferrous sulfate
- Presentation: vomiting, ataxia, drowsy
- Metabolic acidosis (pH 7.35,PO₂ 100,PCO₂ 35, HCO₃ 19.3)
- WBC 17,400/cumm, ALT/AST 229/100 U/L
- Prolonged APTT (48.1/29.9 sec)

Antidote: deferoxamine IV

Clinical experience of acute ferric chloride poisoning. Wu ML, Tsai WJ, Ger J, Deng JF. Vet Hum Toxicol 2003, 45: 243-6.

Case No	Age/ Sex	Route/Reason of exposure	Ingested dose (ml)	Major presentations	Upper GI Endoscopy	Severity of poisoning	Special management	Serum iron (µg/dl)*	Hospital days
1	35/F	inhalation/ occupational	***	nausea, vomiting	<u></u>	mild		NA	
2	31/F	inhalation/ occupational	***	nausea, sore throat, weakness		mild		NA	
3	27/F	inhalation/ occupational		nausea, vomiting	377	mild	***	NA	No.
4	12/M	oral/accidental	a little	nil	U1775	asympotomati		NA	Person .
5	40/F	oral/accidental	30	sore throat	10 	mild		NA	220
6	35/M	oral/accidental	NA	sore throat	***	mild		NA.	
7	21/M	oral/suicidal	NA	vomiting, sore throat		mild	DFO	NA	5
8	70/M	oral/suicidal	50	vomitling, diarrhea, sore throat, abdominal pain	gastritis	moderate	lavage, milk, DFO	day 3: 47	5
9	20/M	oral/suicidal	150	sore throat, oral ulcer, lip bleeding, abdominal pain		moderate	NaHCO ₃ lavage, DFO	NA	5
10	56/M	oral/suicidal	50	vomiting, abdominal pain, metabolic acidosis	gastric and esophageal erosions and ulcers	moderate	lavage, DFO	3.5 h: 304	5
11	26/M	oral/suicidal	25	vomiting, sore throat, oral ulcer, epiglottic erosions and ulcers	esophagitis	moderate	lavage, DFO	day 2: 40	3
12	26/F	oral/suicidal	30	sore throat, oral ulcer, abdominal pain	gastritis	moderate	DFO	5 h: 200	5
13	31/F	oral/suicidal	25	nausea, vomiting, sore throat, oral ulcer, cyanosis, pneumonia		severe	DFO, ventilator	NA	NA
14	18/M	oral/accidental	120	vomiting, sore throat, oral ulcer, abdominal pain, hematemesis, bloody diarrhea, pneumonia, hypotension, metabolic acidosis	maa.	severe	DFO	13 h; 216	12
15	29/M	oral/suicidal	450-500	nausea, vomiting, sore throat, oral ulcer, abdominal pain, metabolic acidosis	severe gastritis	sévere	lavage, DFO	12 h: 127	8
16	25/F	oral/suicidal	200	vomiting, metabolic acidosis hemolysis, coagulopathy, pneumonia, shock		death		4 h: 2440	<1

^{*} Reference values of serum iron=50-160 µg/dl

DFO = deferoxamine

NA=non-available

Deferoxamine

Indications

- If patient is symptomatic (more than transient nausea/vomiting, diarrhea, lethargy, hypotension, bloody emesis or diarrhea)
- If patient is acidotic
- The peak serum iron exceeds 350 to 500 $\mu g/dL$ (most patients with serum iron in this range will be symptomatic)

Thallium Poisoning outbreak

- 31 y/o m, an orthopedic doctor.
- ⇒ Admission 3 days due to Flu-like symptoms, ileus; alopecia loss 2 weeks later
- \Rightarrow 1.5 month later, painful feet, sleepy, hair loss
- → admission presentations: Progressive distal numbness in feet/fingers(1 m), distal weakness, difficulty in walking (walking on cotton), dysarthria, nystagmus, poor accommodative ability of eyes, BW loss, Hair loss and Mees' Line
- Discharge Dx: Thallium intoxication with polyneuropathy, optic neuropathy and brainstem dysfunction.

Thallium level

Case 1 (severe poisoning)

- Blood: 111.64 μg/L, Urine: 616.79 μg/L
- Hair: 10.499 ppm (< 0.01)

Case 2 (moderate poisoning)

- Blood: 102.91 μg/L, Urine: 434.85 μg/L
- Hair: 1.654 ppm

Antidote for thallium poisoning

Prussian blue



Insufficient Stocking

- Although chelators are very essential for heavy metal poisonings, yet insufficiently stocked in health care facilities.
- The cause appears to be related to low incident of metal poisonings, limited hospital resources, cost and unfamiliarity with chelators.

Conclusion

- The chelators are effective in treatment of mercury, arsenic, lead, iron and thallium poisoning.
- Treatment should be initiated as early as possible in acute poisoning.
- Establish a chelator storage and distribution system for the response of the various metal poisoning accidents should be considered at the governmental level.

Taoyuan

Physostigmine: 20amp Methylene Blue: 20 vial

Cyanide: 5pk Ca-EDTA: 16box DMS A: 20hox DMPS(Cap): 2box DMPS(Amp): 8box Physostigmine: 45amp Methylene Blue: 45vial Keelung

Cyanide: 6pk

Taipei City

Hydroxocobalamin: 2set Ca-EDTA: 56box

DMSA: 70box DMPS(Cap): 6box DMPS(Amp): 24box Methylene Blue: 10vial

Physostigmine: 10amp

台北縣

官蘭縣

花蓮縣

南投縣

台東縣

Cyanide: lpk

Taichung Physostigmine: 30amp Methylene Blue: 30vial Cyaride: 4pk Hydroxocob alamin: 2set Ca-EDTA: 24box DMSA: 30box DMPS(Cap): 2box

DMPS(Amp): 8box

Physostigmine:5amp

Methylene Blue:

Cyanide: lpk

Yunlin

Svial

Hsinchu Physostigmine: Samp Methylene Blue: Svial Cyanide: lpk

Miaoli

Physostigmine: Samp Methylene Blue: Svial

Cyanide: lpk

Changhua

Methylene Blue: 15vial

Ca-EDTA: 8box DMSA: 10box

DMPS(Amp): 4box

Tainan Physostigmine: 15amp Methylene Blue: 15vial Cyaride: 2pk Ca-EDTA: 8box DMSA: 10box DMPS(Cap): Ibox DMPS(Amp): 4box

Physostigmine: Samp Methylene Blue: Svial

Physostigmine: 30amp

30 vial

Hydroxocob alamin:

DMSA: 40box DMPS(Cap): 3box

DMPS(Amp): 12box

台北市-

桃園縣·

新竹縣

苗栗縣

台中縣

台中市

嘉義縣

台南縣

高雄縣

高雄市

屏東縣

Physostigmine: 15amp

Cyanide: lpk

DMPS(Cap): Ibox

Chiai

Cyanide: lpk

Kaohsiung

Methylene Blue:

Cyanide: 4pk

2set Ca-EDTA: 32box

Pingtung

Physostigmine: Samp Methylene Blue: Svial

Cyanide: lpk

Taipei

Physostigmine: 15amp Methylene Blue: 15vial

Cyaride: 2pk

Ilan

Physostigmine: Samp Methylene Blue: Svial

Cyanide: lpk

Hualien

Physostigmine: 10amp Methylene Blue: 10vial

Cyanide: 2pk

Hydroxocobalamin: 2set Ca-EDTA: 16box

DMSA: 20box DMPS(Cap): Ibox DMPS(Amp): 4box

Nantou

Physostigmine: 5amp Methylene Blue: Svial

Cyaride: lpk

Taiting

Physostigmine: 5amp Methylene Blue: Svial

Cyanide: lpk

Comments or questions?

Thanks for your attention!

