

巴拉刈(paraquat)中毒

Special lecture

2013.06.04

新光急診VS陳欣伶

農藥 (Pesticides)

- 保護農作物及其生產物或改良作物目的所用之化學藥品; 種類:
 - 殺菌劑 (Fungicide)
 - 殺蟲劑 (Insecticide):
 - 有機磷殺蟲劑(Organophosphates)
 - 氨基甲酸鹽殺蟲劑(Carbamates)
 - 除蟲菊殺蟲劑(Pyrethrin and pyrethroids)
 - 除草劑 (Herbicide)
 - 巴拉刈(Paraquat)
 - 嘉磷塞異丙胺鹽除草劑(Glyphosate-surfactant herbicide)
 - 殺蟎劑 (Acaricide, Miticide)
 - 其他: 植物生長調節劑 (Plant growth regulator, 如葡萄催芽劑: 氯乙醇 ethylene chlorohydrin), 補助劑 (Supplemental agent)

- 農藥的劑型: 水劑, 粉劑……
- 理想的農藥
 - 低毒性
 - 效力大
 - 無藥害
 - 品質安定
 - 價格低廉
 - 物理性質好
 - 使用簡單, 可混用…

表一、臺灣地區導致中毒之毒性物質分類(1985-1993)

毒性物質	≤ 18 歲		> 19 歲		全部	
	N	%	N	%	N	%
農藥	633	10.9	6,239	35.4	6,872	29.3
藥物	1,886	32.4	4,874	27.7	6,760	28.8
清潔劑	410	7.1	1,196	6.7	1,606	6.9
溶劑	285	4.9	736	4.2	1,021	4.4
動物蟻咬	172	3.0	781	4.4	953	4.1
殺鼠劑	148	2.5	658	3.7	806	3.4
化粧品美容用品	246	4.2	383	2.2	629	2.7
防蟲劑	251	4.3	257	1.5	508	2.2
中藥	111	1.9	319	1.8	430	1.8
一氧化碳及有毒氣體	93	1.6	331	1.9	424	1.8
食物性毒素	89	1.5	190	1.1	279	1.2
碳氫化合物	49	0.8	168	1.0	217	0.9

資料來源: Yang CC, et al. Taiwan National Poison Control Center: Epidemiologic Data 1985-1993. Journal of Toxicology-Clinical Toxicology 1996;34:651-663.

Acute Pesticide Poisonings in Taiwan

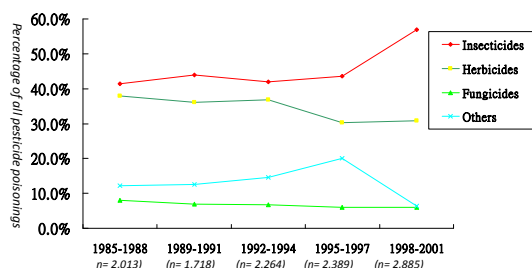


Figure 1. Distribution of poisoning substance by calendar time among 11,269 patients with acute pesticide poisonings in Taiwan

台灣地區的農藥中毒

- 中毒物質以有機磷殺蟲劑(23.3%)、嘉磷塞異丙胺鹽除草劑(15.4%)、巴拉刈除草劑(11.9%)、除蟲菊精殺蟲劑(11.6%)、及氨基甲酸鹽殺蟲劑(6.7%)為主
- 中毒者以30-39歲者最多(19.5%)，其次為19-29歲(18.2%)
- 中毒途徑以口服為主(79.2%)，其次為吸入(13.3%)

- 中毒原因以自殺(66.7%)為主，職業相關者佔13.6%
- 中毒之死亡率為14.5%，以巴拉刈居首(61.5%)，其次為有機磷殺蟲劑(13.1%)、氨基甲酸鹽殺蟲劑(8.2%)等
- 中毒死亡與暴露途徑、中毒物質、中毒原因、其他中毒物質、及年齡等因素有關

Paraquat

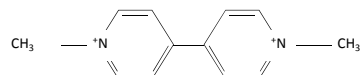
Paraquat 1st day



Paraquat 7 th day



巴拉刈 Paraquat



學名:

1,1'-dimethyl-4,4'-bipyridylium
sulfate or dichloride compounds

化學式: $C_{12}H_{14}N_2C_{12}$

商品名:

克燕啖Weedol、達草淨、可樂松
Gramoxone

分子量: 257.18

PH: ~6 (偏酸)

製劑顏色:

以前深棕色，已改藍綠色，並加催吐劑



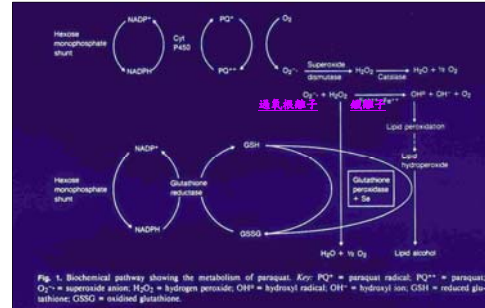
巴拉刈(paraquat)除草劑 (I)

Characteristics of paraquat

- Paraquat is an extremely toxic herbicide which may produce multisystem organ failure and pulmonary toxicity from as little as one mouthful of 20% concentrate.
- Reasons of popularity:
 - Inexpensive
 - Rapid action
 - Favorable environmental characteristics

Toxicologic Mechanism of Paraquat 超強氧化能力的巴拉刈

- 巴拉刈的細胞內毒性，主要經氧化還原反應 (redox cycling) 造成氧化性傷害
- 巴拉刈致毒時，產生大量一氧化氮 + 同存在的過氧根離子 → 形成過氧亞硝酸鹽
- 過氧根離子 + 過氧化氫 + 過氧亞硝酸鹽 + 鐵離子等 → 細胞組織器官傷害



造成器官衰竭的機轉

- PQ toxicity is most severe in **lungs** from taken up by type2 pneumocyte
 - Early stage : acute alveolitis
 - Late stage: Lung fibrosis
- Kidney** injury from proximal convoluted tubule necrosis
- Hepatocellular** injury from mitochondrial damage

巴拉刈之毒物動力學

Absorption

- Low but rapid via GI (5-10%), low via skin
- Peak plasma concentrations < 2hrs following ingestion

Distribution

- Active transporter in alveolar cells
→ Attain higher and prolonged levels in lung
- Volume of Distribution: 2.75 liters/kg

Metabolites

- Nil? (+ by intestinal microflora?)

Excretion

- Rapid via kidneys, 80-90% in 6hrs
- Plasma concentration distribution:
 - Initial ~2 hrs
 - Terminal 12 hrs (half-life)
 - Renal Failure 120 hrs

口服巴拉刈中毒症狀

破壞期	1-2小時內	噁心、嘔吐、腹痛及腹瀉，持續數小時後自然消失，伴發體液電解質流失
	12-24小時	• 口腔及食道潰瘍，有時數天後再發生食道穿孔、破裂、縱膈腔炎 • 嚴重者，急性大量服食> 60-100cc，發病速度很快，出現：心跳加快、心室性心律不整、心肌受損的低血壓、心臟衰竭或休克，加上直接及續發之代謝性酸中毒、肺水腫，很快致死
	2-5天	嚴重者，產生可逆性的肝及腎衰竭，尤其中毒前就有脫水現象者，很快發生急性腎小管壞死，出現乏尿，
	1-4周	肝腎功能好轉，反而肺纖維化漸嚴重，而發生呼吸衰竭，隨後很快因缺氧致死

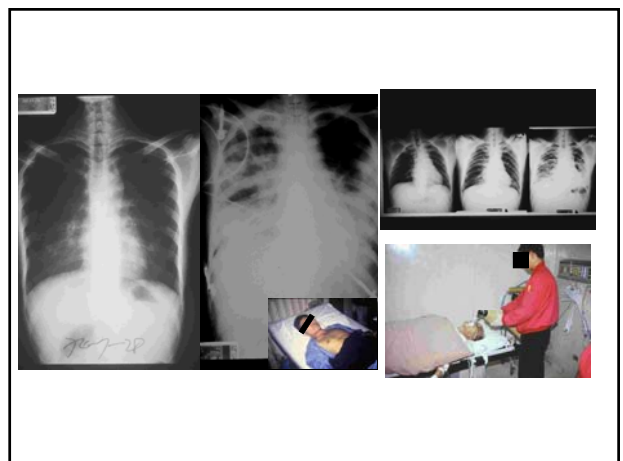
臨床嚴重度

- Depend on amount of exposure
 - **Mild (Ingest <20mg/kg)**
 - Local irritation
 - Recovery without sequelae
 - **Moderate to severe (Ingest 20-40mg/kg)**
 - GI corrosion, acute tubular necrosis, hepatitis
 - **Delayed progressive pulmonary fibrosis**
 - **Delayed mortality (1-4 weeks)** from hypoxia

(cont.)

Fulminant (Ingest>40mg/kg)

- Usually die within few hours to few days
- Acute renal failure, myocardial damage, hepatic failure, pneumonitis,
- Multiorgan failure, shock
- High mortality regardless of management



尿液 Paraquat 半定量測試

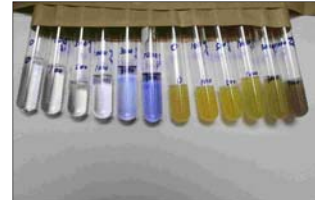


Paraquat
+ **Sodium dithionite**
+ **alkalization** (ex. sodium bicarbonate)
使 pH 7-8
→ Blue complex

Detect limit 1mg/L

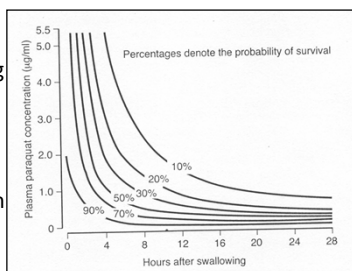
Urine dithionite test

0 3 10 30 100 ug/ml



Diagnosis

- Plasma paraquat
 - Confirm poisoning
 - Predict prognosis
 - Hart's Nomogram
 - Plasma paraquat level drawn within 28 hours



巴拉刈中毒之治療

穩定生命徵象，**不可給予患者氧氣**
以支持性療法為主，目前無有效的解毒劑



去污

皮膚、眼睛、黏膜之清洗

腸胃道：

- ✓ 催吐、洗胃
- ✓ **活性炭**、蒙土乳 (Bentonite)、漂土 (Fuller's earth)
- ✓ 瀉劑

抑制巴拉刈進入肺泡細胞

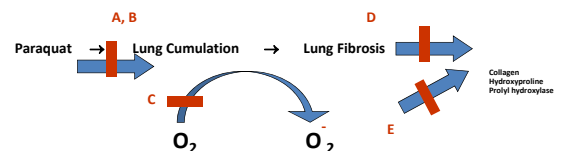
- ✓ Diaminoalkanes (putrescine, spermidine)
- ✓ β -adrenergic antagonist (如propranolol)

遠體內之毒物排除

- ✓ 強迫利尿
- ✓ **血液透析** ?
- ✓ **血液灌流** ?

- 抗氧化：減少 lipid peroxidation
 - ✓ **低氧治療**
 - ✓ 增加過氧化氫解毒 clofibrate
 - ✓ 抑制OH離子基產生 deferoxamine
 - ✓ Superoxide Dismutase (SOD) 加速超氧離子分解
 - ✓ 補充維他命C、E ?
 - ✓ 增加NAD合成，提供還原基(niacin)
 - ✓ **補充glutathione (N-Acetylcysteine)**
 - ✓ 增加過氧化脂質代謝(glutathione peroxidase、selenium)
- 抑制肺纖維化細胞形成或聚集
 - ✓ **類固醇**
 - ✓ 秋水仙素
 - ✓ 肺部低劑量輻射
 - ✓ **抗癌藥物 cyclophosphamide ?**

Toxicologic Mechanism of Paraquat and its Treatments



- A:** Gut Lavage, Fuller's Earth, Charcoal, Diuresis, Hemopurification, Antibody
- B:** Receptor Antagonists - Diaminoalkanes (Putrescine, Spermidine), D-Propranolol
- C:** Low P_{50} , One Lung Ventilation
- D:** Steroids, Immunosuppressants, Fibrinolytics, Radiotherapy
- E:** Superoxide Dismutase
Lung Transplantation

腎功能保護措施的重要性

腎臟是巴拉刈中毒後最重要的排毒器官，因而容易傷害腎臟約佔一半以上的巴拉刈中毒之住院病人

腎臟受損→

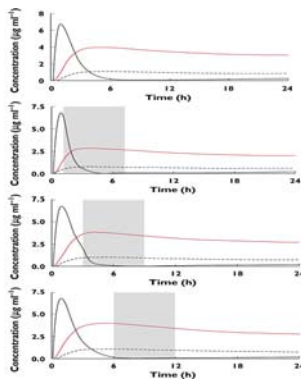
- 排毒量減少→ 其他臟器受害加大
- 需要時給予洗腎治療
- 水份、電解質及營養的給予也變得複雜
- 中毒後口腔潰瘍嚴重
 - 依賴靜脈輸液之營養補給
 - 水分積存
 - 使呼吸衰竭惡化

Controversial(1)

- Elimination enhancement :HD/HP
 - Limited of benefit
 - Most PQ is eliminated rapidly anyway by endogenous clearance in 6-12hr and remaining eliminated slowly
 - Distribution into lung is very fast

Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. *British Journal of Clinical Pharmacology*. 2011 Nov;72(5):745–57.

Elimination enhancement

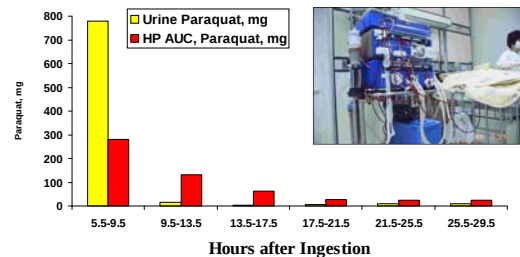


• A model of the time-dependent effect of haemodialysis on plasma (black line), tissue (dashed line) and lung (red line) paraquat concentrations.

There is minimal reduction in lung PQ concentrations when instituted HD/HP at 3 or 6 h post ingestion

Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. *British Journal of Clinical Pharmacology*. 2011 Nov;72(5):745–57.

Paraquat Elimination: Diuresis vs Hemoperfusion



Controversial(2)

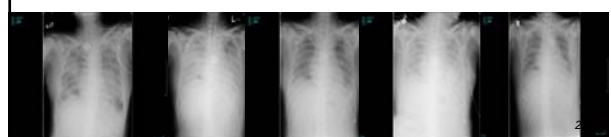
- Antioxidants: Vitamin C, Vitamin E and N-acetylcysteine have never been evaluated in controlled trials.
- Cyclophosphamide with steroid are controversial
 - significant decrease in mortality 25% VS 70% controlled cases among moderate to severe paraquat poisoning

Lin JL, Wei MC, Liu YC. Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat poisoning: a preliminary report. *Thorax*. 1996 Jul;51(7):661–3.

48 Y/O Female suicide attempt with paraquat

June 26: Drank 200mL 24% Paraquat
 June 26: Gastric Lavage, Activated Charcoal, Hemodialysis
 July 26: Methylprednisolone 1 gm qd x 3 days
 June 27: Endotracheal Intubation + Ventilator
 Survived

4th Day 5th Day 8th Day 10th Day 12th Day



Take home message

- 無法以ARDS之治療方式對肺部問題改善
- 無有效之治療方式
- 盡人事、聽天命
- 不要任意給氧