

# 毛地黃 乙型阻斷劑 中毒之治療 鈣離子阻斷劑

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## 台灣山區常見的美麗花朵



## Foxglove 毛地黃 指頂花



## 名稱的由來

- 因為有著佈滿茸毛的莖葉及酷似地黃的葉片；又因為它來自遙遠的歐洲，所以又稱為「洋地黃」。
- 傳說有一個壞妖精將毛地黃的花朵送給狐狸，讓狐狸套在腳上，來避免覓食時發出腳步聲，因此毛地黃又有另一個名字叫「狐狸手套(Foxglove)」

## 簡介

- 毛地黃葉片含強心甘，是極佳的強心利尿劑。
  - Increase systolic contractility (positive inotropic property)
  - Decrease AV nodal conduction (negative chronotropic property)
- 有效劑量與中毒劑量非常接近，極易中毒
  - 噁心、嘔吐、心室顫動等症狀，嚴重時死亡。

## 含強心配醣體的植物

- 毛地黃
- 洋地黃
- 夾竹桃
- 鈴蘭
- 紅海蔥
- 海檬果
- 玉竹
- 馬利筋
- 萬年青
- 側金盞花



## 路邊野花不要採 北市街頭有毒植物64種

2010-07-26 中國時報【中廣新聞／林麗玉】

台北市議員簡余晏、陳建銘等人今天表示，台北市許多路樹、路花其實都有毒，例如南京東路、龍江路口，放置在公車道上的麒麟花其實有刺、也有毒，民眾千萬不能隨意碰觸，另外一款海檬果也含有劇毒，而台北市街頭種植的有毒植物種類竟多達64種，台北市公園處表示，會儘可能將有毒植物移至苗圃，避免民眾誤碰或誤食。

走在台北市路上，真的要小心不要隨意採路花、水果，台北市議員陳建銘、簡余晏、李慶鋒等人質疑，台北市街頭，一共有64種路樹、路花其實有劇毒。

市議員到南京東路、龍江路口會勘，發現這一帶公車專用道上的放置有麒麟花，這種麒麟花有刺，乳汁還有毒，如果有民眾誤食，可能會引發口喉、還有胃部不適，嚴重的話還會嘔吐、腹瀉。

(續)

甚至在台北火車站北一門側，有20-30株5、6公尺高的海檬果，市議員陳建銘說，**這個海檬果植物的果實及植物汁液都有劇毒，如果民眾尤其小孩誤食，嚴重者還可能致死。**

台北市公園處園藝工程隊隊長高民典回應，種植在南京東路、龍江路口的麒麟花，是捷運局擺飾的，後續會要求移到別處；至於公園處種植在台北市街頭的有毒植物，大約有4千株，會後續移到苗圃。

至於台北車站北一門附近的劇毒海檬果植物，台鐵已經設置有毒標誌，北市公園處也會後續協助台鐵移除，至於未來新種植的植物，不會再挑選有毒植物。

## 海檬果



## 含強心配醣體的動物

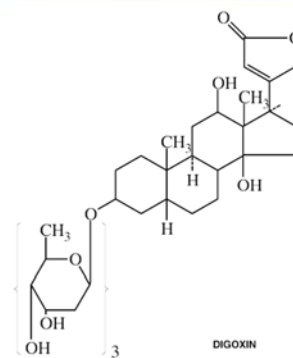
- 黑眶蟾蜍(*Bufo melanostictus* Schneider)
- 中華大蟾蜍(*Bufo gargarizans* Cantor)
  - 含有類強心配醣體的毒性(Bufagins)



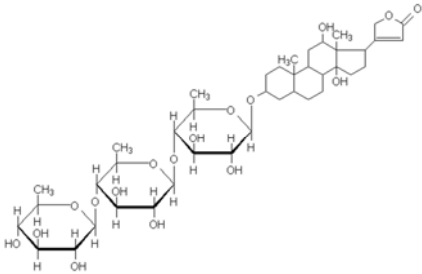
## 用途

- Pharmaceutical preparation
  - Deslanoside, Digoxin, Digitoxin, Powdered Digitalis
  - Typical doses (adult)  
Digoxin: 0.5 mg po or 0.25 mg iv q6h to 1 mg total dose; and then 0.125 to 0.25 mg daily for maintenance
- Unregulated topical aphrodisiacs
  - 印度神油

## Digoxin Lanoxin®



## Digoxin



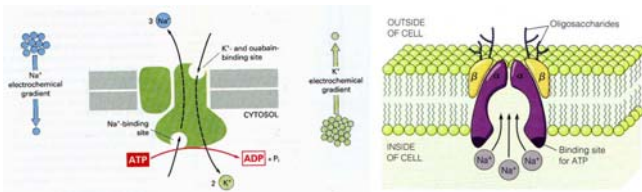
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## Pathophysiology

- **Inhibits cardiac  $\text{Na}^+/\text{K}^+$  ATPase pump**
  - $\uparrow$  intracellular sodium
  - $\downarrow$  calcium excretion
  - $\uparrow$  intracellular calcium concentration
  - $\uparrow$  Contractility (Positive Inotrope)
- **Increases vagal tone**
- **Decreases baroreceptor sensitivity**
  - $\downarrow$  myocardial and AVN conduction
  - $\uparrow$  AVN refractoriness
  - $\downarrow$  heart rate (Negative Chronotrope)

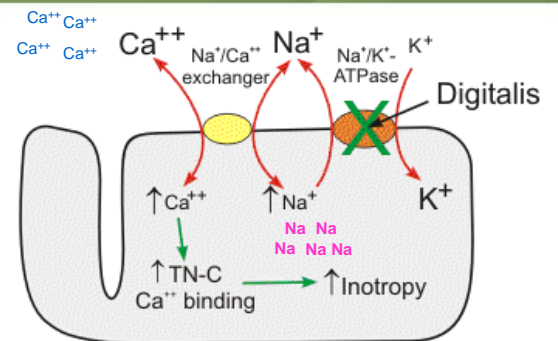
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## 先抑制 $\text{Na}^+/\text{K}^+$ ATPase



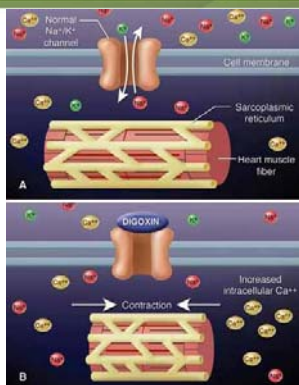
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## 再影響 $\text{Na}^+/\text{Ca}^{++}$ Exchanger



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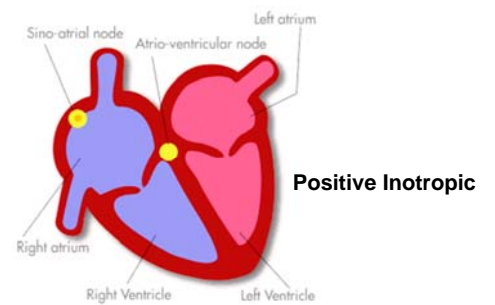
## 細胞內的 $\text{Ca}^{++}$ 濃度上升



增加收縮力

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## Digoxin Effects



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## 為什麼會中毒呢?

- 多半是其他疾病，或者藥物交互作用造成
- 代謝變差：腎功能變差、或者老化
- 自殺（六歲以上）
- 兒童誤食。（小於一歲要考慮兒虐!）



## Disease Interactions

- **Renal failure** decreases digitalis elimination.
- **Hepatic failure** decreases digitoxin elimination.
- **Hypokalemia**
- Hypercalcemia
- Hypomagnesemia
- Hypoxia
- COPD
- Dehydration
- Increased sympathetic nervous system activity
- Hypothyroidism may exacerbate digitalis toxicity

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## Drug Interactions

### Increased Concentration of Arrhythmogenic Drug (1)

Drug	Interacting Drug	Effect
Digoxin	Some antibiotics	Eliminating gut flora that metabolize digoxin
Digoxin	Amiodarone Quinidine Verapamil Cyclosporine Itraconazole Erythromycin	Increased digoxin bioavailability, reduced biliary and renal excretion due to P-glycoprotein inhibition Digoxin toxicity
Quinidine	Ketoconazole	Increased drug levels
Cisapride	Itraconazole	
Terfenadine, astemizole	Erythromycin* Clarithromycin Some calcium channel blockers* Some HIV protease inhibitors (especially ritonavir)	

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## Drug Interactions

### Increased Concentration of Arrhythmogenic Drug (2)

Drug	Interacting Drug	Effect
Beta blockers propafenone	Quinidine (even ultra-low dose) Fluoxetine	Increased beta blockade Increased beta blockade
Flecainide	Some tricyclic antidepressants	Increased adverse effects
Dofetilide	Verapamil Cimetidine Trimethoprim Ketoconazole Megestrol	Increased plasma dofetilide concentration

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## Drug Interactions

### Decreased Concentration of Arrhythmogenic Drug

Drug	Interacting Drug	Effect
Digoxin	Antacids	Decreased digoxin effect due to decreased absorption
	Rifampin	Increased P-glycoprotein activity
Quinidine, mexiletine	Rifampin, barbiturates	Induced drug metabolism

結論是：交互作用極多，開藥之前要注意!  
早年文獻上記載住院中病人使用毛地黃，有中毒現象的病人大約是9.5~30%

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## 中毒有什麼症狀?

- Early signs are **non-specific**: malaise and nausea
- As toxicity increases, interference with cardiac function predominates.
- Acute versus Chronic intoxication

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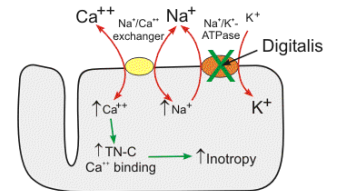
## 早期症狀並不明顯

- Vital signs
  - Bradycardia
  - Tachycardia
  - Hypotension
- HEENT
  - Blurred vision
  - Amblyopia
  - Colored visual halo
- Neurological
  - Headache
  - Weakness
  - Drowsiness
  - Hallucinations
  - Confusion/delirium

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## 特別注意電解質

- Fluids and electrolytes
  - Hyperkalemia (acute overdose)
  - Hypokalemia (chronic toxic or diuretics use)



## 電解質異常

- **Hyperkalemia** (in acute overdose): an indication for digoxin-specific antibodies
- **Hypokalemia**: predispose to cardiac toxicity
- **Hypercalcemia** and **hypomagnesemia**: predispose to dysrhythmia
- Renal insufficiency: impair digoxin clearance
- Hepatic dysfunction increases digoxin levels

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## 造成心臟的症狀往往極嚴重

- Cardiovascular
  - Bradycardia
  - Atrioventricular block
  - Paroxysmal atrial tachycardia with block
  - Intraventricular conduction delay
  - Ventricular dysrhythmias
  - Congestive heart failure

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## 鑑別診斷

- Toxic causes of nausea, hypotension, and bradycardia:
  - 誤食cardiotoxic plants,  $\beta$ -receptor or calcium blockers, and type 1 anti-dysrhythmic agents.
- Nontoxic causes:
  - AGE, small bowel obstruction, myocardial ischemia, hyperkalemia or other electrolyte abnormalities

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## 怎麼確認病人中毒？抽血嗎？

- Serum digoxin levels
  - Digoxin therapeutic range 0.5 to 2 ng/mL
  - Digitoxin therapeutic range 18 to 22 ng/mL
  - Hypokalemia can precipitate toxicity at therapeutic range of digoxin or digitoxin

血中濃度正常並不表示病人沒有中毒！  
中毒的時候血中濃度有可能正常！

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## 毛地黃濃度 vs. 正確診斷比率

各種血清毛地黃濃度範圍(ng/dL)	正確診斷比率
0 ~ 0.99	0.14
1.0 ~ 1.99	0.35
2.0 ~ 2.99	5.18
> 3.0	7.55
> 4.0	11.73

## 會影響濃度的因素

- 最佳抽血時刻：上次服用藥物後六小時
  - Redistributions: 6小時以上才是血清最低點
- 使用digoxin immune Fab antibodies治療
- Digoxin-like immunoreactive substance (DLIS)

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## 心電圖是最重要的檢查

- ECG
  - Nearly every possible dysrhythmia
    - Exception: sinus tachycardia; atrial flutter; PSVT
  - Prolonged PR ; shortened QTc ; sagging ST depression (scooped out)
  - Characteristic
    - Sinus bradycardia
    - Atrial or junctional tachycardia with High grade AVB
    - AV block (AF with fixed RR intervals or complete AVB)
    - Bidirectional VT
    - PAT with 2:1 block

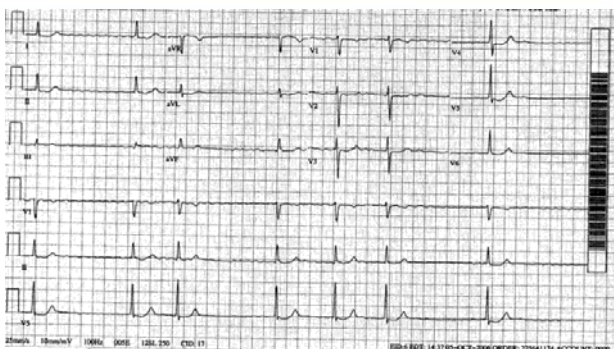
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## 毛地黃中毒典型的心電圖變化

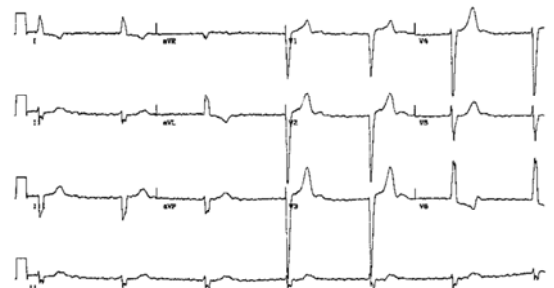
- Odd shaped ST-depression.
- T-wave flat, negative or biphasic
- Short QT interval
- Increased U-wave amplitude
- Prolonged PR-interval
- Brady-arrhythmias:
  - Sinus bradycardia
  - AV block. Including complete AV block and Wenckebach.
- Tachy-arrhythmias:
  - Junctional tachycardia
  - Atrial tachycardia
  - Ventricular ectopia, bigeminy, monomorphic ventricular tachycardia, bidirectional ventricular tachycardia



## Digitalis Effect

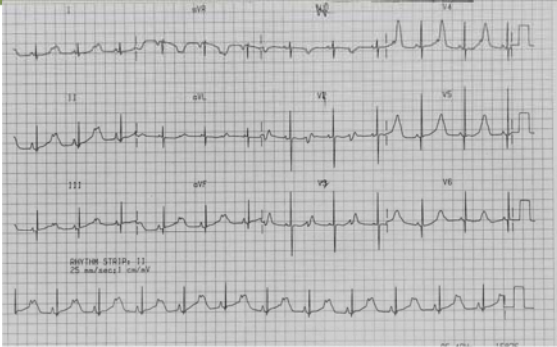


## AF with Fixed RR Intervals



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## AT with 2:1 AV Block



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## Bidirectional VT



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## When to suspect Digoxin toxicity ?

- 心電圖懷疑
- 無法解釋的bradycardia
- Nonspecific GI or neurologic complaints
  - 特別是有心臟病病史的病人身上
- 不明原因的高血鉀
- 有造成慢性中毒的危險因子
  - 電解質異常
  - 肝腎功能異常
  - 藥物交互作用

## 治療

- ABC
- 除污
  - Emesis: 角色不清楚
  - Gastric lavage: not recommended
    - or pre-treat with atropine
  - Activated charcoal
- Antidote: Fab (Digoxin specific polyclonal antibody fragments)

## 治療的重點

- 支持性療法
- 治療致命的心律不整
- 決定是否投予Digoxin immune Fab

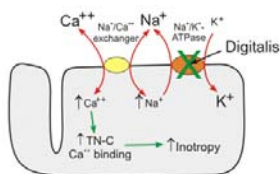
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## 治療心律不整

- According to ACLS
- Atropine + TCP
- Phenytoin: 可加速AV node傳導，digoxin 造成的 ventricular dysrhythmia的首選!
- MgSO<sub>4</sub>
- Electrocardioversion: 易造成Vf，最後一招
  - 10~25J
  - Vasopressor
- Contraindication: Class IA

## 陷阱

- 急性毛地黃中毒容易造成高血鉀
- 治療高血鉀的方式：
  - Burinex
  - Glucose / Insulin
  - Bicarbonate
  - Potassium-binding resin
  - Calcium chloride / Calcium gluconate
  - 都能用嗎?



## 何時使用Antidotes?

- Indications of Digoxin Immune Fab Antibodies
  - CV instability: hemodynamic instability and life-threatening arrhythmias ascribed to digitalis toxicity
  - Rapid progression of toxicity (CV or GI)
  - Serum  $K^+ \geq 5.5$  mEq/L in acute overdose
  - Plasma digoxin  $> 10$ ng/mL
  - Ingestion of  $> 10$ mg in adults or  $> 4$ mg in children
  - Cardiac arrest of short duration
  - Survival rate 50%

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## Digoxin-specific Fab antibody fragment

- Digibind: GlaxoSmithKline
- DigiFab: Savage Laboratories
- 未知食入劑量，且病患狀況嚴重時：
  - 可以先使用5~10 vial
  - 後續的劑量  $\text{Number of vials of Fab} = \frac{\text{serum digoxin level (ng/mL)} \times \text{patient's weight (kg)}}{100}$

## 解藥的機轉

- Digibind: 從綿羊對Digoxin的IgG分離出來
- 使用Fab後血中digoxin濃度會迅速上升
  - 和抗體結合的digoxin上升10~20倍 (inactive)
  - Free digoxin (active) 下降至零
  - 和抗體結合後的Digoxin由腎臟排除。
    - 但對於腎臟功能不佳的患者，有可能在十幾天後再次中毒。



## 病患動向

- Discharge Criteria and Instructions
  - 急診患者
    - 無症狀的患者：Digoxin濃度正常、ECG正常、電解質正常。經過腸胃道除污及留觀12小時之後，可以考慮出院。
  - 住院患者
    - 腸胃道除污後，已無cardiac effect