“Botox” Poisoning
in
Update Series in Child Health
20 May 2017

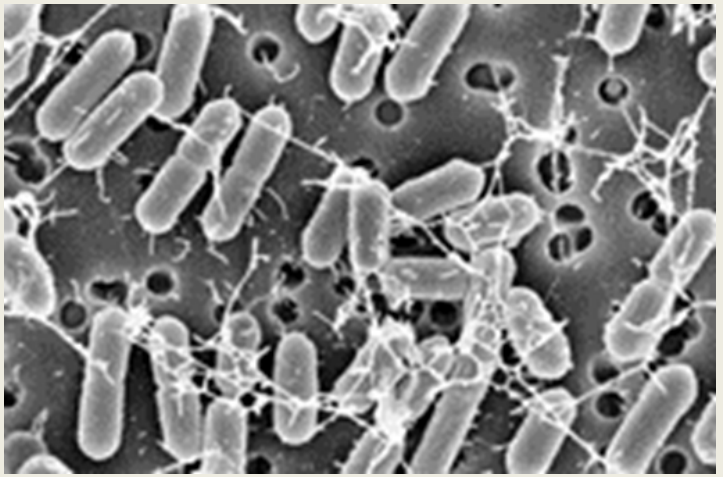
Dr Tse Man Li

Consultant i/c HKPIC

Botulinum Toxin

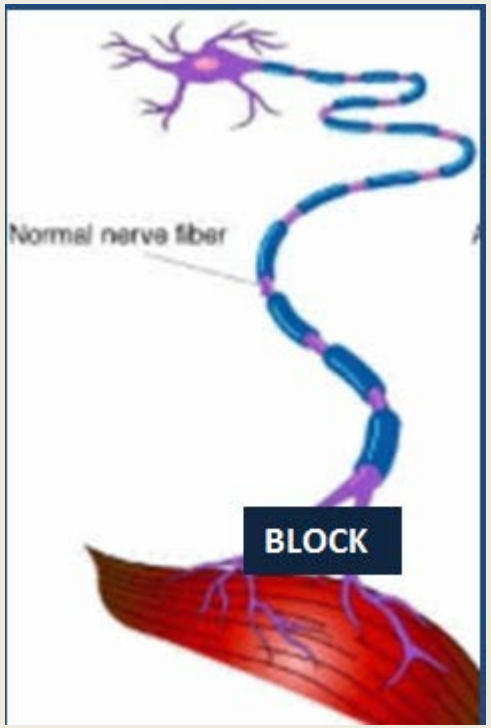
- Produced by bacteria – *Clostridia botulinum*
- Most toxic substance known
- LD50 1-10ng/kg
- >1000X more toxic than VX (nerve gas)
- >1000000 cyanide

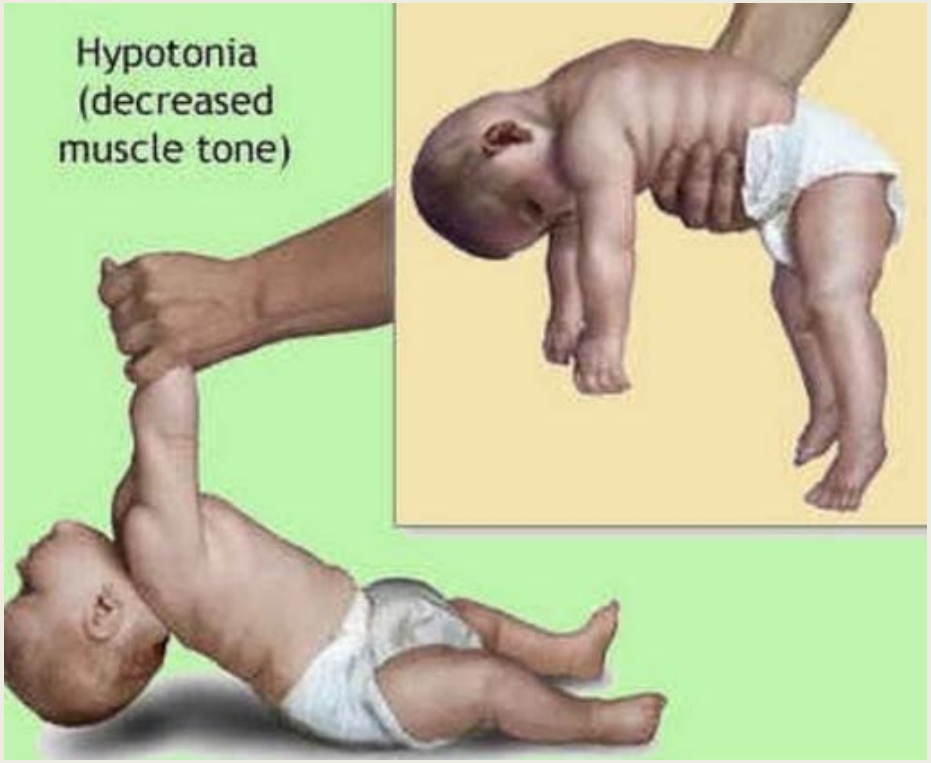
- 1gm kills 1 million people



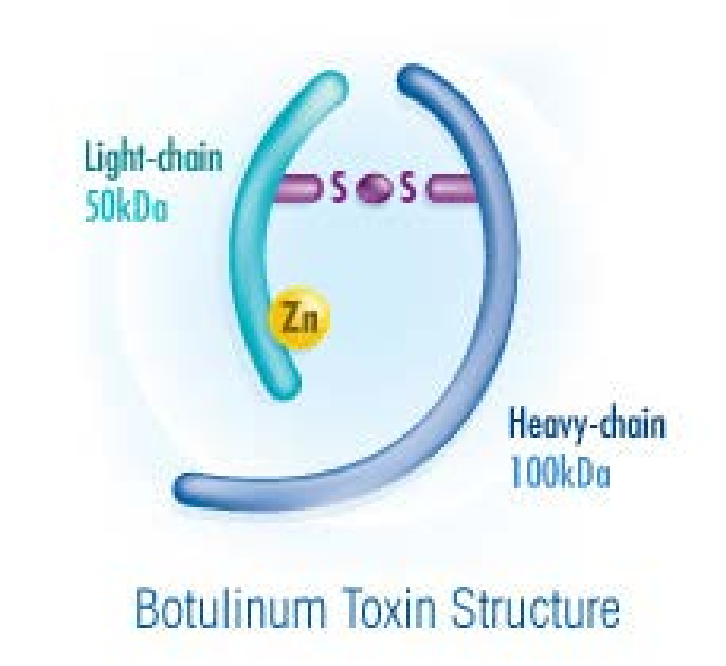
Action

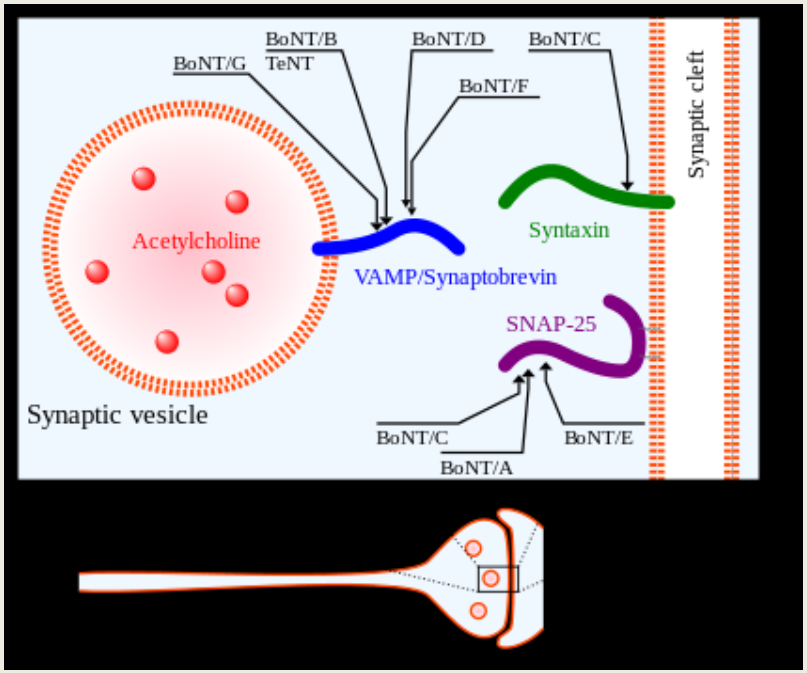
- Medical denervation of muscle
- Block Ach release





Botulinum toxin
Metalloprotease + Trojan horse





Botulism

- Clinical Types

- Food
- Wound
- Intestinal - Infant
- Inhalational
- Iatrogenic

- Toxin subtype

- A → H
- A,B,E,F,H affected human

Incidence (US)

- 110 cases / year in U.S.

- Infant botulism 72%
  - Ingestion of spores found in honey in <6/12 infant
  - Constipation, poor feeding, ↓ suckling and crying, floppy

- Wound 23%
  - Direct contact of open wound, injection drug user

- Food borne 5%
  - Onset : 2hr – 8 days, average 12-72 hr
  - Abdo cramp, N, V, D then paralysis

History of food Botulism

- 900s: typical poisoning by certain food
- 1793: blood sausages – Germany
- 1897: Botulinum bacillus first identified
- 1910: A & B Types toxins
- 1936: Type E isolated from smoked fish
- 1958: 新疆察布查尔病-米送乎乎
- 2006: Thailand - 163 cases
- 2013: Type H from stool sample of infant botulism
- Endemic in China, US, Alaska and Northern Europe


Bolthouse FARMS
Bolthouse FARMS
Bolthouse FARMS
VEDGE
Eye on Health
EYEWITNESS NEWS
Carrot Juice Warning
BOLTHOUSE FARMS

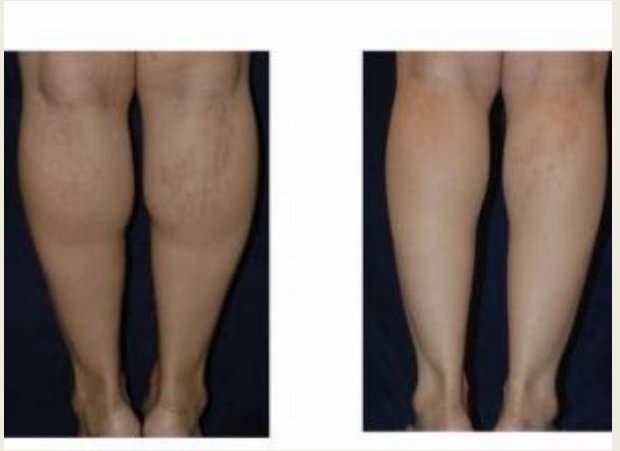
BoNT

- 1930s C. botulinum tested by Unit 731 in Manchuria
- WW II First weaponization test of the toxin by US Army
- 1990s 15000L concentrated BoTx in Iraq. At least 10000L in missiles and bombs
- 1990-1995 at least 3 ineffective attacks by Aum Shinrikyo in Tokyo

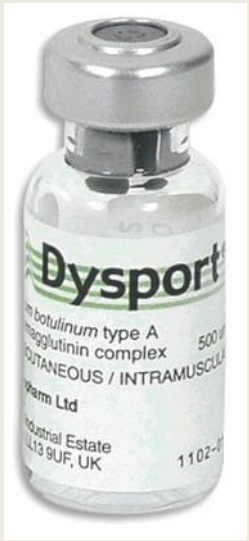
Two R-400A bombs in foreground photographed by UNSCOM inspectors at Murasana Airfield near the Al Walid Airbase in late 1991 bear markings indicating they were to be filled with botulinum toxin. Other bombs appear to have markings consistent with binary chemical agent fill. This evidence contradicted Iraq's declarations that it did not deploy BW munitions to operational airbases and that it destroyed all BW bombs in July 1991—declarations that were subsequently retracted in the face of overwhelming evidence to the contrary.

Therapeutic use

- 1973 Injected to monkey eye
- 1977 First human case for strabismus
- 1992 1st report for wrinkle
- After 2000 widespread cosmetic use
- Therapeutic use
  - Spastic conditions – skeletal and smooth muscles
  - Excessive sweating
  - Pain conditions: Migraine
  - Zoster ….
- **2016 Outbreak of iatrogenic botulism in China including Hong Kong**



Registered BoNT in HK



Therapeutic and Lethal dose

- Usual cosmetic use <200-400U

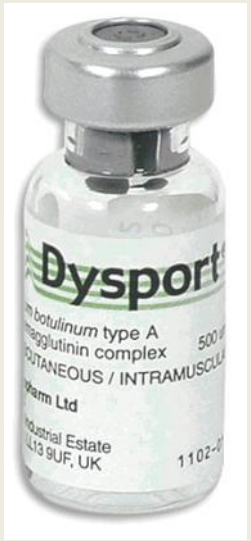
Introduction

Pharmaceutical grade botulinum toxin type A is being used for cosmetic and therapeutic purposes. It is produced from culture of *Clostridium Botulinum*. Registered pharmaceutical preparations in Hong Kong are:

Trade name	Dosage per vial
Botox	100u or 200u
BTXA	50u or 100u (marketed with the name *Lantox* and *Prosigne* in other regions)
Dysport	500u (125u and 300u preparations available in other regions)
Siax	100u (marketed with name *Neuronox*, with 50 and 200u preparations available in other regions)
Xeomin	50 or 100u

- Estimated human lethal dose by injection
  - 2,500 – 3,000U
  - Inhalation (X10)
  - Oral exposure (X500)

Registered BoNT in HK



Clinical Use

- Clinical effects
  - Onset 2-3 days
  - Peak 10- 21 days
  - Duration 8 – 12 weeks

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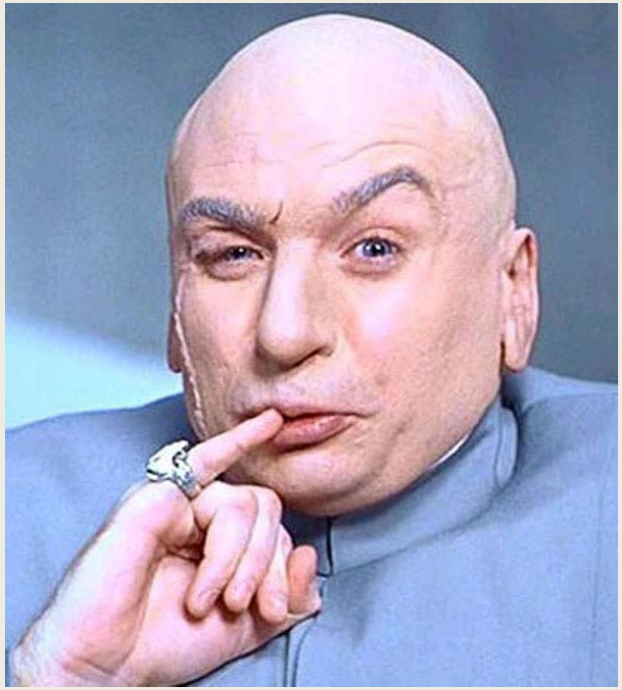
Xeomin	50 or 100u

- Spastic conditions: usual ceiling dose: 1000U but higher dose may be used
- Cosmetic injection: usually <200-400U

Cosmetic Injection – Good/Bad/Ugly

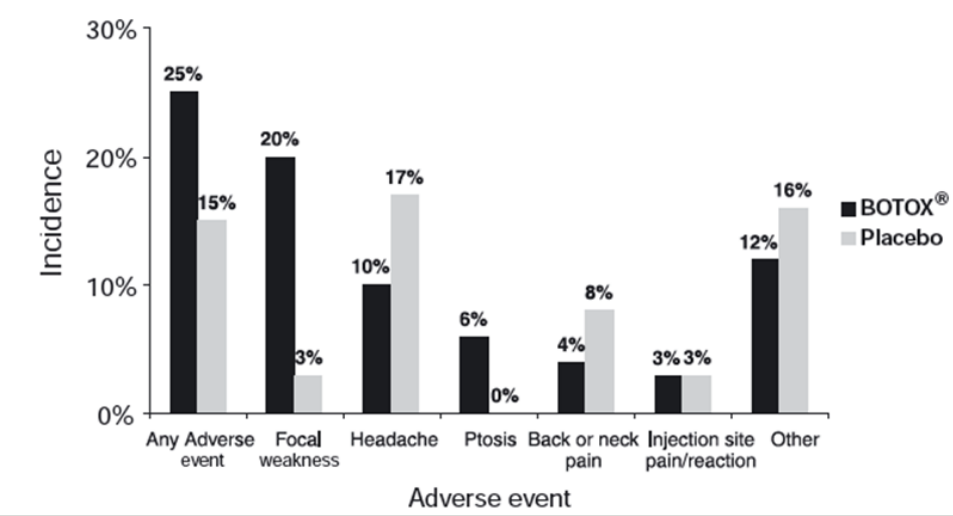


Adverse cosmetic outcome

- Blepharoptosis, eyebrow ptosis, non-allergic eyelid edema, spook's / evil eye brow, diplopia ectropion

Common ADR (1-10%)

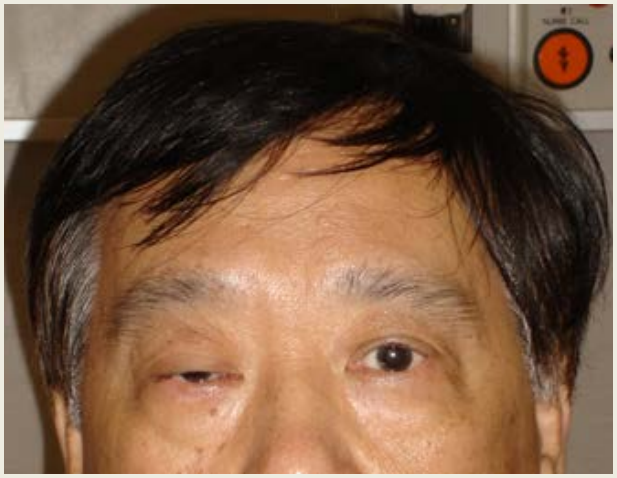
- Headache
- Fatigue
- Ptosis
- Weakness at site of injection e.g. difficulty chewing
- Migration effect: blurred vision, diplopia, dysphagia, dysphonia, dry mouth, weak grip



Naumann M 2004. Safety of botulinum toxin type A: a systematic review and meta-analysis

Therapeutic Use

- Higher dose higher risk
- <1000U or 20U/kg (Botox) recommended
- Units not really standardized
- Botox 100U ~ Dysport 500U
- US (mouse) unit > UK??
- Tolerance effect may limit to one brand but not the other
- Be careful when change of brand same dose may cause excessive weakness



Systemic weakness

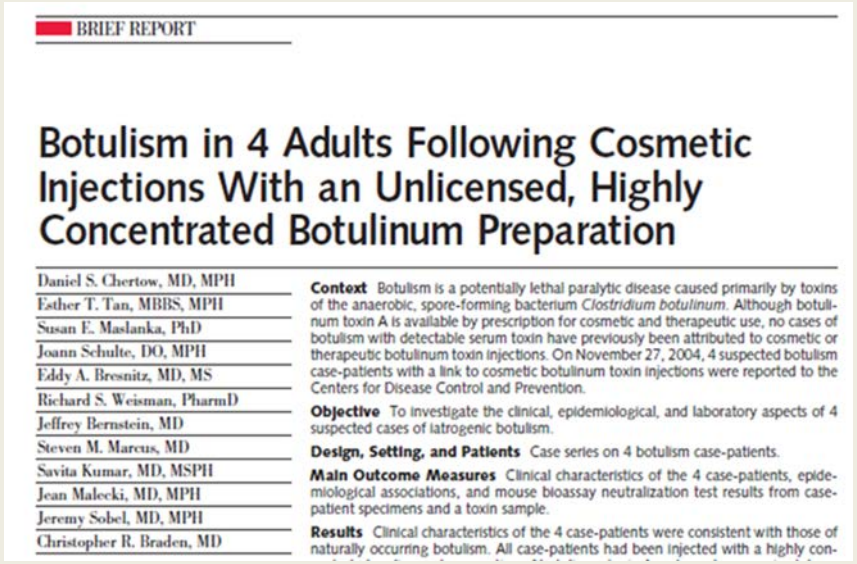
Age/ sex	*Injections for (primary diagnosis)*	*Prior years of injections*	*Muscles injected /total dose*	*Distribution of weakness*	*Onset /duration*
Our patients:					
45/F	Cervical dystonia	5	scm, splenii, /650 U/Dys	Generalised UL>LL dysphagia	1 week /6 months
57/F	Arm dystonia (symptomatic hemidystonia)	2.5	L arm /900 U/Dys	Generalised UL>LL	2 weeks /3 months
32/F	Leg dystonia (symptomatic hemidystonia)	2.5	L foot /600/Dys	Generalised UL>LL dysphagia	1 week /3 months
Reported cases (Bakheit *et al*[8])					
67/F	Spasticity (MS)	nil 1×injection	L leg /250 U/Dys	Generalised LL>UL dysphagia ptosis	4 days /4 weeks
34/F	Torticollis (MSA)	5	scm, splenius /250 U/Dys	Generalised proximal dysphagia	3 weeks /4 months

Bakheit AM 1997
Bhatia KP 1999

- Progressive generalized weakness
- Happened despite received same dose in repeated injections
- Get into blood stream?

Systemic weakness – Iatrogenic botulism

- Occurred rarely
- Death reported in children
- One outbreak reported in US after black-marketed undiluted BoNT used
- Ventilated x ½ year
- Weakness >5 years



BRIEF REPORT

Botulism in 4 Adults Following Cosmetic Injections With an Unlicensed, Highly Concentrated Botulinum Preparation

Daniel S. Chertow, MD, MPH
Esther T. Tan, MBBS, MPH
Susan E. Maslanka, PhD
Joann Schulte, DO, MPH
Eddy A. Bresnitz, MD, MS
Richard S. Weisman, PharmD
Jeffrey Bernstein, MD
Steven M. Marcus, MD
Savita Kumar, MD, MSPH
Jean Malecki, MD, MPH
Jeremy Sobel, MD, MPH
Christopher R. Braden, MD

Context Botulism is a potentially lethal paralytic disease caused primarily by toxins of the anaerobic, spore-forming bacterium *Clostridium botulinum*. Although botulinum toxin A is available by prescription for cosmetic and therapeutic use, no cases of botulism with detectable serum toxin have previously been attributed to cosmetic or therapeutic botulinum toxin injections. On November 27, 2004, 4 suspected botulism case-patients with a link to cosmetic botulinum toxin injections were reported to the Centers for Disease Control and Prevention.

Objective To investigate the clinical, epidemiological, and laboratory aspects of 4 suspected cases of iatrogenic botulism.

Design, Setting, and Patients Case series on 4 botulism case-patients.

Main Outcome Measures Clinical characteristics of the 4 case-patients, epidemiological associations, and mouse bioassay neutralization test results from case-patient specimens and a toxin sample.

Results Clinical characteristics of the 4 case-patients were consistent with those of naturally occurring botulism. All case-patients had been injected with a highly con-

Iatrogenic Botulism outbreak 2016

May 2016

Fan KL. J EM 2016

24 May 2016 -1st case in Hong Kong

- F/47 on 24/5/2016
- D5 after 250 unit “Botox” into both calves
- In friend’s beauty centre in SZ
- Progressive weakness since D1
- Dizziness
- Weakness , mild ptosis, dysphagia and SOB
- FVC = 1.2-1.4L
- 15000IU (20ml) Trivalent Botulinum antitoxin given
- Subjective improvement DAMA 27/5/2016

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4+/4  |  4+/4
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3 /5  |  3 /5
brisk reflexes
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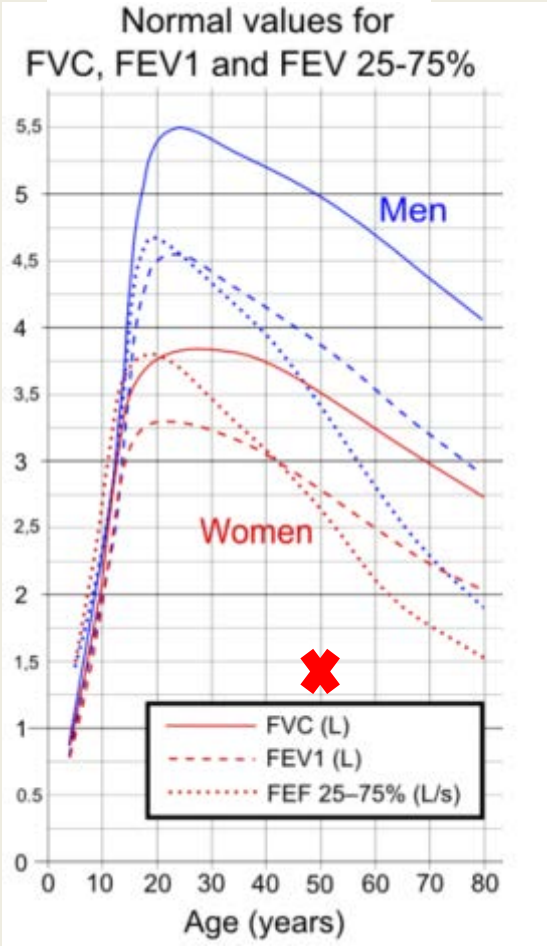


DH: 1st PR and Letter to Doctor

主頁 >> 新聞公報 >> 二零一六

衞生防護中心調查注射肉毒桿菌毒素後懷疑肉毒中毒個案

衞生署衞生防護中心今日（五月二十七日）正調查一宗在內地注射肉毒桿菌毒素後出現肉毒中毒的

根據主診醫生提供的資料，該名四十七歲女病人過往健康良好，自五月二十一日起出現逐漸乏力，
接受治療。她於五月二十五日被轉往深切治療部接受觀察及治理。她昨日被轉往普通病房，情況稳

二零一六年五月二十七日

2nd case

- F/41
- Botox injection in Shenzhen
  - Forehead, neck, cheek, periorbital area on 9/5/2016
- Symptoms onset on 10/5/2016
  - Neck muscle weakness and dysphagia
  - Static over 3 weeks
- Presented on 29/5
  - Antitoxin not recommended
  - Observe and R/O other causes
- D/C on 3/6

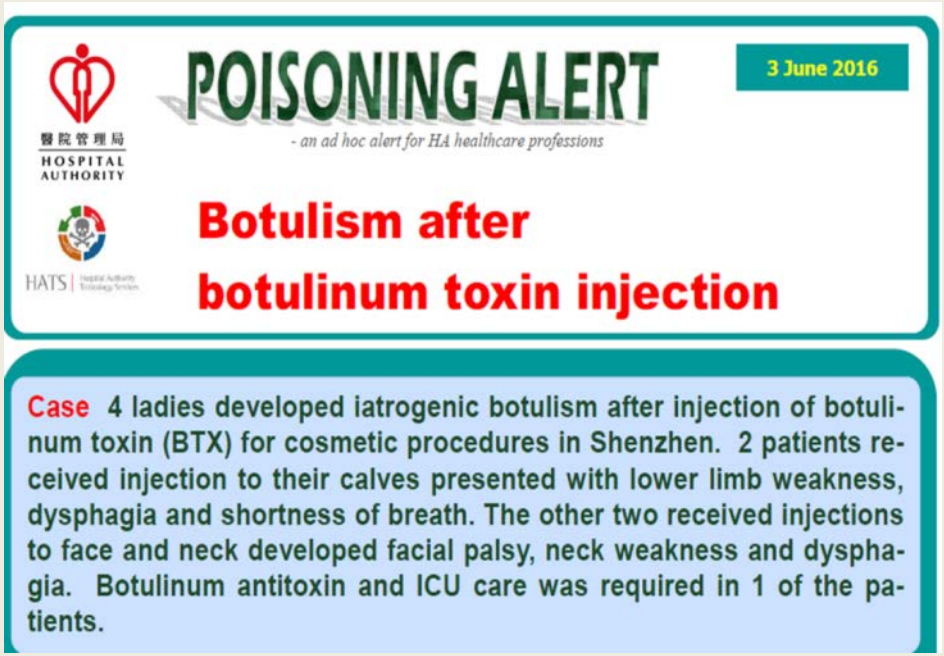
Progress

- Observation and supportive measures

- Power of 4 limbs remained 5/5
- Neck power slowly improving, flexion 3-4/5, extension 4
- No facial asymmetry
- NCS and RST not suggestive of MG

- Discharged on 3/6/2016

Response by HATS



醫院管理局
HOSPITAL AUTHORITY

HATS | Hospital Authority Toxicology Service

POISONING ALERT

3 June 2016

- an ad hoc alert for HA healthcare professions

Botulism after botulinum toxin injection

Case 4 ladies developed iatrogenic botulism after injection of botulinum toxin (BTX) for cosmetic procedures in Shenzhen. 2 patients received injection to their calves presented with lower limb weakness, dysphagia and shortness of breath. The other two received injections to face and neck developed facial palsy, neck weakness and dysphagia. Botulinum antitoxin and ICU care was required in 1 of the patients.

- Increase the stock-level of anti-botulinum anti-toxin to 12 vials
- Each $37500

Case 4

- F/21
- Bought discounted coupon through WeChat in SZ
- 22/5 Calf Injection in SZ
- 24/5 Flu-like + difficulty swallowing
- Subjective weakness face, neck and limbs
- Static x 1/52
- Presented 1/6/2016
- Diplopia → left
- FVC 1.98-2.46L
- Anti-toxin?

Case 4

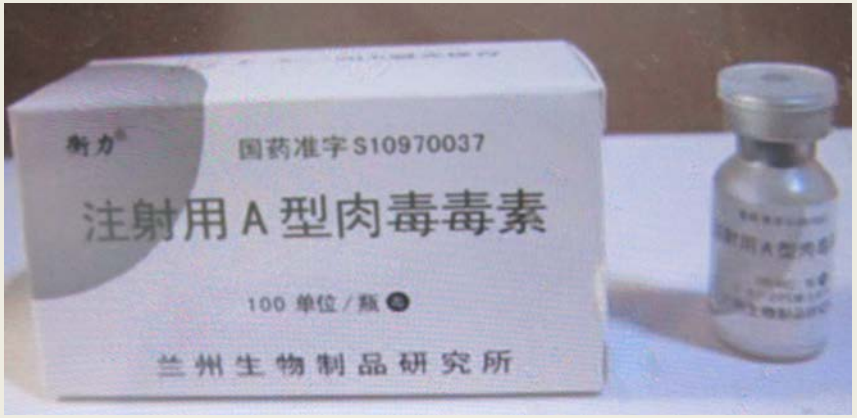


Image of the alleged BoTx injected sent to patient by the beauty centre

Transferred to PTC for clinical observation
Improving symptoms
Anti-toxin not needed

Outbreak of Iatrogenic Botulism- 2016

Sex	Age	Injection date	Injection site	Date of presenetation	Anti-toxin
F	47	20/5/2016	calf	24/5/2016	+ve
F	47	9/5/2016	face	29/5/2016	-ve
F	21	22/5/2016	calf	1/6/2016	-ve
F	21	23/5/2016	calf	9/6/2016	+ve
F	41	24/5/2016	face	2/6/2016	-ve
F	38	20/05/2016 ?20/6/2016	face	21/6/2016	-ve
F	33	late may	upper limbs	21/6/2016	-ve
F	42	8/7/2016	calf	19/7/2016	+ve
F	38	4/7/2016	face	19/7/2016	-ve
F	46	20/7/2016	face	3/8/2016	-ve
F	22	Early April/2016	calves	26/4/2016	-ve
F	32	8-13/2/2017	calves	20/2/2017	-ve

- 12 cases in Hong Kong recorded by HKPIC

Case No 9

- D11 after 300U injection to calves in China for RMB5000
- Blurring of vision, progressive UL weakness
- Walk OK but cannot rise from squatting position
- 3/5 UL ; 5-/5 LL
- PFR : 220-280 L/min

Progress

- IVI 50ml trivalent Botulinum antitoxin (Equine)
- Static condition
- D/C 48 hrs after presentation
- UL 2/5 power
- Cannot comb, brush teeth, feed.

Progress

- FU Day 28 post-injection – can raise UL now, blurring of vision persisted
- D30 (re-presented for fever 39°C, urticarial rash and myalgia
- CRP 24, WCC 9.7, -ve sepsis workup

Serum Sickness

- Rapid resolution of symptoms with Anti-histamine, NSAID and steroid

- Defaulted FU

- Type III hypersensitivity
- Immune complex mediated
- Onset 7 (5-24days)
- Fever + skin + arthralgia
- bronchospasm
- Hypertension, neurological
- Anti-allergy treatment
- Plasmapheresis ?

Hypersensitivity reactions associated with botulinal antitoxin

American Journal of Medicine. 69(4):567-70, 1980 Oct

- 11-year period (1967 through 1977)
- CDC monitored reactions of hypersensitivity to antitoxin of equine origin.
- 9.0 % (24/268) – hypersensitivity reactions

  (5.3 % - acute and **3.7 % - delay reaction** to a skin test or therapeutic dose)
- Non-fatal reaction
- Probably not Fab?

First large scale outbreak of Iatrogenic botulism

- 2016 China
- In most large cities
- Hong Kong 2016 -2017 12 cases
- Likely due to Illicit product with variable BoNT concentration

◀「毒針」風暴後，多個北上「整容團」如常出團，中介更租用豪宅接待港女排隊打針。

兩周5宗中毒
港女唔怕死照北上

短短兩周內，接連有五名貪靚女士在內地注射肉毒桿菌後出現氣促，呼吸困難等嚴重徵狀。打「肉毒針」隨時搞出人命，但本刊發現北上「整容團」依然極之活躍，帶團的中介更在社交平台Instagram，吹噓內地打美容針「平靚正」，「醫生主理，唔使開刀，幾分鐘變女神，天天出發！」吸引不少港女膽粗粗唔怕死「報團」，「香港打一次，（價錢）夠我喺深圳打三次，無咁易中招嘅。」有「團友」說。

本刊跟隨這些「打針團」北上，只見所有「團友」被安排到羅湖一間簡陋的醫生宿舍，由一名自稱是內地的醫生負責打針，但過程相當兒戲，醫生沒詳問病歷，也沒介紹針劑來歷及劑量，打針時更沒戴手套。帶團的中介更「搏死」，為求做成生意，明知記者有藥物過敏，中介仍猛力游說：「打咗先，少少敏感啫，唔緊要。」期間更落足嘴頭硬銷風險極高的抽脂手術。

本刊接觸一名港女，在使用「外賣打針」服務瘦大腿後，出現嚴重炎症，三個月不良於行，「貪平換來一身蟻！」悔不當初的她慨歎說。

▼ 打肉毒桿菌針去皺的需求龐大，針劑產地眾多，包裝素參差，部分更是來歷不明。

亂打來歷不明肉毒針

「李主任」（左一）為賺外快，在簡陋的宿舍為客人打美容針，但全程未戴上手套，衛生意識成疑。

◀ 不少港女貪平，北上深圳打美容針。

Injection打肉毒 on social media


LOT: FAA15103
Exp: SEP.18,2018
Neuronox
100 units


DAEWOONG
BOTULINUM TOXIN TYPE A
NABOTA
BOTULINUM TOXIN TYPE
100


衡力
只看楼主
收藏
回复
衡力900
白肉200u1180
粉肉1190
hardcandy美颜
高级粉丝
送TA礼物
分享
举报 | 来自iPhone客户端 1楼 2016-05-13 19:58 回复


Botulax 100
보툴렉스 100

国家食品药品监督管理总局 CFDA
China Food and Drug Administration

总局关于注射用A型肉毒毒素的消费警示

2016年06月02日 发布

据卫生计生委通报，近期北京、上海、浙江、广东等省（区、市）部分医院陆续收治了一批因在非医疗机构注射不明物质而紧急送治的患者，均有神经中毒的特点。患者入院前，曾为瘦脸、瘦腿等美容需求，在非医疗机构注射过“肉毒素”。为保护消费者切身利益，引导消费者选择合法正规的产品和服务，国家食品药品监督管理总局提醒消费者：

不当使用注射用A型肉毒毒素可能会引起肌肉松弛麻痹，严重时可能会引发呼吸衰竭、心力衰竭等危及生命健康的症状。食品药品监管部门规定，药品生产和进口企业应指定具有生物制品经营资质的药品批发企业作为A型肉毒毒素制剂的经销商；药品批发企业只能将A型肉毒毒素制剂销售给取得《医疗机构执业许可证》的医疗机构或医疗美容机构，未经指定的药品经营企业不得购销A型肉毒毒素制剂。消费者应到取得《医疗机构执业许可证》的正规医疗机构或医疗美容机构进行注射美容。

目前，国家食品药品监管总局仅批准上市了两种注射用A型肉毒毒素，分别为兰州生物制品研究所生产的国产产品（商品名：衡力）和Allergan Pharmaceuticals Ireland生产的进口产品（商品名：保妥适 BOTOX），产品包装见下图，请消费者使用时注意辨别。兰州生物制品研究所在全国29个省份指定了77家经销商（见附件1）。国药控股分销中心有限公司是进口产品（保妥适）的总经销，目前在全国30个省份指定了56家二级经销商（见附件2）。医疗机构或医疗美容机构应当向经药品生产和进口企业指定的经销商采购注射用A型肉毒毒素。

Warning to Public

5/8/2016 CCTV Report

Likely cause

- Illicit BoNT containing product
- Unstable concentration resulting in overdose
- Poor technique
- Black market of BoNT exists!

南京捣毁大型制假肉毒素工厂，案值上千万元

DrZhou皮肤美容医生 V | 2016-06-16 06:46:43 | 举报 | 阅读数：1625

南报网（记者邹伟通讯员杨维斌）

11th case

- F/21 admitted on 26th April for progressive weakness
- Rx as generalized myasthenia gravis with improvement
- Self-cessation of all drugs in July and well
- In September she gave the Hx of BoNT injection to calves in April in SZ
- Actually the last was the first case in 2016 !

Mx of Iatrogenic Botulism

- **Clinical features**
  - **Systemic upset – headache, flu-like, postural symptoms**
  - **Dry mouth, blurred vision**
  - **Descending paralysis**
  - **Onset 24-48 hrs after injection**
  - **Progress and plateau after 1 week**
  - **Improved after months**
- **Dx**
  - **Relies on Hx**
  - **DDx Guillain–Barré syndrome syndrome esp Miller-Fisher variant, Myasthenia, Gelsemium poisoning etc.**
  - **NCS & EMG show motor denervation without slowing in nerve conduction or myoapthy, may help to R/O other causes but not specific**
  - **No diagnostic test available**
- **Rx**
  - **Supportive**
  - **Consider anti-toxin if progressive weakness particularly if swallowing and breathing affected**

Round up

- BoTN is the most toxic substance
- Big therapeutic value but also an extremely lethal bioweapon
- BoTN overdose as a DDx for progressive descending weakness
- Call HKPIC in case of suspected botulism


Hong Kong
Poison Information Centre
2772 2211
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We provide poison information and management advice on:
Pharmaceutical Chinese Medicine Household Products Natural Toxins Industrial Chemicals