三總藥訊
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藥物不良反應之重要性(二)

There are no really "safe" biologically active drugs

There are only "safe" physicians

● 前言:

筆者依據本院91/09/17對醫療相關人員所作的藥物不良反應(Adverse drug reactions, ADRs)回報系統之問卷，經交叉分析綜整得知---有92.6% (1256/1357)的醫療人員覺得此回報系統相當重要，只有3%(41/1357)不在意此回報系統的存在。在此僅就ADR之嚴重性及因果判定關係分述於後。

● 國外嚴重藥物不良反應事件之探討：

1.根據1993年一篇回顧性文章研究顯示：因為藥物不良反應而住院的有0.2-21.7%。

2.1998年發表於JAMA，收集39個前瞻性研究，經meta-analysis 所作的報告指出:

❶ 住院病人發生嚴重ADR的發生率為6.7%，致死性ADR的發生率為0.32%。

❷ 估計美國於1994年，約有220萬住院病人發生嚴重ADR，及約有10萬住院病人發生致命性ADR。

3.根據2001年一篇研究顯示:

◆ 有67%的致死性藥物不良反應是可以被預防的，而其中有57%是由藥師預防的。(表1)

Table 1
Preventability of Fatal Adverse Drug Events (ADEs) by Severity of Illness ($n = 376$)

Patient Status	No. Patients (%)	No. (%) Fatal ADEs	
		Preventable	Preventable by Pharmacist
Relatively healthy	150 (39.9)	101 (67.3)	58 (57.4)
Moderately healthy	136 (36.2)	101 (74.3)	54 (53.5)
Severely ill	74 (19.7)	44 (59.5)	27 (61.4)
Terminally ill	16 (4.3)	7 (43.8)	6 (85.7)

◆ **最常被懷疑造成致死性不良反應的藥物與機轉(表2)**

Table 2.
Drugs and Mechanisms Most Commonly Suspected of Inducing Fatal Adverse Drug Events[a]

Adverse Drug Reaction	Allergy	Error	Interaction	All[b]
Amiodarone	Antineoplastics	Chlorpromazine	Bleomycin	Valproic acid
Bleomycin	Carbamazepine	Halothane	Clozapine	Cyclophosphamide
Carbamazepine	Ciprofloxacin	Lidocaine	Filgrastim	Bleomycin
Cyclophosphamide	Diatrizoate	Meperidine	Hydralazine	Trimethoprim–sulfamethoxazole
Diatrizoate	Diphtheria and tetanus toxoids and pertussis vaccines	Morphine	Hydrochlorothiazide	Diatrizoate
Doxorubicin	Gold salts	Phenylbutazone	Lithium	Halothane
Methotrexate	Lidocaine	Propranolol	Phenytoin	Sulfasalazine
Mitomycin	Methyldopa	0.9% sodium chloride injection	Warfarin	Amiodarone
Propofol	Methylprednisolone	Theophylline		Antineoplastics
Sulfasalazine	Nomifensine	Valproic acid		Methotrexate
Trimethoprim–sulfamethoxazole	Penicillamine			Ciprofloxacin
Valproic acid	Phenobarbital			Carbamazepine
	Quinine			Penicillamine
	Sulfasalazine			Methylprednisolone
	Trimethoprim–sulfamethoxazole			Methyldopa

[a]Listed in order of decreasing frequency.
[b]All drugs causing fatal adverse drug events by all mechanisms. Listed in order of frequency.

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◆ **對病患監控得愈好可能可以預防更多的致死性藥物不良反應事件。對病患較好的監控和病患服用藥物之前對醫囑的回顧是預防致死性藥物不良反應最主要的機轉。(表3)**

Table 3
Possible Mechanisms for Preventing Fatal Adverse Drug Events (ADEs) ($n = 271$)

Mechanism	No. (%) Fatal ADEs
Better patient monitoring	73 (26.9)
Prospective review of orders	55 (20.3)
Computer screening	48 (17.7)
Patient risk assessment	23 (8.5)
Concurrent regimen review	22 (8.1)
Patient education	11 (4.1)
Physician education	9 (3.3)
Other	30 (11.1)

◆ **有26例致死性藥物交互作用產生，依嚴重性分類由Category 1 至 Unclassified 不等。其中42%為Unclassified，而Category 3也有39%之多(表4)。在55%的案例中，發生不良反應之用藥期間為1-7天。在27%的案例中，產生交互作用的藥物使用少於24小時。**

顯著性級數	嚴重度	証據
1	Major	Suspected or >
2	Moderate	Suspected or >
3	Minor	Suspected or >
4	Major/Moderate	Possible
5	Minor	Possible
Unclassified	Any	Unlikely

Table 4
Drug Interactions Suspected of Contributing to Fatal Adverse Drug Events (ADEs) ($n = 26$)

Severity Level*	No. (%) Fatal ADEs	Definition	Object Drug	Participant Drug
Category 1	1 (3.8)	Avoid combination. Risk always outweighs benefit.	Phenelzine	Phenylpropanolamine
Category 2	2 (7.7)	Usually avoid combination. Use combination only under special circumstances.	Apazone Methotrexate	Warfarin Naproxen
Category 3	10 (38.5)	Minimize risk. Take action as necessary to reduce risk.	Acetaminophen Clozapine Cyclosporine Diazoxide Gentamicin Lithium Phenytoin Phenytoin Tarazone	Alcohol Carbamazepine Ketoconazole Hydralazine Amphotericin B Haloperidol Warfarin Isoniazid Trifluperazine
Category 4	2 (7.7)	No action needed. Risk of adverse outcomes appears small.	Lorazepam Streplase	Clozapine Heparin
Category 5	0 (0)	Evidence suggests no interaction.		
Unclassified	11 (42.3)	Not listed.	Amiodarone Bleomycin Bleomycin Cyclophosphamide Hydrochlorothiazide Lithium Magnesium sulfate Medroxyprogesterone Succinylcholine Tolazoline Zinc sulfate	Contrast media Cisplatin Filgrastim Filgrastim Methyldopa Hydrochlorothiazide Hydralazine Radiation therapy Thiopental Dopamine Penicillamine

4.另一篇2002年回顧性研究報告顯示:

- **有**13.8% (94/681) **的病患被斷定因藥物相關問題(**Drug- related problems , DRPs**)而住院，其中有**99**種症狀是因**ADRs **所致。屬於** type A **的藥物不良反應佔**91% **，因果關係確定的有**8**例，可能的有**17**例，而很可能的有**74**例。最常見的不良反應是心臟血管疾病佔**36.3%**。**
- **有**19**位病患被認定為嚴重性不良反應，出血是最常見的現象，其中有**4**位死亡，**3**位被判定與藥物有關— 內因**Aspirin **造成腸胃出血致死有**2**例，因**Tamoxifen**造成肺栓塞而死的有**1**例。(表**5**)**

Table 5 Serious and fatal adverse drug reaction in 19 patients

Drugs	Manifestation
Aspirin	Anaemia
Aspirin	Gastrointestinal bleeding*
Aspirin	Gastrointestinal bleeding*
Aspirin and felodipine	Cerebral haemorrhage
Ciprofloxacin	Seizures
Cyklophosphamide and doxorubicin	Heart failure
Enalapril	Renal failure
Ethinyloestradiol/desogestrel	Renal vein thrombosis
Ethinyloestradiol/levonorgestrel	Venous thrombosis
Ethinyloestradiol/levonorgestrel	Myocardial infarction
Human insulin	Insulin coma
Metoprolol	AV- block III
Naproxen	Anaphylactic shock
Oestriol	Thrombo-embolism
Paracetamol	Liver disorders
Prednisolone	Pulmonary embolism
Tamoxifen	Pulmonary embolism*
Venlafaxine	Liver disorders
Warfarin	Major bleeding

*Fatal outcome possibly related to medication.

◆值得一提的是: 主要的ADRs是屬於 type A的藥物不良反應，而這種 type 的ADRs是可預測和可預防的，由此顯示[提升用藥安全]的重要性。在預防上的措施，包括藥物的監測、增加教育及建議醫療人員重視用藥安全問題等等。

Type A 和 Type B 的比較：

	Type A	Type B
Pharmacologically predictable	Yes	No
Dose-dependent	Yes	No
Incidence	High	Low
Morbidity	High	Low
Mortality	Low	High
Management	Dosage adjustment often	Appropriate

5.以上諸多文獻顯示: 臨床醫療相關人員在使用上述所提及的藥物時，應提高警覺性，以降低致死率及ADRs的嚴重度。

● 藥物不良反應之因果關係判定：

1. 如何確認由某個藥物導致不良反應呢? 可遵循以下五點

❶ 注意發生不良反應時間點所使用的藥物

❷ 注意可能造成不良反應的已存在或不存在的其他因素

❸ 注意停用某藥後的結果(dechallenge)

❹ 注意再給某藥後的結果(rechallenge)

❺ 其它與此不良反應有關的相關資訊(包括:實驗值、過去病史、以前有無此案例等等)

2. 就本院 89-91 三年內發現之藥物不良反應案例，共 155 件。依藥物分類、發生之器官、嚴重度、造成原因、如何處理、處理結果、因果關係、學理分類、可否預防及回報者背景等變項，做分析。
其中總案例之因果分類，根據 Naranjo 之可能性評估表格(見下頁)來判定：以很可能類佔 63%（98/155），可能類佔 32%次之，確定的佔 5%再次之。總案例之因果分類及其所佔百分比如下表所示。

表．總案例之因果分類

很可能	可能	確定	存疑的	非藥物造成
98 例(63%)	50 例(32%)	7 例 (5%)	0 例	0 例

Naranjo questionnaire:

三軍總醫院

不良反應由藥物造成之可能性評估表

病人姓名:_____ 病歷號:_____ 病房/床:_____

請將下列各問題的得分相加，來確認是否真的是由藥物所造成的不良反應

≦0：存疑　　1-4：可能　　5-8：很可能　　≧9：確定

	是的	不是	不知道	分數
1.是否以前有斷定性的報導，的確所懷疑之藥物會產生此不良反應?	+1	0	0	_____
2.此不良反應是否在用了所懷疑的藥物後才出現?	+2	-1	0	_____
3.此不良反應是否在停掉所懷疑的藥物或給予特定拮抗劑後就改善了?	+1	0	0	_____
4.再使用此所懷疑藥物後，不良反應是否又再出現?	+2	-1	0	_____
5.是否有其它的原因(所懷疑藥物以外)會造成此種不良反應?	-1	+2	0	_____
6.當給予安慰劑時，此不良反應是否會出現?	-1	+1	0	_____
7.是否所懷疑藥物之血(或其它體液)中濃度是會造成毒性反應?	+1	0	0	_____
8.此不良反應是否與藥物的劑量高低有關?	+1	0	0	_____
9.病人是否從前對所懷疑藥物或類似結構的藥物有相似的不良反應?	+1	0	0	_____
10.是否有其它客觀的證據可證實目前的不良反應?	+1	0	0	_____

總分:_____

類別:_____

藥師:_____ 日期:_____

3. WHO 在評估因果關係所定之準則如下:

Table . WHO criteria for causality assessment

Certain: a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/likely: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Conditional/unclassified: a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unassessible/unclassifiable: a report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

● 結論：

由於 ADRs 的回報率過低，導致罹病率及致死率低於預估量。根據近年來的流行病學証據顯示，預估 ADRs 將高居死亡的第4至第6位。由此可知藥物不良反應之重要性。
在此提供醫師一些簡單的方法，可預防 ADRs 的發生和用藥疏失----

1. 記錄所有用藥，特別是對某藥過敏及屬於那一種 type的過敏。
2. 專注於處方的書寫: 包含正確劑量、適當劑型(如: Controlled Release 或 Un-CR)、避免縮寫和留意藥名相似的藥物(如: Celebrex vs Celexia)。
3. 熟悉常見的副作用和交互作用。
4. 儘可能選用口服途徑，因為此為最安全的服藥方法。
5. 特殊族群(老年人、幼兒、孕婦等)應給與特別的照顧。

筆者希望能透過此次連載之宣導，喚醒大家對用藥安全之警覺，以提升所有本院病患之醫療品質。

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