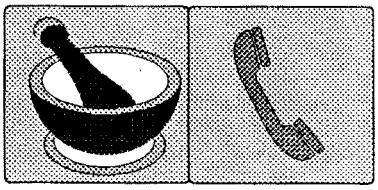
台中榮總藥訊

VGHTC Drug Bulletin



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超級比一比

比較 Fluoroqunolone 引起的 QT interval 延長及 torsade de pointes

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所謂 QT interval 是指心室去極化及再極化的時間。在健康的情況下 QT interval 為小於或等於 400 msec. 而經過與心跳速率關係的校正後（QTc）為小於或等於 440 msec 男女間略有差異：當男士大於 450，女士大於 470 則視為 QT interval 延長。（見表一）

表一、CPMP Suggested Ranges for QTc Intervals (msec)

QTc[a]	Men	Women
Normal	< 430	< 450
Borderline	430-450	450-470
Prolonged	> 450	> 470

QT interval 的過度延長可能導致心室心律不整或昏厥或猝死…等等。Torsade de pointes (Tdp) 是一種快速，多形性之心室心搏過速，係因 QT interval 延長所致。藥品引發的 QT interval 延長，多與鉀離子通道受阻有關，但由於藥品引起的頻率相當低。

會造成 QT interval 延長,甚至是 Tdp 的藥品，依其可能性被劃分成三大類：definite, probable, and proposed association, 詳見下表二。

依據 adverse event data submitted to US Food and Drug Administration（FDA）Spontaneous Reporting System (1969 to 1997) 及 the Adverse Events Reporting System （1997 and thereafter）從 1996 年一月至 2001 年五月的 fluoroquinolone 所做的 the crude rates of TORSADE DE POINTES 針對五個不同的結果。（見表四）

與 ciprofloxacin 相比，gatifloxacin 和 levofloxacin 的 crude rates of torsade de pointes 是 ciprofloxacin 的 90 和 18 倍之多，（p less than 0.001, either comparison），而 gatifloxacin 則為 levofloxacin 的 5 倍（p=0.001）（Frothingham, 2001）.

現將 Fluoroquinolone 對心臟之動物實驗結果整理如下（表五），供大家參考。

表二、Drugs Associated with QT Interval Prolongation

Drugs by Class	Association[a]	Torsadogenic[b]	FDA Labeling[c]	Comments
Gatifloxacin	Probable	---	QT	
Grepafloxacin	Definite	---	NA	Removed from U.S. market
Levofloxacin	Proposed	---	TDP	Lower risk than that of similar agents.
Moxifloxacin	Probable	---	QT	Lower risk than that of similar agents.
Sparfloxacin	Definite	---	NA	Removed from U.S. market

FDA = United States Food and Drug Administration; QT = QT interval prolongation; TDP = torsade de pointes; NA = not applicable;
[a]Associations are based on the strength of evidence that supports whether QT prolongation can occur. This categorization does not delineate an individual patient's risk of QT prolongation.
[b]Torsadogenic potential is divided into four categories as characterized in a previous publication[9]: high = drugs that are potent blockers of currents prolonging myocardial repolarization; medium high = drugs that prolong myocardial repolarization at higher doses, or at normal doses with concurrent administration of drugs that inhibit drug metabolism; low = drugs that prolong action potential duration and QT interval at high doses or concentrations that are clearly above the therapeutic range; and not clear = drugs that block repolarizing ion currents in vitro but that have so far not been shown to prolong repolarization in other in vitro models.
[c]Describes whether the FDA-approved product labeling includes mention of QT prolongation, torsade de pointes, or both.

另外, Fluoroquinolone 所致的 TDP 會因一些個人因素而有差異。以下表三為 FDA 所歸納出可能因服用或注射 Fluoroquinolone 導致 TDP 的個人因素。

表三、Characteristics of Patients Developing Torsade de Pointes From the FDA Adverse Event Reporting System

Characteristics	Macrolide	Fluoroquinolone
Age, y	61+/-22	72+/-15
Female, %	70	67
Mean baseline QT, msec	432+/-50	434+/-44
Event QT, msec	594+/-80	530+/-151
Fatal outcomes, % (n/N)	9 (14/156)	13 (6/46)
Patients receiving concomitant drugs known to prolong QT, %	22	24

表四、Fluoroquinolone 發生 TDP 之比較：

AGENT	NUMBER OF U.S. CASES REPORTED	CASE RATE (PER 10 MILLION PRESRIPTIONS)
Ciprofloxacin	2	0.3
Gatifloxacin	8	27
Levofloxacin	13	5.4
Moxifloxacin	0	0
Ofloxacin	2	1.4

表五、Summary of Fluoroquinolone QTc Interval Data

	Sparfloxacin	Grepafloxacin	Levofloxacin	Trovafloxacin	Moxifloxacin
Animal data	Dogs 25-45 mg/kg, QT prolongation occurred	Rabbits 10-30 mg/kg, arrhythmia developed in 1/4 animals	No data	No data	Dogs 90 mg/kg resulted in a 25-msec QT interval prolongation (no arrhythmias)
QTc interval prolongation in humans	Yes	Yes	Minimal	No	p.o. minimal
Mean ± SD QTc interval prolongation in humans	p.o. 10.3 ± 27.6 msec	p.o. 8 msec	4.6 msec ± 23 msec	No data	p.o. 6 ± 26 msec, i.v. 12.1 msec
QTc interval prolongation outlier values (> 60 msec from baseline or > 500msec overall)	> 500 msec from baseline in 10/880 pts	No data	No data	Not observed in clinical trials	> 60 msec from baseline in 3/107 pts
Additive QTc prolongation effects with other QTc-prolonging agents	Yes	No data	4/37 pts	No data	Yes
Patients at risk for QTc interval prolongation excluded from trials	Yes	No	No	No	Yes

參考資料：

MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado (Edition expires [1999/08/15]).

超級比一比

院內 Benzodiazepines 製劑之比較

吳玫君藥師

Agent	Supply	Time to Peak Blood Level (hr)	Half-life (parent，hr)	Adult Dose (daily)	Onset/ Duration	Adjust dose in renal failure	FDA Indications	Pregnancy Category
Anxiolytics								
Alprazolam (Xanax®)	0.5mg/Tab	1~2	12~15	0.5~4mg	1~1.5hr/ ND	No	*Anxiety(immediate-release only) *Panic disorder(with or without agoraphobia) (immediate-release or extended release)	D
Bromazepam (Lexotan®)	1.5mg/Tab	1~2	8~20	6~30mg	ND	No	*Anxiety	ND
Diazepam (Valium®)	2mg,5mg/ Tab 10mg/2ml/ Amp	0.5~2	20~80	4~40mg	PO 30'/ ND	No	*Acute alcohol withdrawl *Anxiety *Cardioversion *Endoscopic procedure *Skeletal muscle spasm *Seizures	D
Fludiazepam (Erispan®)	0.25mg/Tab	1	23	0.75mg	ND	No	Not approved by FDA *Anxiety	ND
Lorazepam (Ativan®)	0.5mg,1mg/ Tab 2ml/ml/Amp	1~6	10~16	2~6mg	20'~30'/ 8hr	No	*Anxiety *Preanesthetic *Status epilepticus	D
Oxazepam (Serax®)	15mg/Tab	2~3	5~20	30~120mg	2~3hr/ 12~24hr	No	*Alcohol withdrawl *Anxiety	D
Oxazolam (Serenal®)	10mg/cap	rat:30'-rat:60'		30-60mg	30'/		Not approved by FDA *Anxiety *Preanesthetic	D
Hypnotics								
Estazolam (Eurodin®)	2mg/Tab	2	10~24	1~2mg	20'/ 10~24hr	No	*Insomnia	X
Flunitrazepam (Rohypnol®)	1mg/Tab 2mg/Amp	1~2	16~35	1~2mg	20'~30'/ 8hr	ND	Not approved by FDA *Anesthesia adjunct *Anesthesia induction *Insomnia *Local anesthesia supplementation *Premedication *Status epilepticus	D
Clonazepam (Rivotril®)	0.5mg,2mg/ Tab	1~4	30~40	1.5~20mg	20'~40'/ 6~8hr	No	*Panic disorder *Seizure disorders	D

參考資料：

MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado (Edition expires [1999/08/15]).