出國報告（出國類別：其他）

第 25 回 日本藥物動態學會年會

服務機關：嘉南藥理科技大學藥學系
姓名職稱：鄭靜玲 教授
派赴國家：日本
出國期間：99 年 10 月 7 日～99 年 10 月 9 日
報告日期：100 年 6 月 10 日

摘　要

藥物動力學（又稱藥物動態學）在藥物治療學與新藥研發上扮演重要的角色。本學會的研究領域涵蓋藥物代謝酵素，藥品輸送子，基因多型性與其調控機轉，也包含體內藥動/藥效學分析。在亞洲，日本為新藥開發資源較豐富，且藥業市場也相對成熟之國家。在官方與藥廠的配合下，日本學術界在藥物動態的研究成果上不論是在質與量上都是國際知名。

本年度（2010）第 25 屆年會會議在東京舉行，大會本次的主題為「The Role of Drug Metabolism and Pharmacokinetics on Bridging Drug Discovery/Development and Clinical Research」。本人亦在學會上口頭發表論文：「Limited Sampling Strategy for Predicting Mosapride Area Under the Curve in Rats」與大家分享國科會研究計畫 NSC97-2320-B-041-001-MY3 成果。

近年來在 DMPK 的卓越研究貢獻對新藥在發現與研發的時期有極大的貢獻，有效的縮短了新藥上市的時程。但藥品的毒理與藥理有效性方面仍然沒有好的解決方案。日本藥物動態學會今年年會針對如何利用 DMPK 架接新藥的發現與臨床研究為討論主題，並回顧學會 25 年的歷史及提出對未來的展望。

壹、參與目的

藥物動力學在藥物研發及臨床療效監測之應用為本人在所任職的嘉南藥理科技大學藥學系暨藥物科技研究所之授課與研究重點，同時也是在兼職授課的成大醫學院藥學生物科技研究所之發展重點。本次日本藥代 25 週年年會主題為「The Role of Drug Metabolism and Pharmacokinetics on Bridging Drug Discovery/Development and Clinical Research」與本人之專長及所任職的教學與研究發展重點相符，並有重要學科與學會歷史回顧，這是本人此行之主要原因。也希望帶回對國內相對產業與藥品管的新資訊。

貳、會議過程

日本藥物動態學會是藥物動力學領域年度重要的國際學術研討會之一。今年(2010)是在日本東京市舉行，會場主要在国立京都国際会館。主要的會議議程是由 10 月 7 日至 10 月 9 日舉行為期三天。其中包括一開幕典禮(Opening Ceremony)、一個 25 週年專題討論會(JSSX 25th Anniversary Symposium)、一個頒獎典禮(Award Ceremony)、二個特別演講(Distinguished Lecture)、四個專題討論會(Symposium)、一個公開討論會(Forum 2009)、一百零八場個口頭演講(Oral presentation)、一百八十二個壁報論文(Poster presentation)及十一個午餐研討會(Luncheon

Seminar)。

參與的專題討論會主題內容包括:

1. Drug Metabolism Research in Asia: Orphan P450 enzymes, Natural Products, and Human Metabolite Formations.
2. Oral Presentation 7: Drug Interaction
3. Oral Presentation 8: Pharmacokinetics

每一主題皆安排有三至六位的講者講演，場次雖不多，但因會場散佈於不同場地，與會者須根據自身專業興趣選擇到處串場聆聽。可惜日文不好，否則，重要的訊息仍是以日文討論為主。

參與的兩場特別演講，帶給研究者對這類研究的新啟發與感動。相對看到連基本的研究設備--液相層析串聯直譜都很難見到的台灣本土研究環境，感觸很大。國多年，感覺台灣在研究上的心力投注與行政不成正比。幾乎所有的人都為行政而行政，為評鑑而評鑑。研究過度的強調收穫，在真正的大環境並不鼓勵的情況下，研究者越來越寂寞，只怕失去了研究者的熱情與持續度。

本次年會共有來自日本、亞洲、歐洲、美洲等國藥物動態學相關人員與會，台灣與會人數約為5人。

參、與會心得

一、 本次口頭發表研究成果之內容為發表國科會的研究成果：主要參與的 section 為藥物動力學。(附件一)

二、 由於本會是日本藥物動態學會年會，故官方語言為日語而英語為輔。也正因為如此之封閉性，不同於其他國際會議，日本人在此年會所發表的內容往往都是第一手尚未發表在學術期刊。越封閉的，討論可以聽到越多的內涵。壁報論文有許多內容極為精闢的研究，主題相當有前瞻性，令人印象深刻，參加此年會最大收穫即在於此。本次大會嚴格規定非經發表者同意不得對海報拍照攝影，因此壁報展覽現場常見人振筆疾書，令人佩服。

肆、會後建議

一、感謝國科會於經費上補助往返機票、住宿及註冊費等費用，使本人得以赴日本參加此年會。本次與會發表國科會的研究成果外，也吸收了許多學術新知以及研究情資，另外亦有機會與幾位國內外舊識及新交之國際學者專家做交誼，增進學術交流，此行收獲良多。由衷感謝國科會之贊助，讓本人得以參與此次年會，不僅增加個人見聞，擴大國際學術交流，多少有助於進而提升台灣國際研究地位與能見度。

二、攜回本次年會會議摘要集一本，本回(與歷年)日本藥物動態學會年會之演講要旨集可上網查詢，其網址為:

http://www.jstage.jst.go.jp/browse/jssxmeeting

三、與國外的藥廠或學校比起來，有藥學系之學校實應有像液相層析

串聯質譜儀這樣的基礎設備。這樣的儀器進而可讓產業與新的蛋白質體藥物連結，退也才能真正落實對產品的評估與品質的管控。台灣的相關生技產業在這方面的能力，也應提升，否則對原料品質的不重視將對產品品質出現極大的問題。若政策無法實質要求廠商對人才的進用與產品品質管制的落實，台灣將付出極大的代價。

1-E-10-1

25th JSSX Annual Meeting
Omiya Sonic City, 7-9 Oct. 2010

Limited Sampling Strategy for Predicting Mosapride Area Under the Curve in Rats

Ching-Ling Cheng[1], Ya-Win Chang [2] and Chen-Hsi Chou[2]

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Mosapride

Mosapride

- Metabolism :
  - undergo N-dealkylation metabolism to form des-4-fluoro-benzyl metabolite (M-1)
  - by CYP3A
- Elimination :
  - extensively metabolized
  - metabolic clearance seemed to be predominant in the elimination of mosapride from the body, regardless of species

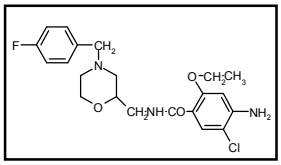
Arzneimittelforschung. 43(8), 867-72, 1993

Objectives

- To characterize the pharmacokinetics of mosapride as well as develop limited sampling strategies (LSSs) for the estimation of mosapride area under the curve (AUC) in the rat.

Mosapride

- Physical and chemical properties
  - a benzamide derivative
  - $C_{21}H_{25}ClFN_3O_3$
  - M.W. : 421.9
  - XLogP: 2.9



- Pharmacology
  - selective 5-HT_4 receptor agonist
  - enhances upper gastrointestinal motor activity
  - prokinetic agent

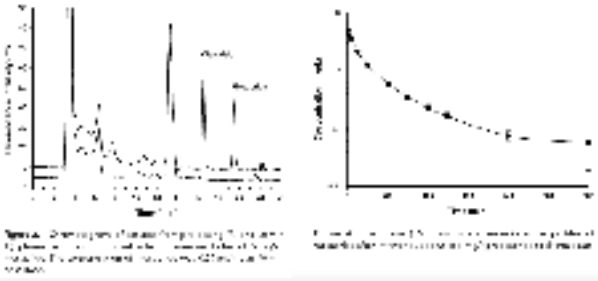
Method

Mosapride

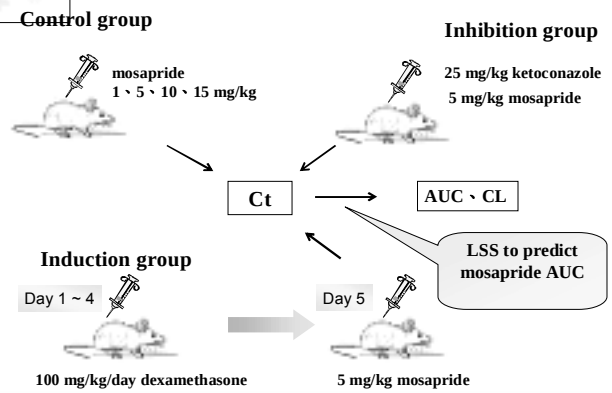
- Pharmacokinetics
  - Absorption :
    - rapidly adsorbed : mainly in upper GI track
    - bioavailability : 7% in male rat ; 47% in female rat
    - T_{max} was significantly delayed in the presence of food
  - Distribution :
    - Vd/F in human : 1.7 ~ 3.5 L/kg
    - Vd in rats : 4 ~ 4.2 L/kg
    - protein binding : 97 %

HPLC-fluorescence assay for measuring mosapride in small volumes of rat plasma

Ching-Ling Cheng[a], Ya-Win Chang[b] and Chen-Hsi Chou[b,c]



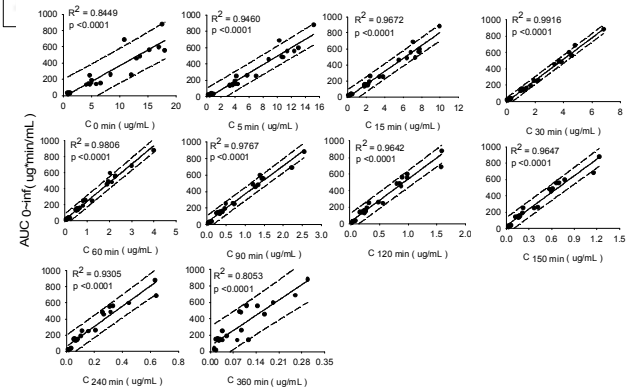
Animal study design



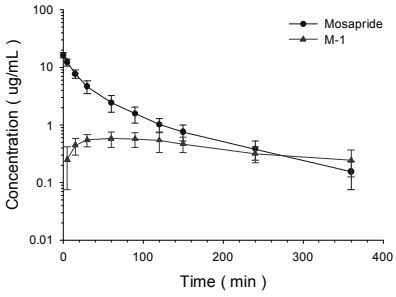
Limited sampling strategy

$CL_{mosapride}$

Pharmacokinetics of mosapride



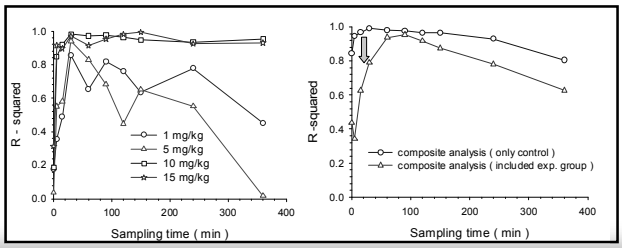
Control group



- Mosapride : two compartment
- M-1 : eliminated slower than mosapride

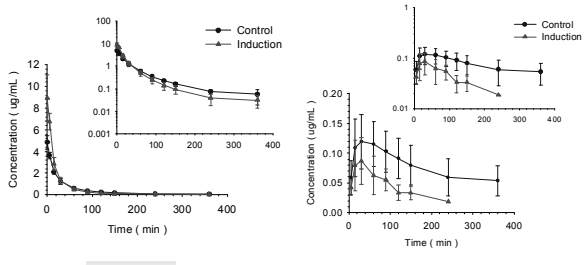
Single point prediction

- **Subset analysis : 1、5、10、15 mg/kg**
- **Composite analysis :**
  - **control**
  - **control and CYP3A modulation group**



CYP3A modulation -- induction

IP 100 mg/kg/day dexamethasone $\xrightarrow{4\ \text{days}}$ IV 5 mg/kg mosapride



Mosapride **M-1**

Limited sampling strategy

- **Va**

$$\%\,\mathrm{MPE} = \sum_{i=1}^{n} \frac{\mathrm{Pe}\,i}{n} \times 100\,\%$$

$$\%\,\mathrm{MAE} = \sum_{i=1}^{n} \frac{|\mathrm{Pe}\,i|}{n} \times 100\,\%$$

$$\%\,\mathrm{RMSE} = \sqrt{\frac{\sum_{i=1}^{n} |\mathrm{Pe}\,i|^2}{n}} \times 100\,\%$$

ons
UC

Pe (prediction error) = $\log \mathrm{AUC}_{ped} - \log \mathrm{AUC}_{obs}$

Sampling time (min)	Training set （N = 29）		Validation set （N = 10）		
	Equations	r^2	% MPE	% MAE	% RMSE
90	$29.58 + 359.34\ C_{90\ min}$	0.95	2.76	11.18	14.37
30 , 360	$4.18 + 104.08\ C_{30\ min} + 631.575\ C_{360\ min}$	0.99	2.31	4.32	5.41
15 , 90 , 360	$1.91 + 37.99\ C_{15\ min} + 138.64\ C_{90\ min} + 523.72\ C_{360\ min}$	0.996	2.25	2.99	4.58
0 , 15 , 90 , 360	$-4.86 + 4.45\ C_{0\ min} + 28.83\ C_{15\ min} + 141.34\ C_{90\ min} + 531.08\ C_{360\ min}$	0.997	1.22	1.47	2.14

- **% MPE (mean prediction error) ; % MAE (mean absolute error) ; % RMSE (root mean square error)**
- **acceptable limit : % MPE (< 5 %) ; % MAE (< 10 %) ; % RMSE (< 15 %)**

Conclusion

Mosapride disposition :

The pharmacokinetics of mosapride in rats following bolus administration was linear.

Limited sampling strategy :

The systemic exposure of mosapride in rats, in terms of AUC, can be precisely predicted using LSSs with one to four concentrations.

出國報告（出國類別：其他）

International symposium on BA/BE of Oral Drug Products:

More Science, Technology and Better Regulatory Standards

服務機關：嘉南藥理科技大學藥學系
姓名職稱：鄭靜玲 教授
派赴國家：日本
出國期間：100 年 06 月 29 日～100 年 7 月 01 日
報告日期：100 年 10 月 31 日

摘　要

2011 年度由 FIP (International Pharmaceutical Federation)主辦的口服製劑產品的生體可用率/生體相等性國際研討會原在東京舉行，後因日本大 311 海嘯的緣故緊急改在神戶舉行。參與研討會的講者為美日歐在此方面的著名學者。由於生體可用率與生體相等性向來為製劑產品能否通過政府產品註冊的重要法規依據與體內參考指標，對於未來藥品政策具有前瞻性的重要指標。各國政府的官員也會蒞臨演說，提出產品的註冊的重要政策方向說明。本人的博士指導教授 Gordon L. Amidon 也受邀發表特別演講：New era in BA /BE world。

本人亦在學會上發表壁報論文：「Pharmacokinetics and bioequivalence of amisulpride immediate-release tablets in healthy Taiwanese volunteers」與大家分享研究成果。其他來自台灣的有業界的佳生公司的一篇壁報論文與設攤推廣業務。在總共參加的 11 國代表中，壁報論文部分：除主辦日本國 27 篇，其他各國共 20 篇（僅次於韓國 5 篇，美國三篇，與巴西、德國、泰國並列兩篇，中國，瑞典，奈及利亞及印度各一篇）。

與過去所認識的及本次新認識的各國師長與朋友們，對現在的研究與教學互相交換意見後，更覺得此次參與除「與有榮焉」外，也對未來執行產品審查案、教學與研究方頗有收穫。

壹、參與目的

本研討會的主題為「口服藥品的生體可用率/生體相等性」，因一開始的特別演講是邀請到國際知名的 Gordon L. Amidon，恰好是我就讀密西根大學安娜堡分校博士班時 的指導教授，主題又與個人回台後的研究主軸相切合，特別是對如何提昇產品的品質管控有很大的影響。法規的走向決定廠商在產品生產與把關時的硬體投資的金額多少，也影響未來產業的人才與方向。因此，一直特別關注。特別是這兩年台灣的藥品食品屢次發生重大事件，對國民健康影響不可謂不大。原想，多找幾家台灣的藥廠一起去增長見聞，也希望能藉由這樣的研討會將學術的精神潛移默化的移植在「廠商」的企業精神中。

貳、會議過程

本研討會原訂在 2011 年 4 月 11 日在東京舉行。在離會議前一個月發生了世紀的大災難 311 海嘯後，原以為如此大的影響（東京也受到不小的損害，加上核電廠洩漏造成的恐慌）大會將會取消。意料之外，在不到一個月(4 月 1 日)就提出更改地點（神戶）的方案，並在原訂時間兩個半月後順利完成，此點，確實值得學習效法。

本次研討會後改在日本神戶市舉行，會場在神戶国際會議中心。

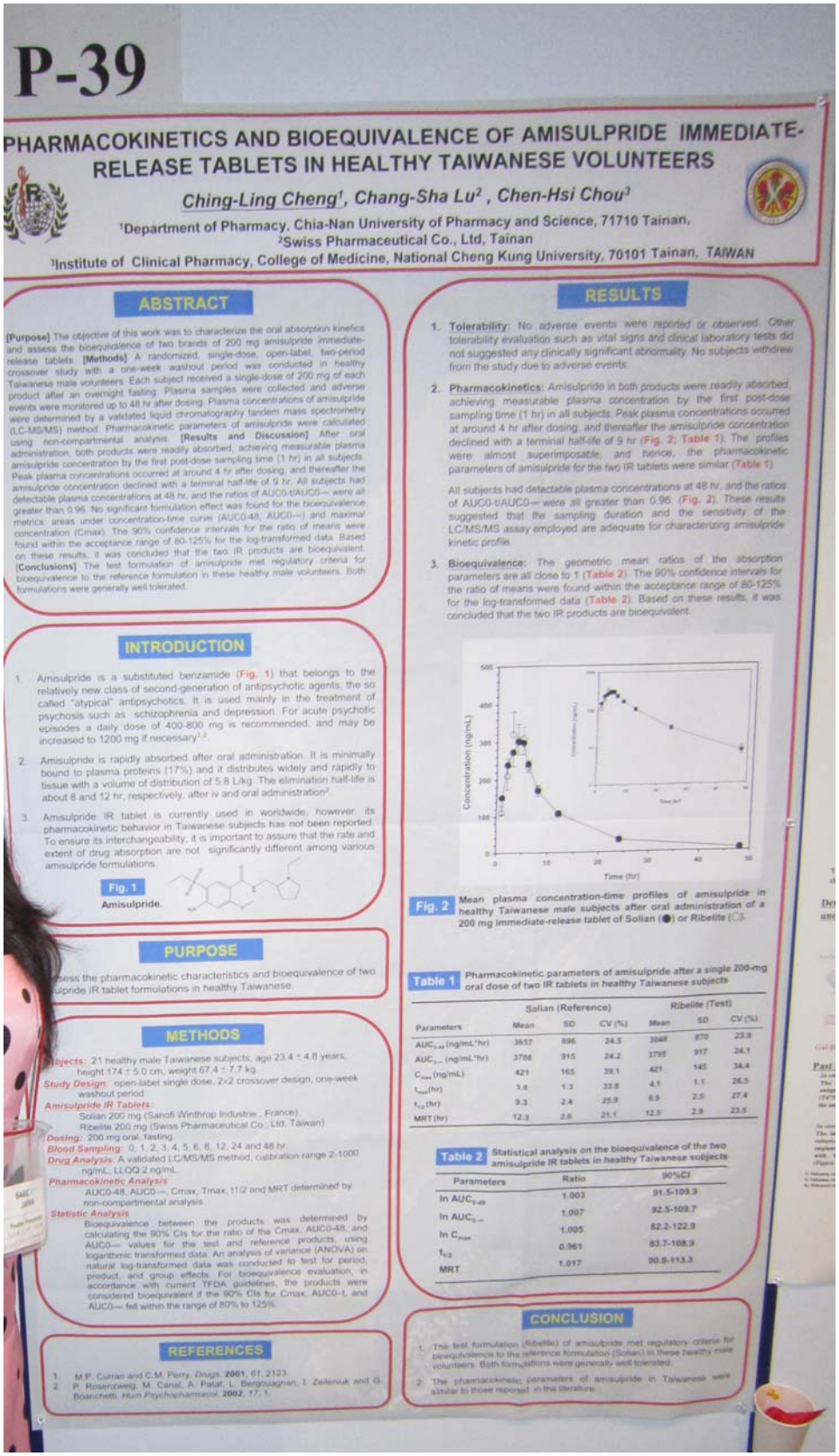
主要的會議議程是由 6 月 29 日至 7 月 1 日舉行為期三天。其中包括一開幕典禮(Opening Session)、四個場次的主題研討會(Sessions) 、及壁報展示(Poster Session)與廠商展示。

參與的專題討論會主題內容包括:

1. Predicting oral BA and DDI to select better compounds
2. Improving oral BA of biopharmaceutical problem compounds
3. IVIVC and BCS for optimizing formulation and streamlining BE study
4. Worldwide standards for regulating oral drug products

每一主題皆安排有五位以上的講者講演，會場集中與會者因領域相近，於會場中可隨時交換意見。

本次年會共有來自日本、亞洲、歐洲、美洲及非洲等國相關人員約250人與會。



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PHARMACOKINETICS AND BIOEQUIVALENCE OF AMISULPRIDE IMMEDIATE-RELEASE TABLETS IN HEALTHY TAIWANESE VOLUNTEERS

Ching-Ling Cheng[1], Chang-Sha Lu[2], Chen-Hsi Chou[3]

[1]Department of Pharmacy, Chia-Nan University of Pharmacy and Science, 71710 Tainan,
[2]Swiss Pharmaceutical Co., Ltd, Tainan
[3]Institute of Clinical Pharmacy, College of Medicine, National Cheng Kung University, 70101 Tainan, TAIWAN

ABSTRACT

[Purpose] The objective of this work was to characterize the oral absorption kinetics and assess the bioequivalence of two brands of 200 mg amisulpride immediate-release tablets. **[Methods]** A randomized, single-dose, open-label, two-period crossover study with a one-week washout period was conducted in healthy Taiwanese male volunteers. Each subject received a single-dose of 200 mg of each product after an overnight fasting. Plasma samples were collected and adverse events were monitored up to 48 hr after dosing. Plasma concentrations of amisulpride were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Pharmacokinetic parameters of amisulpride were calculated using non-compartmental analysis. **[Results and Discussion]** After oral administration, both products were readily absorbed, achieving measurable plasma amisulpride concentration by the first post-dose sampling time (1 hr) in all subjects. Peak plasma concentrations occurred at around 4 hr after dosing, and thereafter the amisulpride concentration declined with a terminal half-life of 9 hr. All subjects had detectable plasma concentrations at 48 hr, and the ratios of AUC0-t/AUC0-∞ were all greater than 0.96. No significant formulation effect was found for the bioequivalence metrics: areas under concentration-time curve (AUC0-48, AUC0-∞) and maximal concentration (Cmax). The 90% confidence intervals for the ratio of means were found within the acceptance range of 80-125% for the log-transformed data. Based on these results, it was concluded that the two IR products are bioequivalent. **[Conclusions]** The test formulation of amisulpride met regulatory criteria for bioequivalence to the reference formulation in these healthy male volunteers. Both formulations were generally well tolerated.

INTRODUCTION

1. Amisulpride is a substituted benzamide (Fig. 1) that belongs to the relatively new class of second-generation of antipsychotic agents, the so called "atypical" antipsychotics. It is used mainly in the treatment of psychosis such as schizophrenia and depression. For acute psychotic episodes a daily dose of 400-800 mg is recommended, and may be increased to 1200 mg if necessary[1,2].
2. Amisulpride is rapidly absorbed after oral administration. It is minimally bound to plasma proteins (17%) and it distributes widely and rapidly to tissue with a volume of distribution of 5.8 L/kg. The elimination half-life is about 8 and 12 hr, respectively, after iv and oral administration[2].
3. Amisulpride IR tablet is currently used in worldwide, however, its pharmacokinetic behavior in Taiwanese subjects has not been reported. To ensure its interchangeability, it is important to assure that the rate and extent of drug absorption are not significantly different among various amisulpride formulations.

Fig. 1 Amisulpride.

PURPOSE

...sess the pharmacokinetic characteristics and bioequivalence of two ...ulpride IR tablet formulations in healthy Taiwanese.

METHODS

Subjects: 21 healthy male Taiwanese subjects, age 23.4 ± 4.8 years, height 174 ± 5.0 cm, weight 67.4 ± 7.7 kg.
Study Design: open-label single dose, 2×2 crossover design, one-week washout period.
Amisulpride IR Tablets:
Solian 200 mg (Sanofi Winthrop Industrie., France).
Ribelite 200 mg (Swiss Pharmaceutical Co., Ltd, Taiwan)
Dosing: 200 mg oral, fasting.
Blood Sampling: 0, 1, 2, 3, 4, 5, 6, 8, 12, 24 and 48 hr.
Drug Analysis: A validated LC/MS/MS method, calibration range 2-1000 ng/mL, LLOQ 2 ng/mL.
Pharmacokinetic Analysis
AUC0-48, AUC0-∞, Cmax, Tmax, t1/2 and MRT determined by non-compartmental analysis.
Statistic Analysis
Bioequivalence between the products was determined by calculating the 90% CIs for the ratio of the Cmax, AUC0-48, and AUC0-∞ values for the test and reference products, using logarithmic transformed data. An analysis of variance (ANOVA) on natural log-transformed data was conducted to test for period, product, and group effects. For bioequivalence evaluation, in accordance with current TFDA guidelines, the products were considered bioequivalent if the 90% CIs for Cmax, AUC0-t, and AUC0-∞ fell within the range of 80% to 125%.

REFERENCES

1. M.P. Curran and C.M. Perry, *Drugs*, **2001**, 61, 2123.
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RESULTS

1. **Tolerability**: No adverse events were reported or observed. Other tolerability evaluation such as vital signs and clinical laboratory tests did not suggested any clinically significant abnormality. No subjects withdrew from the study due to adverse events.
2. **Pharmacokinetics**: Amisulpride in both products were readily absorbed, achieving measurable plasma concentration by the first post-dose sampling time (1 hr) in all subjects. Peak plasma concentrations occurred at around 4 hr after dosing, and thereafter the amisulpride concentration declined with a terminal half-life of 9 hr (Fig. 2; Table 1). The profiles were almost superimposable, and hence, the pharmacokinetic parameters of amisulpride for the two IR tablets were similar (Table 1).

   All subjects had detectable plasma concentrations at 48 hr, and the ratios of AUC0-t/AUC0-∞ were all greater than 0.96. (Fig. 2). These results suggested that the sampling duration and the sensitivity of the LC/MS/MS assay employed are adequate for characterizing amisulpride kinetic profile.
3. **Bioequivalence**: The geometric mean ratios of the absorption parameters are all close to 1 (Table 2). The 90% confidence intervals for the ratio of means were found within the acceptance range of 80-125% for the log-transformed data (Table 2). Based on these results, it was concluded that the two IR products are bioequivalent.

Fig. 2 Mean plasma concentration-time profiles of amisulpride in healthy Taiwanese male subjects after oral administration of a 200 mg immediate-release tablet of Solian (●) or Ribelite (○).

Table 1 Pharmacokinetic parameters of amisulpride after a single 200-mg oral dose of two IR tablets in healthy Taiwanese subjects

	Solian (Reference)			Ribelite (Test)		
Parameters	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-48} (ng/mL*hr)	3657	896	24.5	3648	870	23.9
$AUC_{0-\infty}$ (ng/mL*hr)	3786	915	24.2	3795	917	24.1
C_{max} (ng/mL)	421	165	39.1	421	145	34.4
t_{max} (hr)	3.6	1.3	33.8	4.1	1.1	26.5
$t_{1/2}$ (hr)	9.3	2.4	25.9	8.9	2.5	27.4
MRT (hr)	12.3	2.6	21.1	12.5	2.9	23.5

Table 2 Statistical analysis on the bioequivalence of the two amisulpride IR tablets in healthy Taiwanese subjects

Parameters	Ratio	90%CI
ln AUC_{0-48}	1.003	91.5-109.9
ln $AUC_{0-\infty}$	1.007	92.5-109.7
ln C_{max}	1.005	82.2-122.9
$t_{1/2}$	0.961	83.7-108.9
MRT	1.017	90.8-113.3

CONCLUSION

1. The test formulation (Ribelite) of amisulpride met regulatory criteria for bioequivalence to the reference formulation (Solian) in these healthy male volunteers. Both formulations were generally well tolerated.
2. The pharmacokinetic parameters of amisulpride in Taiwanese were similar to those reported in the literature.

本次開會時間，時值海嘯之後，日本的遊客數不多。顯然，對核電廠的情況與日本的食物及環境的安全仍多有疑慮。另外，本次開會在日本限電前，並沒有感受到用電的差異。夜晚的神戶港，仍然燈火通明，夜景相當美麗。

參、與會心得

一、 本次口頭發表研究成果之內容為 amisulpiride 之速放劑型的生體相等性及相關藥物交互作用。內容請詳見附錄。本藥原為日本開發之新藥成分。因此有互動與迴響。

二、 本次有一特別課程演講主題為 Innovative strategies for drug

development using microdose clinical study.「microdose」這個部分由於需龐大投資金額來做新藥篩選，目前在台灣並未受到重視。但台灣的新藥開發，仍須密切注意本新興學得的未來動態與發展。特別是讓學生們聽過這個主題。

三、 各國的法規與台灣法規的一致性，也需特別注意。若台灣的市場仍如此獨特，又無法加入相對其他經濟實體。則，未來的健康照護時仍需謹慎以對。

肆、會後建議

一、特別感謝國科會於經費上補助往返機票及註冊費等部份費用，使本人得以赴日本參加此藥物動態學年會。本次與會除了可展示本人與成大臨床藥學所周辰熹老師合作的研究成果外，也吸收了許多學術新知以及研究情資，另外亦與多位國內外舊識及新交之國際學者專家做交誼，增進學術交流，此行收獲良多。由衷感謝國科會之贊助，讓本人得以參與此次年會，不僅增加個人見聞，擴大國際學術交流，多少有助於進而提升台灣國際研究地位與能見度。老師們亦建議對岸人士應先至台灣學習，應可減少對岸人士直接到歐美學習的語言障礙。

二、攜回本次研討會議摘要集一本 ，其他相關廠商資料數冊。

Abstract

Pharmacokinetics and bioequivalence of amisulpride immediate-release tablets in healthy Taiwanese volunteers

Ching-Ling Cheng 1, Chang-Sha Lue2, Chen-His Chou3

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[Purpose] The objective of this work was to characterize the oral absorption kinetics and assess the bioequivalence of two brands of 200 mg amisulpride immediate-release tablets.

[Methods] A randomized, single-dose, open-label, two-period crossover study with a one-week washout period was conducted in healthy Taiwanese male volunteers. Each subject received a single-dose of 200 mg of each product after an overnight fasting. Plasma samples were collected and adverse events were monitored up to 48 h after dosing. Plasma concentrations of amisulpride were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Pharmacokinetic parameters of amisulpride were calculated using non-compartmental analysis.

[Results and Discussion] After oral administration, both products were readily absorbed, achieving measurable plasma amisulpride concentration by the first post-dose sampling time (1 h) in all subjects. Peak plasma concentrations occurred at around 4 h after dosing, and thereafter the amisulpride concentration declined with a terminal half-life of 9 h. All subjects had detectable plasma concentrations at 48 h, and the ratios of AUC0-t/AUC0-∞ were all greater than 0.96. No significant formulation effect was found for the bioequivalence metrics: areas under concentration-time curve (AUC0-48, AUC0-∞) and maximal concentration (Cmax). The 90% confidence intervals for the ratio of means were found within the acceptance range of 80-125% for the log-transformed data. Based on these results, it was concluded that the two IR products are bioequivalent.

[Conclusions] The test formulation of amisulpride met regulatory criteria for bioequivalence to the reference formulation in these healthy male volunteers. Both formulations were generally well tolerated.

PHARMACOKINETICS AND BIOEQUIVALENCE OF AMISULPRIDE IMMEDIATE-RELEASE TABLETS IN HEALTHY TAIWANESE VOLUNTEERS

Ching-Ling Cheng[1], Chang-Sha Lu[2] , Chen-Hsi Chou[3]

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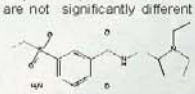
ABSTRACT

[Purpose] The objective of this work was to characterize the oral absorption kinetics and assess the bioequivalence of two brands of 200 mg amisulpride immediate-release tablets. **[Methods]** A randomized, single-dose, open-label, two-period crossover study with a one-week washout period was conducted in healthy Taiwanese male volunteers. Each subject received a single-dose of 200 mg of each product after an overnight fasting. Plasma samples were collected and adverse events were monitored up to 48 hr after dosing. Plasma concentrations of amisulpride were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Pharmacokinetic parameters of amisulpride were calculated using non-compartmental analysis. **[Results and Discussion]** After oral administration, both products were readily absorbed, achieving measurable plasma amisulpride concentration by the first post-dose sampling time (1 hr) in all subjects. Peak plasma concentrations occurred at around 4 hr after dosing, and thereafter the amisulpride concentration declined with a terminal half-life of 9 hr. All subjects had detectable plasma concentrations at 48 hr, and the ratios of AUC0-t/AUC0-∞ were all greater than 0.96. No significant formulation effect was found for the bioequivalence metrics: areas under concentration-time curve (AUC0-48, AUC0-∞) and maximal concentration (Cmax). The 90% confidence intervals for the ratio of means were found within the acceptance range of 80-125% for the log-transformed data. Based on these results, it was concluded that the two IR products are bioequivalent. **[Conclusions]** The test formulation of amisulpride met regulatory criteria for bioequivalence to the reference formulation in these healthy male volunteers. Both formulations were generally well tolerated.

INTRODUCTION

1. Amisulpride is a substituted benzamide (Fig. 1) that belongs to the relatively new class of second-generation of antipsychotic agents, the so called "atypical" antipsychotics. It is used mainly in the treatment of psychosis such as schizophrenia and depression. For acute psychotic episodes a daily dose of 400-800 mg is recommended, and may be increased to 1200 mg if necessary[1,2].
2. Amisulpride is rapidly absorbed after oral administration. It is minimally bound to plasma proteins (17%) and it distributes widely and rapidly to tissue with a volume of distribution of 5.8 L/kg. The elimination half-life is about 8 and 12 hr, respectively, after iv and oral administration[2].
3. Amisulpride IR tablet is currently used in worldwide, however, its pharmacokinetic behavior in Taiwanese subjects has not been reported. To ensure its interchangeability, it is important to assure that the rate and extent of drug absorption are not significantly different among various amisulpride formulations.

Fig. 1 Amisulpride.



PURPOSE

To assess the pharmacokinetic characteristics and bioequivalence of two amisulpride IR tablet formulations in healthy Taiwanese.

METHODS

Subjects: 21 healthy male Taiwanese subjects, age 23.4 ± 4.8 years, height 174 ± 5.0 cm, weight 67.4 ± 7.7 kg.

Study Design: open-label single dose, 2×2 crossover design, one-week washout period

Amisulpride IR Tablets:
Solian 200 mg (Sanofi Winthrop Industrie., France).
Ribelite 200 mg (Swiss Pharmaceutical Co., Ltd, Taiwan)

Dosing: 200 mg oral, fasting.

Blood Sampling: 0, 1, 2, 3, 4, 5, 6, 8, 12, 24 and 48 hr.

Drug Analysis: A validated LC/MS/MS method; calibration range 2-1000 ng/mL; LLOQ 2 ng/mL

Pharmacokinetic Analysis
AUC0-48, AUC0-∞, Cmax, Tmax, t1/2 and MRT determined by non-compartmental analysis.

Statistic Analysis
Bioequivalence between the products was determined by calculating the 90% CIs for the ratio of the Cmax, AUC0-48, and AUC0-∞ values for the test and reference products, using logarithmic transformed data. An analysis of variance (ANOVA) on natural log-transformed data was conducted to test for period, product, and group effects. For bioequivalence evaluation, in accordance with current TFDA guidelines, the products were considered bioequivalent if the 90% CIs for Cmax, AUC0–t, and AUC0-∞ fell within the range of 80% to 125%.

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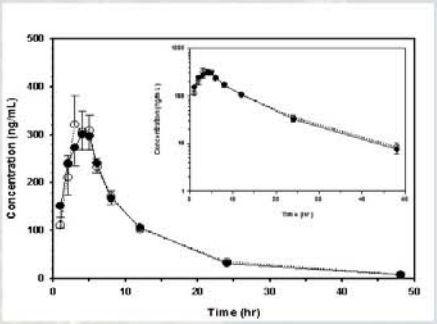

Fig. 2 **Mean plasma concentration-time profiles of amisulpride in healthy Taiwanese male subjects after oral administration of a 200 mg immediate-release tablet of Solian (●) or Ribelite (○).**

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Parameters	Ratio	90%CI
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