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• 計畫中文名稱	銜接性試驗之相關性研究 -- 共變數共線性關係對不同參數分佈模式之人群模式參數評估的影響性
• 計畫英文名稱	Relative Research on Bridging Studies -- the Influence of Collinearity of Covariates on Parameter Estimates in Population Models with Different Distribution for Parameters
• 主管機關	行政院衛生署
• 計畫編號	DOH91-TD-1103
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• 研究人員	葉健全 Yen, Geng-Chang
• 中文關鍵字	銜接性試驗；電腦模擬；共線性共變數；人群分布模式
• 英文關鍵字	bridging study；computer simulation；collinear covariate；population distribution model
• 中文摘要	本研究計劃之目的在於探討共變數之共線性對於不同模式評估時，於不同藥動學或藥效學參數分佈模式下，對其人群模式參數評估的影響。模擬參數包括清除率 (CL)、分佈體積 (Vd)、與吸收速率常數 (Ka)，而清除率與分佈體積的相關性爲 (0.0, 0.25, 0.50, 0.70)，並假設只有 CL 與兩個共變數 (身高 與年齡) 之間存在固定程度的相關性 (分別爲 0.3 與 0.25)，而共變數之間存在不同程度的相關性 (0.0, 0.25, 0.50, 0.75, 0.9)，並預設人群的 CL 參數有不同高中低值 (100、75、50 L/h) 的不同比例分佈 (機率分別爲 1.0、0.0、0.0 或 0.8、0.1、0.1 或 0.9、0.0、0.1) 作爲不同人群分佈模式的模擬。採用的藥動學模式是口服單室分佈藥物，共取樣 500 志願者的模擬參數，每個志願者以每天劑量 40 mg 連續給藥十天，在此期間亂數的由此 500 個志願者各取兩個血液樣品濃度，利用此些藥動學數據比較 SAS 非線性迴歸、WinNonMix、與 NONMEN 三種建構模式方法對於參數迴歸預估之準確度與精確度。結果顯示，三種方法對於含與不含共變數模式於迴歸模式中，所得的參數評估值之精確度與準確度的影響性相近，如果考慮人群分佈模式時，對於共變數相關程度的影響性與影響程度之解析可能較爲可靠。但如果沒有考慮時，就會因爲 confounding 的結果而造成無法解析共變數相關程度的影響性與影響程度，這些狀況在不同的參數相關係數時也是相類似。所以總結對於銜接性試驗的人群模式的建構應考慮人群參數的亞群分佈模式，進而有效的建構參數與共變數間的相關性及可能存在的共線性問題
• 英文摘要	The purpose of this study was to evaluate the influence of population distribution model of pharmacokinetic parameters on the parameter estimation of population with covariates of parameters having collinearity. Parameters, including clearance (CL), volume distribution (Vd), and

absorption rate constant (Ka), were selected with different correlation coefficient (0, 0.25, 0.5, 0.7) existed between CL and Vd only. And there existed a fixed extent of correlation between CL and height (0.3) and between CL and age (0.25). Correlation between these two covariates was defined in various values (0.0, 0.25, 0.50, 0.75, and 0.95). There also presumed that three population distribution models composed of three subpopulations of having different CL (100, 75, and 50 L/h) with different percentage (1.0, 0.0, 0.0 or 0.8,0.1,0.1 or 0.9,0.0,0.1). Based on oral one-compartment absorption pharmacokinetic model, 500 volunteers with simulated parameters according to the above condition were generated. These volunteers were given daily dose of 40 mg for consecutive 10 days and two blood samples were collected within the 10-day period randomly from each volunteer. Those pharmacokinetic data were subjected to regression based on population model with or without covariate factors by SAS nonlinear regression, WinNonMix, or NONMEN method to examine the accuracy and precision of parameter estimates. The results demonstrated that the influence on the accuracy and the precision of parameters estimation were quite similar by three regression methods based on population model with or without covariate factors. However, when population distribution model was included in consideration, the influence of collinearity of covariates on the accuracy and precision of parameter estimates could be more reliably evaluated. Nevertheless, confounding effect could be so profound to be undifferentiated between the possible influencing factors on the parameter estimates. Similar results were observable no matter what values of correlation between parameters were used. In conclusion, bridging study is optimally requested to provide information of possible subpopulations for pharmacokinetic parameters. This should be included for consideration in the building process of population model to effectively construct the relationship between parameters and covariates and to clarify the potential problem of collinearity.