Warfarin 療效與安全性評估

Evaluation of the Safety and Efficacy of Warfarin

中文摘要

Warfarin 雖已上市超過 60 年，經臨床試驗證明預防栓塞的效果， 但因其治療指數狹窄，及藥物食物的交互作用，基因差異等原因使得 warfarin 在臨床使用上仍然具有挑戰性。根據國內外治療指引，心房顫動或是靜脈栓塞的病人建議使用 warfarin 預防栓塞，多半建議 International normalized ratio (INR) 控制在 2-3 之間。但國內甚至香港等亞洲國家普遍認爲東方人較易出血且較不易栓塞，而傾向將 INR 控制的較低。本研究希望藉由評估 INR 和栓塞/出血事件的關係建立合理的 INR 控制範圍。

本研究第一部份納入 2006 年 3 月 1 日至 2008 年 9 月 30 日止，在萬芳醫院門診使用 warfarin 5mg/tab 且持續每月返回門診領藥連續達 24 個月者，最長追蹤至 30 個月。並以病歷回溯方式記錄所有栓塞及嚴重出血事件及 INR 值，接著將 INR 分爲<1.5，1.5-1.9，2.0-2.4，2.5-2.9，3.0-3.4，^{3}3.5 六個等級，計算所有病人在各 INR 分級所佔的時間和栓塞及/或出血發生率。另比較 warfarin 用於初次栓塞與再次栓塞預防的成效以及危險因子分析。本研究第二部分爲分析 2008 年 10 月 1 日萬芳醫院新引進 warfarin 1mg/tab 品項後，比較由既有之 warfarin 5mg/tab 品項轉換爲 warfarin 1mg/tab 品項前後 5 個月 INR 分布於六個等級的時間、用法(QD vs.Non-QD) 及每日平均使用劑量差異。

本研究第一部份共納入 161 人，平均年齡 68.8 ± 13.4 歲，觀察時間共爲 3504 個病人月，分布於 INR<2 的時間佔 70%；適應症包括心房顫動、人工瓣膜置換、靜脈栓塞治療、腦中風後預防復發等。結果發現在 INR<1.5、1.5-1.9、2.0-2.4、2.5-2.9、3.0-3.4、^{3}3.5 六個等級的栓塞或出血事件發生率分別爲 8.1、5.6、2.0、7.6、33.3、121.2/1000 病人月; 以 INR<2，INR2-3 及 INR>3 分爲三個區間，合併所有栓塞及出血事件發生率作比較，則 INR>3 不論與 INR<2 或是 INR2-3 相較事件發生率均明顯變高(P<0.001)。另比較 warfarin 用於初次栓塞與再次栓塞預防病人，發現再次栓塞預防的病人 INR<2 時較易發生栓塞(P<0.05)。分析發生栓塞或出血的危險因子，在校正過性別、高血壓、糖尿病、高血脂、心臟衰竭、冠狀動脈心臟疾病、腎功能後，年齡是唯一影響栓塞事件發生的危險因子(odds ratio=1.102，95% CI=1.004-1.209，P=0.041)。同時年齡大於 73 歲也較易發生栓塞。

本研究第二部份共有 111 人由 warfarin 5mg/tab 既有品項轉換爲 warfarin 1mg/tab 新進品項， 轉換前 QD 用法佔 85.6%，Non-QD 用法佔 14.4%，轉換後 QD 用法佔 84.7%，Non-QD 用法佔 15.3%。轉換前後 INR 檢測次數均≧2 次有 27 人，比較 27 人在轉換前後 5 個月，每日平均使用劑量在轉換後有顯著降低(P<0.001)，但分布於 INR<1.5，1.5-1.9，2.0-2.4，2.5-2.9，3.0-3.4，^{3}3.5 六個等級的天數並無

統計學上差異。
臨床上使用 warfarin 時，預防栓塞與出血的發生同樣重要。本研究結果發現 warfarin 無論用於心房顫動，心臟瓣膜置換，心因性中風，靜脈栓塞治療等疾病，INR>3 以上事件發生率明顯增加；warfarin 作爲預防再次栓塞復發時，INR 控制在<2 時較易再次發生栓塞事件。此結果與 ACCP guideline 所建議 INR 一般控制在 2-3(目標值 2.5)大致上相符，故在台灣 INR 控制在<2 並不可行。未來仍需要加強 warfarin 的使用衛教與 INR 監測率提升，才能有更多的研究來證明東方人 INR 是否真的需要控制的較低。

英文摘要

Warfarin has been the mainstay of oral anticoagulant therapy for more than 60 years. Their effectiveness has been established by well-designed clinical trials for the prevention of thrombus formation and subsequent thrombo-embolic events. Warfarin is still challenging to use in clinical practice due to its narrow therapeutic window, considerable genetic variability between patients, and interactions with drugs and diet. The American College of Chest Physician (ACCP) guideline recommends a target INR of 2.0–3.0 for stroke and venous thromboembolism prevention. However, physicians in Taiwan or HongKong tend to consider Chinese are less prone to thromboembolic events and more likely to have bleeding complications from warfarin. The purpose of the study is to determine an optimal INR range for patients at Wan Fang Hospital, Taipei, Taiwan.
A total of 161 patients with warfarin use were enrolled in this retrospective study from March 1 2006 to September 30 2008. The mean age was 68.8 ± 13.4 years. The INR range was divided into six categories: <1.5, 1.5-1.9, 2.0-2.4, 2.5-2.9, 3.0-3.4, and ^{3}3.5. The overall incidence rate of the events was defined as the ratio of the number of events that took place at that range of INR to the number of patient-months at that range. Total follow-up time was 3504 patient-months. The overall incidence rates of INR range <1.5, 1.5-1.9, 2.0-2.4, 2.5-2.9, 3.0-3.4, and ^{3}3.5 were 8.1, 5.6, 2.0, 7.6, 33.3, and 121.2 per 1000 patient-month, respectively. Thrombosis is significantly likely to occur when INR is less than 2.0. Bleeding is significantly likely to occur when INR is higher than 3.0. The overall incidence rates at INR of >3 is higher than that at INR of <2 or 2-3($P<0.001$). The incidence rates of thrombosis is significant higher when INR<2 for secondary prevention ($P<0.05$). Age is the risk factor of thrombosis after adjusted by sex, hypertension, diabetes, hyperlipidemia, heart failure, coronary artery disease, renal function (odds ratio =1.102, 95% CI=1.004-1.209, P=0.041). Thrombosis is more likely to occur when age is greater than 73 years old.
During the course of this study, 1 mg warfarin was added into the hospital formulary. Among the patients who were shifted from 5 mg to 1 mg, no difference in daily

dosing and percentage of patient in target INR range was found before and after the switch. The average daily dose is lower after the switch($P<0.001$).

These results suggest that the dose of warfarin can be adjusted to maintain a target INR of > 2 for secondary prevention, and <3 for all patients in the studied population. Further warfarin education and INR monitoring are warranted to discover the most safe and effective INR range in Taiwanese .