比較兩非麥角多巴胺受體致效劑的小型第四期臨床試驗：帕金森氏症病人由力必平劑量逐步調整爲樂伯克之評估

A Small-scale Phase IV Clinical Trial of Two Non-ergot Dopamine Agonists: Slowly Switching from Ropinirole to Pramipexole in Patients with Parkinson's Disease

中文摘要

研究背景：

多巴胺第二亞型受體致效劑 (DAs)可作爲早期帕金森氏症單獨治療方式，或因長期使用左多巴 (L-DOPA)而產生併發症的晚期病人之輔助治療。 DAs依化學結構分爲麥角及非麥角。 最近研究指出，使用高劑量麥角類DAs會增加心臟瓣膜疾病發生率。 因此，由麥角換成非麥角DAs以預防此類副作用爲近期研究目標。 然而，非麥角DAs間的直接替換較少被研究，因此力必平 (Requip®)及樂伯克(Mirapex®)的轉換因子多由間接比較所得，數值也不盡相同。 樂伯克與力必平不同之處在於樂伯克有較高的生體可用率及較長的半衰期。 樂伯克不經肝臟代謝酵素系統代謝也不與此系統有相互作用，腎臟爲其主要排除方式。 此外，樂伯克對於多巴胺第三亞型受體有較高的親和力，以及具有可能潛在的神經保護效果。 這些性質使得樂伯克具有額外的抗憂鬱作用。

研究目的：

本研究主旨是探討台灣帕金森氏症病人由力必平換成樂伯克後所得的轉換因子，並評估樂伯克可能具有的抗憂鬱效果。

研究方法：

本研究爲前瞻性開放標籤的小型第四期臨床試驗，在臺北醫學大學附設醫院進行爲期一年之研究 (九十七年六月到九十八年六月)。 帕金森病人(四十五歲到八十歲)參與此試驗前已服用固定劑量的力必平或併服左多巴達四週者，可加入此研究。 病人停用力必平後，以劑量逐步調整方式換成樂伯克。 當達到與換藥前相同效果之劑量時，即以此穩定有效劑量維持十二週。 病人換藥前爲自己換藥後的對照組，此前後測的配對實驗可減少干擾因子，因此小樣本數即可用於測試結果。 主要結果依據帕金森氏症狀衡量表(UPDRS-III)評估動作功能，探討十二週後力必平與樂伯克的轉換因子。 次要結果包括換藥前後貝氏憂鬱量表(BDI-II)及帕金森生活品質量表 (PDQ-39)的分數改變。 此外，病人主觀滿意度(TSQM)及換藥期間安全性也納入評估。

研究結果：

共十七位病人參與此研究，其中十位完成此試驗。 換藥前力必平平均每天劑量爲 3.1 毫克，換藥後樂伯克平均每天劑量爲 0.6 毫克。 依每位病人結果所得轉換因子爲 5.6±2.8。 帕金森氏症狀衡量表從 22.4±10.2 分降爲 15.8±6.6 分，顯示動作功能進步。 貝氏憂鬱量表分數在換藥

期間無顯著改變，而帕金森生活品質量表及藥物治療滿意程度量表的效果及整體滿意度兩部分，在維持穩定有效劑量第二個月時均有明顯分數改變。 暈眩及便秘爲換藥期間常見副作用。

研究結論：
在維持樂伯克穩定有效劑量十二星期後，所得轉換因子爲 5.6 時動作有明顯進步。 此轉換因子可應用於台灣帕金森氏症患者由力必平隔夜迅速換成樂伯克時所需劑量的計算。

英文摘要

Background:
Dopamine receptor agonists (DAs), especially D2 subtype could be used as monotherapy in patients with early Parkinson's disease (PD) or adjunctive therapy to L-DOPA in advanced PD with motor complications. DAs are divided into ergot and non-ergot agents. Recent studies indicate that taking high dosages of ergot-derived DAs are associated with valvular heart disease. Therefore, switching from ergot to non-ergot DAs to prevent such adverse drug reactions is the main research goal of many clinical trials. To the best of our knowledge, very few studies have investigated the direct switch between non-ergot DAs. The conversion factor between ropinirole and pramipexole is calculated indirectly and thus the published values are inconsistent. Pramipexole is a non-ergot DA, which has more bioavailability (> 90% vs. 50%) and longer half-life (8~12 hours vs. 6 hours) than ropinirole. Moreover, pramipexole is not metabolized by cytochrome P450 enzymes and it does not have interactions with this enzyme system; pramipexole is primarily eliminated through the kidneys. Furthermore, pramipexole has been shown to have relatively high affinity for the D3 receptor and putative neuroprotective effects. These properties of pramipexole may lead to additional antidepressant action.

Objectives:
The mission of this study was to determine the conversion factor between two non-ergot DAs, ropinirole (Requip®) and pramipexole (Mirapex®) in Taiwanese PD patients and evaluated the possible antidepressant effect of pramipexole.

Methods:
In this prospective open-label pilot study, a small-scale phase IV clinical trial of two non-ergot DAs was carried out at Taipei Medical University Hospital, during the period of June, 2008 to June, 2009. Patients with PD (aged 45 to 80 years old) had taken stable doses of ropinirole with or without L-DOPA (Madopar®) for at least 28 days were recruited. After stopping ropinirole treatment, patients were switched to pramipexole with a log escalating dose until reaching the optimal motor control. The

effective dosage of pramipexole was kept unchanged in the three-month maintenance period. This paired design would minimize confounding factors and thus a small sample size was needed for studying the primary and secondary endpoints. The primary endpoint was to determine the conversion factor between ropinirole and pramipexole at the end of the 12-week maintenance period, assessed by the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III). The secondary outcomes included changes in the Beck Depression Inventory-Second Edition (BDI-II) and the 39-item Parkinson's Disease Questionnaire (PDQ-39) scores during the study period. Patient's satisfaction with pramipexole by Treatment Satisfaction Questionnaire for Medication (TSQM) and safety of the switch were also evaluated.

Results:
A total of 17 PD patients were recruited and 10 of them completed the 12-week maintenance course. The pre-switch dosage of ropinirole was 3.1 mg/day and the post-switch maintenance dosage of pramipexole was 0.6 mg/day. The dosage of pramipexole was lower than that in the western countries. The conversion factor was 5.6 ± 2.8 ($n = 10$), that was directly derived from each patient's paired data. The UPDRS-III score showed a significant decrease from 22.4 ± 10.2 to 15.8 ± 6.6 ($p < 0.05$), reflecting an improvement in motor performance. There was no significant change in the BDI-II during the switch period. However, a significant difference in the PDQ-39 summary index was obtained after the second month of the maintenance period. There were significant changes in both effectiveness and global satisfaction scores of the TSQM simultaneously. The most common adverse events while switching to pramipexole were dizziness and constipation.

Conclusions:
In summary, a directly slow switch from ropinirole to pramipexole at a conversion factor of 5.6 showed the motor improvement after a 12-week maintenance period. This factor derived from the present study could be useful in developing a protocol of an overnight switch from ropinirole to pramipexole in Taiwanese patients with PD.