

Ariflo™ — A Brief Report On A New Second-Generation Phosphodiesterase 4 Inhibitor

Yu-Wung Yeh, Jiunn-Song Jiang, Shang-Jyh Kao

Even though the search for new medications continues, at the end of the day, we still rely on time-honored drugs such as β -agonist, anti-cholinergics, steroids, and theophylline for the treatment of asthma and chronic obstructive pulmonary diseases. Phosphodiesterases play a very important role in terms of biological functions in the human body. They affect the concentration of cyclic AMP and cyclic GMP. Theophylline, in fact, is a non-specific phosphodiesterase inhibitor. As different isozymes of phosphodiesterases have different distribution properties in various tissues, by targeting different isozymes, one can theoretically develop drugs with different properties acting on different target organs. Since the 1970's, there has been intensive research on the potential use of phosphodiesterase inhibitors, and in particular, the phosphodiesterase 4 (PDE4) inhibitors, in treating asthma and chronic obstructive pulmonary diseases. PDE4 inhibitors can inhibit neutrophil functions, decrease TNF α production, impair mast cell degranulation, and decrease T cell proliferation. However, the known PDE inhibitors have not been proved to be clinically useful due to their side effect profiles. SmithKline Beecham Pharmaceuticals is planning to launch a new second-generation PDE4 inhibitor Ariflo™. In phase II trials, Ariflo™ could effectively improve exercise dyspnea scores, increase FEV₁, and improve small airway closures. Compared to the first-generation phosphodiesterase 4 inhibitors, Ariflo™ has markedly improved side effect profiles. (*Thorac Med* 2000; 15: 157-164)

Key Words: Ariflo™, phosphodiesterase, asthma, chronic obstructive pulmonary disease (COPD)

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Ariflo™：新第二代 Phosphodiesterase 4 阻斷劑之簡介

葉育雯 江俊松 高尚志

治療氣喘以及慢性阻塞性肺病的藥物日新月異，但最常用的仍不外乎乙型交感神經興奮劑、抗乙醯膽鹼、類固醇、以及茶鹼類藥物，phosphodiesterases 在人體的生理機能中佔了一極重要之地位，可調節 cyclic AMP 以及 cyclic GMP 之作用。如今常用之茶鹼類藥物即為不具特異性之 phosphodiesterase 阻斷劑，由於不同種類的 phosphodiesterase 在人體各個器官中分佈不同，理論上可依此選擇性地研發不同效用的藥品。自 1970 年代起，便有許多研究報告探討具特異性之 phosphodiesterase 阻斷劑在治療氣喘及慢性阻塞性肺病上潛在性之運用。其中又以 phosphodiesterase 4 (PDE4) 阻斷劑在肺部疾病的作用最為有效；它可抑制嗜中性白血球(neutrophil)的作用、減低腫瘤壞死因子(TNF- α 的合成、抑止肥胖細胞 mast cell) 顆粒之釋放、以及減低 T 細胞的增生。但是，目前已研發出的 phosphodiesterase 阻斷劑由於副作用過大，在臨床上之運用並不廣泛。史克美占藥廠(SmithKline Beecham Pharmaceuticals)即將推出一新的第二代 phosphodiesterase 4 阻斷劑 Ariflo™。在第二階段實驗中，Ariflo™ 可有效地改善運動產生之呼吸困難，增進第一秒最大呼氣量(FEV1)，以及減低小支氣管的關閉(small airway closures)，比較第一代的 phosphodiesterase 4 阻斷劑，其副作用遠較第一代之 phosphodiesterase 4 阻斷劑為少。此藥之臨床運用功效曾在去年歐洲呼吸年會引起熱烈討論，與會專家感認其將為慢性阻塞性患者增添一治療的新利器，在第三階段實驗結果揭曉之前，為文介紹，以饗讀者。(胸腔醫學 2000; 15: 157-164)

關鍵詞：Ariflo™，phosphodiesterase，慢性阻塞性肺病，氣喘

Hypersensitivity Pneumonitis with Recurrence—A Case Presentation and Review of the Literature

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A 76-year-old farmer suffered from fever, general malaise, and headache after he had trimmed the bushes near his farm. A chest radiograph revealed diffuse reticulonodular lesions, and thoracic high resolution computed tomography (HRCT) demonstrated patches of ground-glass opacity and reticulonodular centrilobular opacities. Based on the exposure history and HRCT findings, hypersensitivity pneumonitis was highly suspected. The symptoms subsided dramatically and the pulmonary infiltrates subsided gradually after corticosteroid prescription. Recurrence of hypersensitivity pneumonitis was noted two months after he had returned to his normal living and working environment. (*Thorac Med* 2000; 15: 165-171)

Key words: hypersensitivity pneumonitis, extrinsic allergic alveolitis.

過敏性肺炎—病例報告與文獻回顧

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過敏性肺炎，或稱外因性過敏性肺泡炎，是一種免疫反應性肺疾病。許多抗原可引起過敏性肺炎，包括微生物(黴菌、原蟲、細菌等)、動物性蛋白、昆蟲蛋白及某些低分子量無機化學物。臨床及病理上過敏性肺炎可分為三期：急性期、亞急性期及慢性期。急性期常表現發燒、咳嗽、全身不適等類似感冒的症狀。長期暴露在過敏抗原下(慢性期)，可導致體重減輕與肺纖維化。適度的治療與避免暴露過敏原方可根治肺部發炎。持續性過敏原暴露可能導致瀰漫性不可逆的肺纖維化。

過敏性肺炎的診斷並無特殊的檢查方法。血清中存在對過敏原具特異性抗體(precipitins)對診斷雖有幫助，但陰性反應並不能排除診斷。急性及亞急性期胸部影像檢查可呈現毛玻璃樣型態或細微顆粒影像；慢性期可見瀰漫性網狀結節樣肺浸潤及肺纖維。肺功能檢查通常呈現侷限型通氣障礙及肺彌散量低下。肺部巨噬細胞被活化及抑制型淋巴球(CD8+ lymphocyte)無法抑制活化型巨噬細胞，可能是導致過敏性肺炎發炎反應的免疫機轉。

在急性及亞急性期，類固醇的使用可加速肺損傷的復原。避免致病抗原的繼續暴露，是預防慢性不可逆肺纖維化的唯一也是最重要的準則。(胸腔醫學 2000; 15: 165-171)

關鍵詞：過敏性肺炎，外因性過敏性肺泡炎

DOTS－結核防治之最佳策略

江振源

DOTS 是世界衛生組織推薦的結核防治策略。DOTS-- Directly Observed Treatment, Short Course, 不只是短程直接監督治療，不只是看著病人服藥，DOTS 是一個包括五大要項的配套策略：(1)結核防治之政治承諾，(2)痰塗片檢驗、因症就診之被動式病人發現法，(3)標準化之短程治療，且至少前兩個月之直接監督療法，(4)充足之藥物供應，(5)標準化之登記與通報系統。DOTS 源自於不當的治療比不治療更糟的觀念變革，以及國際抗癆暨肺病聯盟之國家結核防治典範計劃(Model National Tuberculosis Programme)之經驗累積。世界衛生組織於 1993 年史無前例地宣佈單一疾病--結核病之全球危機。至 1998 年底，採行 DOTS 的國家已增加到 119 個，DOTS 的涵蓋面已達全球 43%的人口。台灣每年約有一萬三千五百個新病人發病，結核疫情每十萬人口 61.3，而且原發性抗藥率逐步攀升，我們需要 DOTS 策略。(胸腔醫學 2000; 15: 172-177)

關鍵詞：DOTS，直接監督療法，結核病

DOTS – The Most Effective Strategy For Tuberculosis Control

Chen-Yuan Chiang

DOTS (Directly Observed Treatment, Short-course) is the brand name of the WHO-endorsed tuberculosis control strategy. DOTS strategy has five components: (1) government commitment to sustained TB control, (2) case detection by sputum smear microscopy among symptomatic patients self-reporting to health services, (3) standardized short-course chemotherapy with directly observed treatment (DOT) for at least the initial two months, (4) a regular, uninterrupted supply of all essential anti-TB drugs, (5) a standardized recording and reporting system. The DOTS strategy was modeled after the program developed by Dr. Karel Styblo of the International Union Against Tuberculosis and Lung Disease. The issue of tuberculosis control has been ignored for more than 20 years by World Health Organization (WHO) when considering health priorities in low-income countries. The announcement by the WHO in 1993 that tuberculosis has become a global emergency was unprecedented. By the end of 1998, 119 countries had adopted the DOTS strategy for TB control; 43% of the global population had access to DOTS. There were 13,496 newly diagnosed TB cases with the incidence rate of 61.3 per 100,000 population in 1999 in Taiwan, and the antituberculosis drug resistance rate is increasing. We should implement DOTS strategy for tuberculosis control in Taiwan. (*Thorac Med* 2000; 15: 172-177)

Key Words: DOTS, Directly Observed Treatment, tuberculosis

呼吸衰竭病患使用壓力輔助控制通氣 與容積輔助控制通氣的比較

李俊德

正壓呼吸器在臨床應用上甚為廣泛，現行使用的呼吸器常可提供多種不同的通氣模式，給予重症病患適當的呼吸照護。壓力輔助控制通氣是一種由病患或時間來驅動，經壓力限制及時間週期的運作，以完成通氣支持的呼吸型態，而傳統的容積輔助控制通氣則差別在以預設的潮氣容積及氣流速率來決定病患的吸吐比例。為了檢測壓力輔助控制通氣在呼吸衰竭但意識清晰的病患是否優於容積輔助控制通氣，我們進行此研究。20 位在加護病房中使用呼吸器的病患，若血流動態穩定且有驅動通氣能力者，即予壓力輔助控制通氣及容積輔助控制通氣各 45 分鐘，並分別記錄比較病患在使用這兩種通氣模式時的狀況變化。結果顯示，當病患使用壓力輔助控制通氣時，其血流動力變化、動脈血液氣體分析值及肺部機械功能的數據並未優於容積輔助控制通氣模式，反而在病患的主觀舒適上，容積輔助控制通氣較壓力輔助控制通氣模式為佳。

結論：臨床醫師在處理呼吸衰竭病患時，仍以容積輔助控制通氣模式為首要選擇。(《胸腔醫學》2000; 15: 178-182)

關鍵詞：壓力輔助控制通氣，容積輔助控制通氣

Comparison of Pressure Assist-Control Ventilation and Volume Assist-Control Ventilation in Patients with Respiratory Failure

Jiunn-Der Lee

Positive pressure ventilation has gained wide application in clinical medicine and currently available ventilators provide many different ventilatory modes for use in the critical care settings. Pressure assist-control ventilation (PACV) is a patient- or time-triggered, pressure-limited, time-cycled mode of ventilatory support, characterized by a rapid increase of airway pressure with a decelerating inspiratory flow pattern. To ascertain whether PACV offers any advantage in comparison with volume assist-control ventilation (VACV) in clearly conscious patients with respiratory failure, we study 20 patients with ventilatory support in intensive care unit. Patients are awake and hemodynamically stable without use of sedative or muscle relaxant. Each patient is ventilated with PACV and VACV, in random sequence, for 45 min. respectively. The results show that no evidence of the benefit with PACV in comparison with VACV on hemodynamic effect, blood gas exchange and lung mechanics. Patients feel more comfortable when using VACV than PACV.

We conclude that VACV is still a mode of first choice in the management of patients with respiratory failure. (*Thorac Med 2000; 15: 178-182*)

Key Words: Pressure assist-control ventilation (PACV), Volume assist-control ventilation (VACV)

Clinical and Radiological Manifestations of Pulmonary Sequestration

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Pulmonary sequestration is a rare congenital pulmonary disorder defined as an area of dysplastic and non-functioning pulmonary tissue with an anomalous systemic blood supply. In the past 11 years, we have identified 5 cases of pulmonary sequestration in National Cheng Kung University Hospital. Two patients had extralobar sequestration (ELS) and three patients had intralobar sequestration (ILS). All the ILSs were in the left lower lobes. The two patients with ELS were a neonate and a 13-year-old. The neonate presented with congenital pleural effusion which required repeated chest tapping, and the 13-year-old boy presented with right hemothorax with chest pain. Among the patients with ILS, 2 suffered from chronic cough and the third one presented with hemoptysis. A preoperative diagnosis of pulmonary sequestration was made in three patients after the computerized tomography scan of the chest, and the final diagnosis of these five patients was confirmed by operation and pathological findings. The prognosis after operation was good in all patients. (*Thorac Med* 2000; 15: 183-188)

Key words: pulmonary sequestration, hemoptysis, hydrothorax, hemothorax, Spiral computed tomography

游離肺之臨床和影像學上之表現

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游離肺是一種少見的先天性肺部異常，它是一種無功能的肺組織而有異常的系統性動脈血流供應。解剖上它可分為 (1)肺葉內型：游離肺存在正常的肺葉之內 (2)肺葉外型：游離肺在正常的肺葉之外，並有其個別的肋膜包覆。我們醫院 11 年來經開刀及病理證實共有 5 名確定病例，其中 2 例是肺葉外型，3 例是肺葉內型。全部肺葉內型病例均位於左下肺葉，其中兩人表現為慢性咳嗽，另一人表現為復發性咳血。此三人之年齡在 26-38 歲間。2 個肺葉外型病人年紀都很輕，一為剛出生，一為 13 歲。這新生兒是以先天性肋膜腔積水來表現，並且在母體內時即曾接受過 4 次抽胸水；另外那 13 歲男孩是以血胸來表現。此五位病人有三位在手術前經由電腦斷層攝影已診斷為游離肺。全部病人接受手術後預後均良好。(胸腔醫學 2000; 15: 183-188)

關鍵詞：游離肺，咳血，水胸，血胸，電腦斷層

哮喘或慢性阻塞性肺疾之門診患者不正確使用 霧氣治療之評估

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霧氣治療對於氣喘患者是相當經濟、方便且有效的治療。治療效果的好壞取決於吸入器的設計和人為操作的正確性。常用之吸入器有兩種：1) 定量噴霧吸入器 (metered-dose inhaler, MDI)；與 2) 乾粉式吸入器 (dry-power inhaler, DPI)。有研究報告指出患者常有明顯誤用吸入器的情形。本研究之目的是在評估患有哮喘或慢性阻塞性肺疾之門診患者對於定量噴霧吸入器與乾粉式吸入器是否能正確的操作。

研究對象為南部某醫學中心胸腔科門診患有哮喘或慢性阻塞性肺疾之患者 75 人。實施方法為觀察與記錄患者對於定量噴霧吸入器與乾粉式吸入器 (包括準納乾粉定量吸入器, Accuhaler 及易吸乾粉定量吸入器, Easyhaler) 的各個操作步驟，能否正確達成，而予以評分。並依操作評比將受測者區分為良好、普通與不好之等級，來比較不同吸入器的差異。

結果顯示有相當高比率的患者 (定量噴霧吸入器 76%，乾粉式吸入器 58%) 未能良好的操作各種吸入器。常見之共同錯誤步驟是在吸藥前未能將氣儘量吐出以及吸藥後未能閉氣；操作定量噴霧吸入器另外之缺點在於未能達到手啟動-吸氣協調；而乾粉式吸入器則是未能快速的深吸氣。統計上，患者能良好操作乾粉式吸入器 (Accuhaler) 的比率比其使用定量噴霧吸入器者有顯著的增加 (48% vs 24%, $p=0.002$)；反之，在操作不好的患者中，其使用定量噴霧吸入器的比率比使用乾粉式吸入器 (Accuhaler) 者亦有顯著的增加 (17% vs 7%, $P=0.044$)。

要正確使用吸入器需仰賴於正確的衛教示範與個人的反覆練習。研究顯示氣喘患者對於吸入器的操作確有加強的必要。面對推陳出新的吸入器，醫護人員當把握各進修機會充實霧氣治療的技能，才能提供患者正確的衛教，而獲得最有效的治療。(胸腔醫學 2000; 15: 189-194)

關鍵詞：霧氣治療，定量噴霧吸入器，乾粉式吸入器

Evaluation of Misuse of Aerosol therapy by Patients with asthma or COPD in Outpatient settings

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Aerosol therapy is an economic, convenient and effective treatment for patients with dyspnea. The efficiency of the aerosol therapy depends on the design of the inhalers and correct performance of the patients. The major inhaler devices include 1) metered-dose inhaler (MDI), and 2) dry-powder inhaler (DPI). Many studies have demonstrated the misuse of aerosol therapy by the patients. The aim of present investigation was to evaluate the knowledge and skill of the patients with dyspnea in the proper use of aerosol therapy.

Seventy-five patients of asthma or COPD in the chest medicine clinic of a medical center in Southern Taiwan were included. They were assessed as to their proficiency in the use of MDI (including Ipradol and Atrovent) or DPI (including Accuhaler and Easyhaler). We recorded correct steps of each inhaler achieved by the patients and divided the patients into three groups: good, fair and poor according to the achievement. Statistical analysis was carried out to evaluate the difference between inhalers.

The study confirms that a large percentage of patients used MDI (76%) or DPI (58%) incorrectly. The most common problems were a) failing to keep breath-holding after inspiration, and b) failing to exhale out before drug inhalation. The other major problem in MDI was discordance between actuating and breathing; however, the problem in DPI was failing to breathe-in forcefully and deeply. Statistically, the incidence of good score in the performance of DPI (Accuhaler) was much higher than that in the MDI performance (48% vs 24%, $p=0.002$). Similarly, significant difference was also demonstrated between MDI and DPI (Accuhaler) performance in the groups of poor score. (MDI 17% vs DPI 7%, $p=0.044$)

Both correct demonstration and repeated practice are necessary to achieve proper performance of the inhalers. The physicians and nurses should try hard to learn each kind of new inhaler devices before the can demonstrate correctly to the patients. (*Thorac Med* 2000; 15: 189-194)

Key words: aerosol therapy, metered-dose inhaler, dry-powder inhaler

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Pulmonary Nocardiosis – A Case Report

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Pulmonary nocardiosis is an infrequent but severe infection presenting with a variety of radiographic abnormalities. It is most common in immunocompromised patients or in those being treated with corticosteroid for chronic obstructive pulmonary disease or other systemic disease, but otherwise it may occur in healthy persons. Pulmonary nocardiosis is mainly acquired by direct inhalation of *Nocardia* spp. from contaminated soil, and presents as a subacute or chronic suppurative pulmonary disease. *Nocardia* is relatively difficult to culture and nocardiosis can coexist with diseases that are more easily diagnosed, so it is essential to make a proper diagnosis on the basis of a high level of suspicion and the full acknowledgement of the patient.

We report a patient with pulmonary nocardiosis who improved after sulfa drug and minocycline treatment. (*Thorac Med* 2000; 15: 195-199)

Key words: pulmonary nocardiosis, corticosteroid, sulfa drug

肺部奴卡氏菌病－病例報告

楊俊杰 謝俊民 江國華 柯獻欽

肺部奴卡氏菌病是一種不常見且具有多種肺部病狀表現的嚴重感染，主要發生在免疫功能低下或接受類固醇治療的慢性阻塞性肺疾病及其他內科疾病患者，但亦能在正常之宿主上造成感染。其傳染途徑主要是存在土壤中的奴卡氏菌經由空氣吸入肺部而呈現出亞急性或慢性肺部發炎。因奴卡氏菌不易培養且能伴隨其他較易診斷之肺部疾病共同發生，故診斷不易，唯有高度的警覺配合對病患的了解，方能獲致正確之診斷。

在此我們報告一例肺部奴卡氏菌病經磺胺藥物治療痊癒的經過。(胸腔醫學 2000; 15: 195-199)

關鍵詞：肺部奴卡氏菌，類固醇，磺胺藥物