

Evaluation of Effect of Statin and Fibrate Drugs on Hypercholesterolemia

林雅玲、張耀南

E-mail: 9417974@mail.dyu.edu.tw

ABSTRACT

In this study, the 556 patients with hypercholesterolemia (330 men and 226 women) were diagnosed clinically by physicians in certain local hospital, Changhua county, Taiwan, from January in 2004 to March in 2005. The total cholesterol (TC) or triglycerides (TG) of the patients was out of normal level ($>240\text{mg/dL}$ TC or $>150\text{mg/dL}$ TG), as described in clinical trials. The effect of drug treatment of Statin or Fibrate on blood lipoprotein properties of the patient cases, such as lowering serum TC、TG、LDL or increasing serum HDL, was investigated. It was found that the percentage of the patient TC below 200mg/dL was 65% in average. For the patient cases after Statin drug treatments the percentage of LDL below 100mg/dL and TG below 150mg/dL was around 45% and 13%, respectively, while the percentage of HDL over 60mg/dL was around 5%. For the cases after Fibrate drug treatments the percentage of LDL and TG below normal level was about 12% and 51%, respectively, while the percentage of HDL increasing over normal level was about 23%. The result of this study will be good for the physicians by using Statin or Fibrate drug treatment to improve the patients' metabolic disorder of serum lipoprotein.

Keywords : Statin ; Fibrate ; Hypercholesterolemia ; Cholesterol ; Triglyceride

Table of Contents

封面內頁 簽名頁 授權書iii 中文摘要iv 英文摘要v 誌謝vi 目錄vii 圖目錄ix 表目錄x 第一章 前言1 第二章 文獻回顧3 2.1脂質的功能3 2.2血脂異常原因3 2.2.1原發性血脂異常3 2.2.2續發性血脂異常4 2.3美國國家膽固醇教育計畫對脂質異常之分類8 2.4降血脂劑的主要類別10 2.4.1 Statins的歷史13 2.4.2膽固醇生合成途徑14 2.4.3藥理作用/作用機制14 2.4.4藥動學16 2.4.5適應症16 2.4.6安全性19 2.4.7藥物交互作用 20 2.4.8劑量及給藥方法24 2.5纖維酸衍生物Fibric Acid Derivatives作用機制24 2.5.1適應症26 2.5.2降低冠狀動脈心臟病之危險性26 2.5.3安全性27 2.5.4劑量和用法29 第三章 材料與方法32 3.1研究方法32 3.2藥物32 3.3分析儀器32 3.4分析項目33 3.5分析方法33 第四章 結果與討論34 第五章 結論44 參考文獻45 附錄53 圖 目錄 圖2.1膽固醇生合成途徑15 圖4.1 個案數性別比35 圖4.2 五種不同藥物治療個案比36 圖4.3 Fibrate藥物治療個案性別比37 圖4.4 Statin藥物治療個案性別比38 圖4.5 不同藥物治療監測期TC -C降至理想值個案比40 圖4.6 Fibrate and Statin藥物降TG至理想值個案比41 圖4.7 Fibrate and Statin藥物降LDL-C至理想值個案比42 圖4.8 Fibrate and Statin藥物提昇HDL-C理想值個案比43 表 目錄 表2.1飲食中的脂肪5 表2.2美國國家膽固醇教育計畫之分類9 表2.3評估降低低密度脂蛋白膽固醇的主要危險因子 12 表2.4藥動動力學資料之比較17 表2.5處方每個Statin時必須進行肝功能檢測的時間21 表2.6 Statins與其他藥品間之交互作用23 表2.7 Statins之使用劑量表25 表2.8 Fibric Acid Derivatives之副作用28 表2.9全民健康保險降血脂藥物給付規定表30

REFERENCES

- 1.中央健康保險局全民健康保險藥品給付規定，2004年修訂版。 2.行政院衛生署。2004a。國人血清三酸甘油脂的平均值、標準差、過高比率依性別、年齡層之比較。第19-22頁。台北，臺灣。 3.行政院衛生署。2004b。國人血清總膽固醇的平均值、標準差、過高比率依性別、年齡層之比較。第16-20頁。台北，臺灣。 4.行政院衛生署。2004c。92年國人主要死因與主要癌症統計結果。第21-24頁。台北，臺灣。 5.林興中。2004。糖尿病併血脂異常的處理。臺灣醫界47:1-10。 6.莊書碩、陳仲達、傅振宗。2002。第二型糖尿病血脂異常機轉與治療。基層醫學17:173-178。 7.張國欽、林興中。1992。九十年代高血脂症新貌。臺灣醫界35:94-103。 8.顧志政。2001。預防與治療高脂血症的新趨勢。藥學雜誌18 (2) :55-60。 9.Adhikari, M. R., Prabha, J., Kannampilly, J., Hegde, B. M., Pereira, P. and Maya, P. D. 1997. Chowta Nityananda of Medicine, Kasturba Medical College, Mangalore - 575 001 and ' Port Trust Hospital.,Vascoagama Manuscript. Indian Journal of Pharmacology 29: 314-317. 10.ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. 2002. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 288: 2998 – 3007. 11.Bradford, R. H., Shear, C. L., Chremos, A. N., Dujovane, C. A., Franklin, F. A., Grillo, R. B., Higgins, J., Langendorfer, A., Nash D. T., Pool, J. L. and Schnaper, H. 1994. Expanded Clinical Evaluation Lovastatin(EXCEL) study results two-year efficacy and safety follow-up. Am. J. Cardiol. 74: 67-73. 12.Cannon, C. P., Braunwald, E., McCabe, C. H., Rader, D. J., Rouleau, J. L. and Belder, R. 2004. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. N. Engl. J. Med. 350: 1495 – 1504. 13.Colhoun, H. M., Betteridge, D. J., Durrington, P. N., Hitman, G. A., Neil, H. A. and Livingstone, S. J. 2004. Primary prevention of cardiovascular disease with atorvastatin in type 2

diabetes in the Collaborative Atorvastatin Diabetes Study(CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 364: 685-696.

14.Frick, M. H., Elo, O., Haapa, K., Heinonen, O. P., Heinsalmi, P. and Helo, P. 1987. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N. Engl. J. Med.* 317(20): 1237-1245. 15.Grundy, S. M., Cleeman, J. I., Bairey, C. N., Brewer, J. R., Merz, H. B., Clark, L. T. and Hunninghake, D. B. 2004. NCEP Report: Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation* 110: 27-39. 16.Haffner, S. M. 1998. American Diabetes Association: Management of dyslipidemia in adults with diabetes (Technical review). *Diabetes Care* 21(1): 160 – 178. 17.Haffner, S. M., Lehto, S., Ronnema, T., Pyorala, K. and Laakso, M. 1998. Mortality from Coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New Engl. J. Med.* 339: 29-34. 18.Heart Protection Study Collaborative Group. 2003. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. *Lancet* 361: 2005-2016. 19.Herlitz, J., Malmberg, K., Karlson, B. W., Ryden, L. and Hjalmarson, A. 1988. Mortality and morbidity during a five-year follow-up of diabetics with myocardial infarction. *Acta. Med. Scand.* 224: 31 – 38. 20.James, R. and Sowers, M. D. 2004. Treatment of Hypertension in Patients With Diabetes. *Arch Intern Med.* 164: 1850-1857. 21.Kannel, W. B. and McGee, D. L. 1979. Diabetes and cardiovascular disease: The Framingham study. *JAMA.* 241: 2031-2034. 22.Kannel, W. B. and McGee, D. L. 1979. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care* 2: 120 – 126. 23.Kornitzer, M., Dramaix, M., Vandebroek, M. D., Everaert, L. and Gerlinger, C. 1994. Efficacy and tolerance of 200 mg micronised fenofibrate administered over a six month period in hyperlipidemic patients: an open Belgian multicenter study. *Atherosclerosis* 110: 49-54. 24.Libby, P. 1995. Molecular bases of the acute coronary syndromes. *Circulation* 191(11): 2844-2850. 25.Maas, I. 1994. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study(MAAS). *Lancet* 344: 633-638. 26.Mark, L., Britton, N., Letassy, A. and Sirmans, S. M. 1994. Managing High Blood Cholesterol in Patients with Coronary Artery Disease. *Pharmacy Times* 2: 64-70. 27.Mostaza, J. M., Vega, G. L., Snell, P. and Grundy, S. M. 1998. Abnormal metabolism of free fatty acids in hypertriglyceridemic men: apparent insulin resistance of adipose tissue. *J. Intern. Med.* 234: 265-274. 28.Mycek, R., Mary, J., Harvey, A. and Pamela, C. Lippincott 's Illustrated Reviews: Pharmacology 2nd Edition 29.Nil. 1984. The Lipids Research Clinics coronary primary prevention trial results, II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. Lipid Research Clinics Program. *JAMA.* 251(3): 365-374. 30.Nil. 1989. The lipid reduces medicines in the course of scleratheroma – HMG-CoA reductase inhibitor. *Clin expands Hypertens A.* 11(5-6): 927-941. 31.Nil. 1991. In: Wingard et al (Eds.), *Human Pharmacology Molecular-to-Clinical*, ISE. Wolfe Publishing Ltd, London, *Lipid-Lowering Drugs and Atherosclerosis*. pp. 266-282. 32.Nil. 2001. Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. *JAMA.* 285(19): 2486-2497. 33.Nil. 2004a. American Diabetes Association: Dyslipidemia management in adults with diabetes. *Diabetes Care* 27: 68-71. 34.Nil. 2004b. American Diabetes Association: Physical activity/exercise and diabetes. *Diabetes Care* 27: 58-62. 35.Nil. 2004c. American Diabetes Association: Standards of medical care in diabetes. *Diabetes Care* 27: 68-71. 36.Pyorala, K., Pedersen, T. R., Kjekshus, J., Faergeman, O. and Olsson, A. G., 1997. Thorgeirsson G: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Study (4S). *Diabetes Care* 20: 614-620. 37.Ralph, H. 1992. In: Koda-Kimble et al (Eds.), *Applied Therapeutics The Clinical Use of Drugs*, Fifth edition. Applied Therapeutics, Inc, WA. 73: 1-15. 38.Rosenson, R. S. and Tangeney, C. C. 1998. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. *JAMA.* 279(20): 1643-1650. 39.Rubins, H. B., Robins, S. J., Collins, D., Nelson, D. B., Elam, M. B. and Schaefer, E. J. 2002. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch. Intern. Med.* 162: 2597-2604. 40.Sacks, F. M., Pfeffer, M. A., Moye, L. A., Rouleau, J. L., Rutherford, J. D. and Cole, T. G. 1996. For the Cholesterol and Recurrent Events Trial Investigators: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N. Engl. J. Med.* 335: 1001-1009. 41.Scandinavian Simvastatin Survival Study Group. 1994. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study(4S). *Lancet* 344: 1383-1389. 42.Scott, C. L. 2003. Diagnosis, prevention, and intervention for the metabolic syndrome. *Am. J. cardiol.* 92(1A): 35-42. 43.Sever, P. S., Dahlof, B., Poulter, N. R., Wedel, H., Beevers, G. and Caulfield, M. 2003. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm(ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 361: 1149 – 1158. 44.Shepherd, J., Blauw, G. J., Murphy, M. B., Bollen, E. L., Buckley, B. M., Cobbe, S. M. 2002. Pravastatin in elderly individuals at risk of vascular disease(PROSPER): a randomised controlled trial. *Lancet.* 360(9346): 1623 – 1630. 45.The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. 1998. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N. Engl. J. Med.* 339: 1349-1357. 46.The UK Prospective Diabetes Study Group. 1998. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes(UKPDS 34). *Lancet* 352: 854-865. 47.The West of Scotland Coronary Prevention Study Group. 1998. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study(WOSCOPS). *Circulation* 97: 1440-1445. 48.Turner, R. C., Millns, H., Neil, H. A., Stratton, I. M., Manley, S. E. and Matthews, D. R. 1998. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus(UKPDS 23). *BMJ.* 316: 823-828.