光敏感性藥物研究

第壹部分 鈣離子阻斷劑光分解反應研究

第貳部分 非固醇類抗發炎藥物光分解產物及其抗發炎活性

Photosensitivity drugs
(I) Photodegradation of calcium channel blockers
(II) Photoproducts of NSAIDs and their anti-inflammatory activities

中文摘要

光敏感性是藥物常見的不良影響，本研究第一部份爲尼卡迪平的光分解反應，尼卡迪平暴露於汞燈下，以 LC/MS 鑑定共 8 個光分解產物，主產物爲 4-(3''-硝基苯基)吡啶衍生物(NIC-7)。尼卡迪平於照光後進行一系列的硝基還原反應，並提出其可能的反應途徑。

研究第二部份目的是選擇特定之非固醇類抗發炎藥物(氟白普洛芬與吲哚美洒辛)在醇類溶媒中以汞燈照射探討其光解情形，以 GC/MS 與 LC/MS 進行其光解產物結構之鑑定，並檢查吲哚美洒辛及其產物一些藥理作用。總計以 GC/MS 與 LC/MS 光譜分析氟白普洛芬與吲哚美洒辛於甲醇溶媒中之光分解，各鑑定出 10 個與 4 個光解產物，並進而推測其反應途徑。在藥理研究方面，吲哚美洒辛比較其所衍生之光解產物，具有最強的氫氧自由基與黃嘌呤氧化酵素抑制活性，IC50 各爲 65 μM 與 86 μM。此外，吲哚美洒辛甲基酯衍生物(IN-3)其在 LPS 刺激 RAW 264.7 巨噬細胞誘導發炎的實驗模式中具有優於 IN 的抑制 NO 及 PGE2 生成與 iNOS 及 COX-2 蛋白表現的能力，類似一般 NSAIDs 的作用。對 HL-60 之細胞毒殺效果是以 MTT 法檢驗，結果顯示 HL-60 細胞毒殺 IC50 爲 36.9 g/mL，效果強於 IN。再者，由生化檢驗發現 IN-3 會引起 HL-60 細胞凋亡、DNA 裂解，並增強 PARP 與 pro-caspase 3 的裂解作用，以上結果支持光解產物 IN-3 具有優於母藥吲哚美洒辛的抗發炎(LPS 刺激 RAW 264.7 巨噬細胞)及細胞毒殺(HL-60)效果。

英文摘要

Photosensitivity is a commonly adverse effect of drugs. The purpose of the first part of this study is focus on the photodegradation of nicardipine. When nicardipine was exposed to the Hg lamp, eight photoproducts of nicardipine were identification by LC/MS. The main degraded product was a pyridine analogue (NIC-7). Nicardipine apparently undergoes a series of nitro group photo-reduction pathways under irradiation leading to a complex formation of mainly the reduced products. A reaction scheme of nicardipine was proposed.

The second part, gives a study on the photochemical behavior when NSAIDs (flurbiprofen and indomethacin) in alcoholic solvents are exposed to Hg lamps. GC/MS and LC/MS were applied to determine the structure of photoproducts. In addition, some pharmacological effects were also examined. In total, ten and four photoproducts derived from flurbiprofen and indomethacin methanolic samples, respectively, were identified by GC/MS and LC/MS. Furthermore, the reaction schemes of flurbiprofen and indomethacin in methanol are proposed. As to the study of pharmacological effects, results suggested that among all the related photoproducts, Indomethacin stand out and showed the strongest hydroxyl radical-scavenging effect with an IC50 of 65 μM and the strongest xanthine oxidase inhibitory effect with an IC50 of 86 μM. We also found that the methyl ester derivatives of indomethacin (IN-3) could more-potently inhibit PGE2 and NO production and iNOS and COX 2 protein expression from LPS-stimulated RAW 264.7 cells than indomethacin, similar to the effect of a typical NSAID. The cytotoxic effects of the test samples were measured using the MTT assay. The results showed that IN-3 with an IC50 value maintained at 36.9 ?慊/mL for 12 h that exhibited stronger cytotoxicity than indomethacin in HL-60 cells. Moreover, IN-3 caused apoptotic bodies, DNA fragmentation, and enhanced PARP and pro-caspase 3 degradation in HL-60 cells as determined by a series of biochemical analyses. The above results indicated that the photoproduct, IN-3, had stronger anti-inflammatory in LPS-stimulated RAW 264.7 cells and cytotoxicity effects in HL-60 cells than the parent drug, indomethacin.