吩坦尼穿皮輸藥製劑的研究

Study of Fentanyl Transdermal Delivery

中文摘要

有效的控制慢性疼痛在治療學上具有相當的價值，因此選擇小分子量、強止痛效果、作用時間短、高脂溶性、屬於合成鴉片類的中樞神經類止痛劑—吩坦尼(fentanyl)來作爲皮膚投予的藥物研究。本研究主要在探討以高分子界面活性劑之嵌段式共聚合物(block copolymer)來作爲吩坦尼穿皮製劑的控釋基劑，並研究其穿透的機制。在實驗的設計上，首先(1)利用[4-14C]-氫偶素(estradiol)與 D-[1-14C]-甘露醇(mannitol)評估不同冷凍時間裸鼠(nude mouse)皮膚以及腹部(abdominal)與背部(dorsal)皮膚對於藥物穿透的影響，(2)使用芘(pyrene)作爲螢光探針(fluorescence probe)與光散射(quasi-elastic light scatter)技術評估嵌段式共聚合物的物理化學性質，(3)使用纖維素膜(cellulose membrane)來評估不同濃度吩坦尼及不同濃度基劑控釋對於吩坦尼在體外基劑控制穿透的影響，(4)以不同濃度吩坦尼與不同濃度基劑進行體外裸鼠腹部評估吩坦尼在皮膚穿透的表現，(5)利用不同親水性質的試藥([4-14C]-氫偶素、D-[1-14C]-甘露醇、螢紅異硫氰酸(FITC))評估不同濃度的嵌段式共聚合物對藥物在穿透上的差異，(6)使用聚苯乙烯(polystyrene)評估不同粒徑大小以及電荷的分子對於藥物在穿透上的差異，(7)利用家兔來研究含 46% 嵌段式共聚合物之吩坦尼貼劑的體內初步藥物動力學。經由評估結果，腹部皮膚穿透係數(P 值 2.24±0.47×10-6 cm/sec) 較背部皮膚大(P 值 1.41±0.30×10-6 cm/sec)，立即取下的皮膚與冷凍的皮膚也有差異，而以立即取下的裸鼠腹部皮膚較接近真實的的生理模式。嵌段式界面活性劑嵌段式共聚合物物理化學性質結果顯示其臨界膠體質濃度(critical micelle concentra-tion)在 0.1% w/w 的濃度。在嵌段式共聚合物作爲吩坦尼穿皮製劑的控釋基劑方面，在達到46%的嵌段式共聚合物時，能夠在 37OC 下形成凝膠態；並具有持續釋放的效果(flux 值爲 0.0121 mg/cm2/hr)；而隨著嵌段式共聚合物濃度的增加，吩坦尼的釋放速率有遞減的現象(46%濃度時，flux 值 0.0664 mg/cm2/hr)。在裸鼠腹部皮膚的穿透速率也有遞減，亦以46%濃度時爲甚 (P 值 2.24±0.47×10-6cm/sec 到 2.41±1.36 ×10-7cm/sec)。而在不同濃度吩坦尼的 46% 嵌段式共聚合物凝膠態製備中，隨著吩坦尼的增加，在纖維素膜與裸鼠腹部皮膚穿透量也隨著增加。不同親水性質的試藥在嵌段式共聚合物的製劑上發現，疏水性(hydrophobic)的藥物會受到在嵌段式共聚合物逐漸提高時會讓其穿透量逐漸減少(吩坦尼、氫偶素、螢紅異硫氰酸)，親水性的藥物則沒有差異(甘露醇)。經由芘螢光探針技術可發現，隨著共聚合物嵌段式共聚合物的濃度的增加，形成膠體質而造成疏水性的藥物轉移到屬於厭水區的膠體質核(core)部位，而減緩了藥物的釋出速率；而帶正電荷以及粒徑較小的分子在穿透係數上有較高的值；嵌段式共聚合物在製劑上是可以穿透纖維素膜與裸鼠皮膚並且可以達到臨界膠體質濃度。在家兔的初步藥物動力學結果顯

示出此 46% 嵌段式共聚合物的吩坦尼穿皮輸送貼劑在家兔可以產生控釋的效果，在 24 小時後可以達到穩定的血中濃度，並且持續釋放出吩坦尼至少在體內維持達 72 小時之穩定的血中濃度。

英文摘要

Purpose Effective control of chronic pain can be of enormous therapeutic value. Fentanyl, because of its rapid onset, short duration of action, and high potency, is suitable for transdermal application. The primary objective of this present study is to investigate the feasibility of the block copolymer as a re-lease vehicle for percutaneous administration of fentanyl. Method (1)[4-14C]-estradiol and D-[1-14C]-mannitol were investigated in the permeabilities through different frozen time and different part of the nude mouse skins. (2)Characterization of surface-active block copolymer micelle formation in an aqueous medium was examined by a combination of fluorescence probe (pyrene) and quasi-elastic light scatter techniques. (3)The sustained release effects of fentanyl was studied by cellulose membrane with different concen-trations of block copolymer and series drug concentrations. (4)Different con-centrations of fentanyl with 46% block copolymer and series concentrations of block copolymer with fentanyl were also investigated through nude mouse skin transport. (5)Different hydrophilicity drugs were studied in presence of various concentrations of block copolymer by using [4-14C]-estradiol, D-[1-14C]-mannitol, and fluorescent labeled FITC. (6)Different size and charge agents were studied by the 46nm latex beads with amine and carboxylate modified. (7)The preliminary pharmacokinetic behaviors of fentanyl patch was studied in rabbits with transdermal administration. Results Abdominal part of nude mouse skin has a higher permeability coefficient than the dorsal site (permeability coefficient, P, 2.24±0.47×10-6cm/sec vs. 1.41±0.30×10-6cm/sec). A significant difference among different frozen time nude mouse skin was also observed as well as sacrificed immediately. The critical micelle concentration of the copolymer range in 0.1% w/w was found by the fluorescence probe technique. The copolymer can forms gel in the concentra-tion of 46% in 37℃, and it performs sustained release effect as flux 0.0121 mg/cm2/hr. With increasing concentration of block copolymer in cellulose transport, the apparent release rate of fentanyl decreased (flux, 0.0664 mg/cm2/hr in water and 0.0121 mg/cm2/hr in 46% block copolymer). Assess-ment of the polymer's effect in the abdominal nude mouse skin was also shown a decrease in the permeability coefficient (PH2O value 2.24±0.47×10-6cm/sec and P46% block copolymer 2.41±1.36×10-7cm/sec). In addition, in-creasing in drug concentration, the drug release rate and permeability was increased. On the other hand, a meaningfully decreased permeability in hy-drophobic drugs (fentanyl, estradiol, and FITC) were

found, while increasing the concentration of block copolymer, but there was no affected in the hydro-philic drug, mannitol. Molecules with positive charge and smaller size have higher permeability coefficient. block copolymer is able to transport through the nude mouse skin and the cellulose membrane by the evidence of pyrene fluorescence spectrophotometry. In the preliminary pharmacokinetics of fen-tanyl patch contains 46% block copolymer in rabbit, fentanyl performs sus-tained release effect and maintains in steady state at least 72 hours. Summary Sustained permeability occurred in hydrophobic drugs showed the transfer of these agents into the hydrophobic domain of the polymeric micelle, and as a release vehicle for percutaneous administration of fentanyl was exhibited in this study.