天然辣椒素及合成辣椒素水性凝膠之體外穿透與皮膚藥物動力學研究

In vitro permeations and in vivo dermatopharmacokinetics of topically applied capsaicin and nonivamide from hydrogels

中文摘要

番椒晶素 (Capsaicin)是茄科番椒屬植物果實的主要有效抽取成分，其在心血管、周邊血管、消化、免疫及神經系統皆有藥理活性，FDA 已核准辣椒藥膏用於疱疹後神經痛、關節痛及糖尿病神經病變。Nonivamide 爲 capsaicin 之合成同類物，它保留番椒晶素之藥理活性及辛辣刺激性，但其由合成而得，成本低，且無雙鍵結構較安定。

依據美國食品藥物管理局，藥物評估及研究中心，1998 年公布的「局部用藥新藥申請(NDA)時，體內生體可用率(BA)、生體相等性(BE)、體外釋出及相關研究」草案中，以膠帶撕除法測定角質層中的藥物含量，檢測市售 capsaicin 霜劑及一系列自製製劑，比較各種製劑的體內吸收能力。歐洲替代方法確效中心所推薦的經皮吸收評估方法中，則嘗試以體外方法替代來源有限的人體和動物體內試驗。於此研究亦以體外及體內方法探討自製水性凝膠中 capsaicin 和 nonivamide 經由裸鼠、大白鼠、人皮膚的吸收能力，同時也評估市售 capsaicin 霜劑(cream)，以便與水性凝膠相互比較。由膠帶撕除角質層技術，MexameterÒ、Colorimeter 之皮膚色差測定，TewameterÒ 的表皮水分散失測量等評估角質層中（皮內）藥物含量，及體內吸收的 capsaicin 或 nonivamide 所引起的皮膚發紅、表皮水分散失效應與藥理作用。

研究結果顯示藥物在皮膚及水性凝膠基質(vehicle)之間的分配(partitioning)，似乎在穿透皮膚過程中佔有重要角色。由水性凝膠釋出的 capsaicin 之結果發現體外穿透皮膚能力，視所使用聚合物的物化性與濃度而定。加入非離子性的 Pluronic F-127 高分子聚合物的水性凝膠會延滯 capsaicin 的釋出。另一方面，在 capsaicin 的皮膚穿透能力的體外試驗結果發現，含陽離子的聚甲殼糖(chitosan)水性凝膠及含陰離子的 carboxymethyl cellulose (CMC)水性凝膠的穿透力，都比霜劑基劑爲高。在裸鼠皮體外試驗發現，nonivamide 的皮膚穿透是在投藥的後期，有阻礙吸收效應。個體間的差異，在體內人體研究比在體外動物皮膚穿透試驗中顯著。霜劑在體內試驗中所誘發的皮膚發紅現象視藥物劑量而定，但在水性凝膠中則並未觀察到此劑量相關性（dose-dependency），推測可能是受體被飽和。在皮膚出現發紅反應上，投與 nonivamide 較 capsaicin 強烈。此研究指出：局部投與 capsaicin 和 nonivamide 時，體外試驗的皮膚穿透能力和體內試驗中的發紅反應間有相關性；同時也觀察到體內試驗中，角質層中藥物含量和皮膚發紅試驗間也有相關性。由大白鼠的動物模式探討 nonivamide 的體外穿透與體內藥效反應。Pluronic 會造

成 nonivamide 的釋出受阻，因此不論體外穿透速率、皮內藥物含量，及體內表皮水分散失、皮膚色差試驗中，其比市售霜劑的皮膚穿透更差。而 chitosan 及 CMCNa 水性凝膠製劑由於比霜劑更親水，因此脂溶性的 capsaicin、nonivamide 更易穿透皮膚。
市售處方及 capsaicin、nonivamide 於水性凝膠中，其皮膚穿透、皮內藥物含量，及表皮水分散失都有藥物劑量相關性。
各種處方在總穿透量與皮內藥物含量、皮內藥物含量與表皮水分散失、總穿透量與表皮水分散失均有相關性，因此如同歐洲替代方法確效中心的建議，精確的體外評估方法可替代體內的評估。

英文摘要

Capsaicin (8-methyl N-vanillyl-6-nonenamide), a pungent principle of red pepper, has a variety of pharmacological actions on cardiovascular, peripheral vascular, digestive and nervous system. Various therapeutic advantages of capsaicin such as antinociceptive, hypotension and hypolipidemia activities have been reported previously. Capsaicin cream had been approved by FDA in the treatment of postherpetic neuralgia, arthritis pain and diabetic neuropathy. Nonivamide (N-nonanoyl vanillyamide) is a synthetic analogue of capsaicin. The pharmacological and pungent profiles of nonivamide were found similar to those of capsaicin, but nonivamide is cheaper and more stable than capsaicin.
The goals of this study are to investigate the skin absorption profiles of commercial capsaicin creams and new-developed hydrogel preparations, and to compare the difference of skin absorption between capsaicin and nonivamide. The feasibility of dermatopharmacokinetic (DPK) approach was also investigated in this study. In vitro models were used to determine the skin permeation by nude mouse and Wistar rat, as well as the amount of agents in skin by Wistar rat. In vivo tests included measuring the transpeidermal water loss by Tewameter, skin erythema by Mexameter or Colorimeter, and the concentration in stripped human stratum corneum. The skin stripping method was based the draft of “Topical dermatological drug product — In vivo bioavailability, bioequivalence, in vitro release and associated studies”, which is the DPK approach published by CDER, FDA in 1998.
The partition of drug between skin and the hydrogel matrix seems to play an important role in the permeation process. The in vitro permeation of capsaicin from hydrogels depended on the physicochemical nature and the concentration of the polymer used. The incorporation of nonionic Pluronic F-127 polymer into hydrogels resulted in a retarded release of capsaicin. On the other hand, the in vitro capsaicin permeation study showed higher levels in cationic chitosan and anionic carboxymethylcellulose (CMC) hydrogels than cream bases, because they are more

hydrophilic than cream. It is easily to permeate to skin for capsaicin with lipophilic character. The permeation of nonivamide was retarded at the late stage of in vitro application.

In vivo Wistar rat study, we use colorimeter to evaluate skin erythema and tewameterâ to evaluate the transepidermal water loss. In vivo skin erythema induced by creams depended on the drug concentration, however, the dose-dependency relation was not observed in hydrogels, so it is possible due to the saturation of the nociceptor. Nonivamide-treated skin showed stronger erythema than capsaicin-treated skin. The present study indicates that there is a moderate correlation between in vitro skin permeation and in vivo erythema responses of topically applied capsaicin and nonivamide.

In vivo human study, we used skin stripping technique to evaluate the drug retained in stratum corneum and used Mexameterâ to evaluate skin erythema. The inter-subject variation was more significant in the in vivo study than in vitro skin permeation experiments. The correlation between drug amount in SC and skin erythema test in vivo was also observed.

The skin permeation, the total amount in skin residue, and transepidermal water loss of commercial creams and new hydrogel of capsaicin and nonivamide showed dose-dependent relationship. In all hydrogel formulations, the amount in skin residue was significantly correlated with the skin permeation as well as transepidermal water loss. The skin permeation was also found to be well correlated with transepidermal water loss. There meaningful correlations validated that in vitro permeation method can be an alternative method for the in vivo method as expected by ECVAM (European center for the validation of alternative methods).