中山醫學大學醫學研究所碩士論文

Master Thesis,Institute of Medicine, Chung Shan Medical University

以 5-Hydroxytryptamine Type 3(5-HT_3) 接受器之拮抗劑 Ondansetron 用來治療肝硬化合併膽汁鬱積性搔癢的療效

Effectiveness of Ondansertron on Treatment of Cholestatic Pruritus in Advanced Cirrhotic Patients

指導教授：林中生教授

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中華民國九十二年六月
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授權書

（博碩士論文）

本授權書所授權之論文為本人在 中山醫學大學醫學研究所 臨床醫學組 91 學年度第 2 學期所撰 碩士 學位論文。

論文名稱：以 5-Hydroxytryptamine Type 3(5-HT_3) 接受器之拮抗劑 Ondansetron 用來治療肝硬化合併膽汁鬱積性搔癢的療效

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本論文為中山醫學大學授予醫學碩士學位之必備條件之一，經中山醫學大學醫學研究所碩士論文考試為委員審查合格及通過口試。

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中華民國九十二年六月

學生洪弘昌論文題目為：以 5-Hydroxytryptamine Type 3(5-HT_3) 接受器之拮抗劑 Ondansetron 用來治療肝硬化合併膽汁鬱積性搔癢的療效。其論文已經中山醫學大學醫學研究所碩士論文考試委員審查合格及口試通過，並由其指導教授核閱後無誤。

指導教授　林中生　　簽名 _____

中華民國九十二年六月

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中文摘要：

全身性搔癢是一種常見於膽汁鬱積性肝病患者之不舒服的肝外表徵。其治療效果常不盡理想。膽汁鬱積性搔癢不只干擾日常作息，嚴重時甚至剝奪睡眠或造成自殺傾向。近年來發現，以 serotonin type 3($5\text{-}HT_3$)接受器之拮抗劑，可用來紓解對傳統止癢療法(如 cholestyramine, antihistamine)無反應之膽汁鬱積性搔癢。

目的：針對有膽汁鬱積性搔癢之肝硬化病患，評估對其靜脈投予 ondansetron 之治療效果。

方法：此為控制對照研究，在 12 例有膽汁鬱積性搔癢但對於傳統止癢療法無反應之肝硬化患者(年齡由 46 至 74 歲不等，其中 男/女:8/4。生化檢查各項平均值—總膽紅素 T.B.: 3.85 ± 1.17mg/dl；麩氨基轉化胺 γ-GT: 334.78 ± 116.05u/l；鹼性磷酸胺 ALK-P: 573 ± 373.59u/l)，在接受治療前五天起停止使用所有止癢藥物。每位病人分別依序由前臂靜脈投予 8 毫克的 ondansetron、對照組(即生理食鹽水)、4 毫克的 ondansetron；注射時間間隔為 48 小時，藉此以評估各組不同之短期療效。 如果在靜脈投予後 2 小時內，病人的搔癢程度能減少百分之五十以上，便視為成功療效。搔癢程度由 visual rating scale(VRS) 從 0(無搔癢)到 10(病人所能想像最難以忍受的搔癢)逐級區分，且分別於注射後 15、30、60 及 120 分鐘時作成記錄。注射後病人所產生之副作用亦予以記錄。在注射 24 小時內，患者須評估搔癢回復到治療前之強度時的時距。

結果：由靜脈注射 ondansetron 8 毫克與 4 毫克均可於 60 分鐘內將搔癢強度減少百分之五十。產生成功療效所需時間以注射 8 毫克組為短(30 分鐘內產生成功療效,8 毫克組:4 毫克組:對照組 為 100%:75%:0%)。注射 4 毫克及 8 毫克的 ondansetron 之成功療效與對照組相比在第 30 到 120 分鐘時，都具有統計學上明顯的差異($p<0.001$)。成功療效在 8 毫克組可持續較長的時間（ 8 毫克組: 4 毫克組為 8.33± 1.30 小時:4.00 ±0.95 小時，$p<0.01$)。此外，治療過程中並無副作用產生。

結論：Ondansetron 能有效地緩解膽汁鬱積性搔癢，可能與降低膽汁鬱積性患者對搔癢的感受度有關。Serotonin 則被認為經由 $5\text{-}HT_3$ 接受器與搔癢形成或感度有關。因此，$5\text{-}HT_3$ 接受器之拮抗劑可能是治療膽汁鬱積性搔癢之重要原則。然而，受限於價格及靜脈注射之不方便性，$5\text{-}HT_3$ 接受器之拮抗劑宜用於接受傳統止癢治療失敗之持續搔癢病例。

English summary：

Generalized pruritus as an extrahepatic manifestation of cholestatic liver disease is a well-known, uncomfortable symptom. Its treatment is often unsatisfactory. Cholestatic pruritus may not only interfere with normal activity but may lead to sleep deprivation and suicidal attempt. The pruritus may have a severe impact on a patient’s quality of life and may be an indication for liver transplantation Because the pathogenesis and etiology of cholestatic pruritus is only not well understood and several hypothesis have been proposed Treatments of cholestatic pruritus consist mainly of bile acids chelating agents (e.g., cholestyramine), antihistamine, hepatic enzyme inducers (phenobarbitone, rifampin), propofol, anabolic steroids, and Heroic measures (for example, charcoal hemoperfusion, partial external diversion of bile) have also been tried. But all these conventional antipruritic treatment are not consistent efficacious.

Treatment of patients with cholestatic pruritus with opiate receptor antagonist (e.g., naloxone, nalmefene) lead to a relief of pruritus but can induce an opioid withdrawal syndrome, suggesting the participation of endogenous opioids in the generation and/ or sensation of pruritus But no signs of withdrawal syndrome or known side effects could be observed under treatment with ondansetron a specific serotonin type 3 receptor antagonist (5-HT_3).

In conclusion, ondansetron administration is associated with amelioration of the perception of pruritus in cholestatic patients. It is suggested that serotonin, acting via the 5-HT_3 receptor antagonist is involved in the generation or sensation of pruritus. Furthermore, the 5-HT3 receptor antagonist may be a novel therapeutic principle for the treatment of cholestatic pruritus.

緒論

（一） 前言

膽汁鬱積性搔癢(cholestatic pruritus)常見於急慢性肝炎、各種原因引起之肝硬化或惡性腫瘤等引起膽汁滯留之患者。這個問題常造成日常生活莫大的困擾。輕者影響睡眠作息，重者影響心理調適，甚至產生重度憂鬱或自殺傾向。過去除了肝臟移植及膽汁引流外，內科治療包括血漿置換、紫外光照射、或抗組織月安(antihistamine)及膽鹽結合劑(如 cholestyramine, ursodeoxycholic acid)。此外，也有麻醉鎮靜藥物(如 phenobarbital, propofol)[1]、抗生素(如 rifampicin)、或類固醇類激素之臨床經驗報告。然而, 以上藥物之療效及作用機制仍不明確。近年來的研究方向，則著重於膽汁鬱積性搔癢之可能機制，及針對此機轉，選擇具特異性的阻斷藥物。這包括了 opioid 接受器之拮抗劑(如 naloxone)及 5-HT_3接受器之拮抗劑(如 ondansetron)兩類藥物。本文將回顧過去之醫學文獻報告及近年來的研究成果，以期增進對此問題之了解。

（二） 研究動機：膽汁鬱積性搔癢之可能機轉

探究膽汁鬱積性搔癢之機轉，將有助於尋求具特異性的阻斷藥物。過去曾提出過的假說包括: (1)滯留的膽汁中含有致癢的物質，如膽鹽；(2)高濃度的膽鹽破壞肝細胞膜，使其釋出不明致癢物質；(3)膽鹽在腸道中之代謝發生改變，從而形成致癢物質，當這些物質作用於皮膚中的神經末梢時，便於局部產生搔癢感[3-5]。

然而，對膽汁鬱積性患者之觀察顯示，搔癢程度與黃疸之嚴重程度並無正向關係, 其搔癢之部位並無明顯的皮膚病灶(搔癢造成的次發性變化，如脫屑，破皮，或結節性癢疹(prurigo nodularis)除外)，且搔癢部位之皮膚病理切片，也無較高濃度之膽鹽沉積[3]，而膽鹽結合劑(如cholestyramine, ursodeoxycholic acid)之療效不彰，也顯示可能另有不同之機制造成膽汁鬱積性搔癢。另一種可能的致癢物質是組織月安[6]，但並無明顯的證據顯示其與膽汁鬱積性搔癢之關係。同樣地，抗組織月安也無法有效解除膽汁鬱積性搔癢.。事實上，膽汁鬱積性搔癢更可能是藉由神經傳導物質在中樞的作用而引發的。

自 1980 年以來動物實驗及臨床研究開始著重於 opiate 之致癢作用及 opiate 接受器之拮抗劑之療效。近年來研究之重點則轉移到 serotonin(5-HT，5-hydroxytryptamine)

在膽汁鬱積性搔癢上所扮演的角色及 5-hydroxytryptamine type 3(5-HT_3) 接受器之拮抗劑於臨床上的應用。

（三） 研究目的：Opioid system 與膽汁鬱積性搔癢之關係

Jaffee 等人[7]認為，搔癢可能與 opioids 與神經元的交互作用有關。因 opioids 可引發搔癢，而低劑量的 opiate 接受器之拮抗劑可快速解除搔癢.，Parker 等人[8]則提出，搔癢是藉由位於中樞之 opiate 接受器所造成。事實上，“癢覺”與“痛覺”同被視為嗎啡在中樞神經系統所產生的作用之一。1981 年，Yaksh 等人[9]發表在硬脊膜內(intrathecal)注射嗎啡可於人及猴子身上引發搔癢。1986 年之一項動物實驗[10]，則是以顯微注射方式將嗎啡注入猴子延髓之背根神經中，結果發現在 16 分鐘之內，注射嗎啡之同側肢體會產生搔癢並持續達 128 分鐘之久，且搔癢的部位主要在眼眶周圍及鼻子，與注射部位所支配的知覺感受區域重疊。此外，Bergasa 等人於 1993 年進行的另一項研究[11]，則是以膽汁鬱積患者的血漿注入猴子延髓之背根神經中而引起猴子的臉部搔癢。此反應可由 opioid 接受器之拮抗劑(naloxone)來解除或預防，但有膽汁鬱積而無搔癢患者之血漿則無法造成以上反應。因此作者推論膽汁鬱積性搔癢患者之血漿中含有可藉中樞之 opiate 接受器造成搔癢之物質。而這些物質，到底是什麼呢?

於1992年, Swain[12]等人發表其動物實驗，將老鼠分為三組, 第一組接受膽管切除；第二組接受剖腹探查(sham operation)，但不施行膽管結紮或切除；第三組則完全不施予手術。五天後，第一組血漿中 opioid 類物質的總活性比其他兩組高了三倍(P＜0.05)。其中 methionine-enkephalin 之血中濃度，第一組比第二組高了6倍以上(P＜001)，且比第三組高17倍以上(P＜0.001)。此外，enkephalin 可通過血腦障壁[13-15]，而 methionine-enkephalin 及 leucine-enkephalin 會在原發膽汁鬱積性肝硬化(primary biliary cirrhosis)及其他肝病患者體內累積，且其血漿濃度高低被視為判斷預後之指標[16-18]。另一方面，Bergasa 等人[18]發現在膽管切除五天後，產生膽汁鬱積之老鼠的腦部組織中，μ-opioid 接受器有 down regulation 之現象。這可能表示在膽汁鬱積之老鼠中，μ-opioid 接受器暴露於較高濃度之內生性 opioids 下，從而產生 down-regulation。有趣的是，在膽管切除後，產生膽汁鬱積之老鼠中，可發現有痛感降低(antinociception)情形，且此現象可被 naloxone 所拮抗，顯示膽汁鬱積患者之 central opioidergic tone 已上升[19]，此外，由於痛及癢都是由 non-myelinated C-fiber 及 spinothalamic tract 傳導之 nociceptive stimuli，μ-opioid 接受器可能在癢感上扮演了一個角色，至於膽汁鬱積性搔癢之患者體內，是那一部位在製造 opioids 呢?

過去曾認為是腎上腺[20]，然而，兩側腎上腺摘除並不影響 enkephalin 之血漿濃度[21]。其他可能的來源尚包括腸胃道[22]、交感神經、神經節[23]、及腦部[13]。而 Bergasa 等人[24]認為 endogenous opioids 可能是由膽汁鬱積的肝細胞所製造的，因接受膽管切除後的老鼠肝細胞表現出在胚胎期肝臟才具有的 preproenkephalin mRNA，其為 endogenous opioid 之前驅物，研究者發現其主要由 periportal 肝臟細胞所表現。另一方面, preproenkephalin mRNA 並不會表現於由 thioacetamide 所造成的急性壞死肝細胞中。

（四） 研究對象:Opioid 接受器之拮抗劑於膽汁鬱積性搔癢上的療效評估

Opiate 接受器之拮抗劑，如靜脈注射的 naloxone 及口服的 nalmefene，可能對減輕膽汁鬱積性搔癢有幫助，首見於 1979 年 Bernstein 等人的病例報告[25]。1988 年, Thornton 等人[17]於 11 位肝硬化患者施予 nalmefene，發現其中 9 位患者的搔癢獲得明顯改善。除此之外，所有患者在用藥初期都有嚴重的 opioid withdrawal reaction，顯示其中樞 opioidergic neurotransmission 之活性有增強現象。

另一方面，在一項針對 8 位原發膽汁鬱積性肝硬化患者施行之單盲控制對照研究中[26]，使用靜脈注射 naloxone，再統計一段固定時間內患者搔癢的次數製成 ”搔癢活性指數”(“scratching activity index”)，顯示其搔癢活性平均降低了百分之五十(P<0.001)。

1995 年，另一項在 29 位合併有肝病及搔癢之患者身上進行之雙盲控制對照研究中[27]，以接受 naloxone(治療組)或安慰劑(對照組)前後對搔癢的主觀感受給予 visual analog score(0:完全不癢，10:劇癢)。結果顯示，治療組的平均分數比對照劑組低了 0.582 分(P<0.01)，且搔癢活性指數之比值(治療組/對照組)為 0.727，由此更進一步肯定了 opioid 接受器之拮抗劑於膽汁鬱積性搔癢的療效。

至於 naloxone 為何無法完全阻斷 scratching activity，作者認為可能是基於下列的原因:(1)劑量不足；(2)患者尚處於慢性習慣性搔癢之過渡期(carryover state)；(3)除了 opiate 外，另有引起搔癢的物質存在。根據最近數年來的研究，這種物質極可能是 5-hydroxytryptamine。

材料與方法

此為控制對照研究，在 12 例有膽汁鬱積性搔癢但對於傳統止癢療法無反應之肝硬化患者(年齡由 46 至 74 歲不等，其中 男/女:8/4 。生化檢查之各項平均值—總膽紅素 T.B.: 3.85 ± 1.17mg/dl；麩氨基轉化胺 γ-GT: 334.78 ± 116.05u/l；鹼性磷酸胺 ALK-P: 573 ± 373.59u/l)，在接受治療前五天起停止使用所有止癢藥物。每位病人分別依序由前臂靜脈投予 8 毫克的 ondansetron、對照組(即生理食鹽水)、4 毫克的 ondansetron；注射時間間隔為 48 小時，藉此以評估各組不同之短期療效。 如果在靜脈投予後 2 小時內，病人的搔癢程度能減少百分之五十以上，便視為成功療效。搔癢程度由 visual rating scale(VRS) 從 0(無搔癢)到 10(病人所能想像最難以忍受的搔癢)逐級區分，且分別於注射後 15、30、60 及 120 分鐘時作成記錄。注射後病人所產生之副作用亦予以記錄。在注射 24 小時內，患者須評估搔癢回復到治療前之強度時的時距。

結果

由靜脈注射 ondansetron 8 毫克與 4 毫克均於 60 分鐘內將搔癢強度減少百分之五十。產生成功止癢療效所需時間以注射 8 毫克組為最短(30 分鐘內產生成功止癢療效，8 毫克組:4 毫克組:對照組 為 100%:75%:0%)。注射 4 毫克及 8 毫克的 ondansetron 之成功止癢療效與對照組相比在第 30 到 120 分鐘時，都具有統計學上明顯的差異($p<0.001$)。成功止癢療效在 8 毫克組可持續較長的時間(8 毫克組: 4 毫克組為 8.33±1.30 小時:4.00 ±0.95 小時，$p<0.01$)。此外，治療過程中無副作用產生。

討論

＊新的研究方向: 5-hydroxytryptamine receptor 及其拮抗劑

5-hydroxytryptamine(5-HT, serotonin)在中樞及週邊神經的不同位置上，藉由不同的接受器(5-HT_1、5-HT_2、5-HT_3)來調節對痛的感知程度(nociception)[28,29]。舉例來說，5-HT_3接受器位於脊神經背柱第一級傳入神經纖維的末稍，可接受serotonin刺激而增強具有致痛效果的物質，如bradykinin的強度。因此，選擇性5-HT_3接受器之拮抗劑被認為可減輕偏頭痛、發炎反應及心肌梗塞時由於serotinin釋出所造成的疼痛。另一方面，癢覺本身可視為痛覺的一種特殊型態[30,31]，因它們都由non-myelinated C fiber所傳遞，故選擇性5-HT_3接受器之拮抗劑應有助於解除搔癢。

Ondansetron為近年來最常被採用於臨床試驗的選擇性5-HT_3接受器之拮抗劑。根據1993年的兩篇病例報告[32,33]顯示，靜脈注射ondansetron後，平均30至60分鐘內即可達到止癢效果，此效果在膽汁鬱積性搔癢患者尤為顯著。在另一針對10位膽汁鬱積性搔癢患者之控制對照研究中[34]，發現注射ondansetron後，搔癢程度可減輕百分之五十以上，且較高劑量可持續較長療效，這種劑量相關之效果也強烈暗示ondansetron之止癢效果。另一方面, 由於opioid接受器之

拮抗劑可能在緩解搔癢的同時也減弱了 morphine 的止痛效果。 因此其於需要 opioid 止痛之膽汁鬱積性搔癢患者的使用上勢必受到限制。Ondansetron 則可避免這方面的困擾。於 1996 年發表的病例報告[35]即顯示 ondansetron 成功地紓解了兩位注射嗎啡於硬脊膜內作為疼痛控制之剖腹產婦的搔癢。

膽汁鬱積性搔癢, 是非常惱人而不易控制的問題。過去數年來，學者致力於搜尋產生膽汁鬱積性搔癢的可能機轉來 "對症下藥"，使得其治療出現了令人期待的新方向。 然而, 目前進行試驗之止癢藥物，若應用於臨床治療中，仍有一些需要克服之問題。舉例來說，naloxone 受限於其半衰期短而需要持續靜脈注射, 如此勢必影響其適用性及病人的接受度。因此，可口服、代謝速率較慢、藥效（potency）較佳及生體利用率更高之 opioid 接受器之拮抗劑，如 nalmefene, 被視為一適用性較高的藥物。但這一類藥物都會減弱嗎啡的止痛效果，因而限制了其於癌症疼痛病人的使用. 選擇性 5-HT_3 接受器之拮抗劑雖不致影響 morphine 的止痛效果，但目前進行臨床試驗之 ondansetron 同樣為靜脈注射藥物，且其療效持續時間尚有待評估。故對於口服選擇性 5-HT_3 接受器之拮抗劑之研究, 或許為一可行的方向。

表列

Table 1. Patient characteristics and laboratory data before treatment

Patient	Sex	Age	T.Bil(MG/DL)	γ-GT(U/L)	Alk-P(U/L)	AST(U/L)	ALT (U/L)
Normal range			0.2-1.6	4-61	10-100	5-45	0-40
1	M	48	3.2	274	827	45	31
2	M	54	3.8	432	264	66	46
3	F	66	6.1	627	1464	84	68
4	M	58	2.7	166	232	56	42
5	M	70	4.2	286	462	48	33
6	M	68	2.6	324	842	76	80
7	F	62	3.5	374	674	62	88
8	M	65	4.8	566	320	56	40
9	F	57	3.9	427	370	36	38
10	M	46	5.7	411	692	74	66
11	M	74	3.1	344	566	26	52
12	F	68	2.6	186	423	46	62

T.Bil: total bilirubin；γ-GT: γ-glutamyltransferase；ALK-P: alkaline phosphatase ；AST: serum aspartate aminotransaminase；ALT: serum alanine aminotransaminase

Table 2. The visual rating scale of pruritus and duration of effect before and after treatment with Ondansetron or placebo

Patient	Treatment	Minutes after treatment					Duration
	(8→P→4)	0	15	30	60	120	hours
1	8	9	5	2	1	1	10
	P	9	8	7	7	7	
	4	9	6	4	2	1	6
2	8	8	6	3	2	2	8
	P	8	8	8	8	8	
	4	8	5	2	2	2	4
3	8	8	4	2	1	1	7
	P	8	7	9	8	8	
	4	8	7	6	4	2	3
4	8	9	5	3	2	2	9
	P	9	8	7	9	8	
	4	9	6	4	3	1	4
5	8	8	3	2	1	1	8
	P	8	7	8	8	8	
	4	8	4	2	1	0	5
6	8	8	4	2	0	1	7
	P	9	9	8	9	8	
	4	9	7	3	3	1	3
7	8	9	5	4	3	2	7
	P	9	8	8	8	9	
	4	9	5	3	2	0	4
8	8	8	6	3	1	1	11
	P	8	9	8	9	8	
	4	8	6	4	3	2	4
9	8	9	5	3	2	2	9
	P	9	8	9	8	8	
	4	9	6	4	4	2	3
10	8	7	5	2	0	1	9
	P	8	7	8	7	8	
	4	8	7	5	4	2	4
11	8	9	8	4	1	0	8
	P	8	8	8	8	8	
	4	9	6	5	3	2	3
12	8	8	6	3	1	0	7
	P	9	8	7	8	9	
	4	9	7	4	3	1	5

8: 8mg of ondansetron; P: placebo; 4: 4mg of ondansetron.
Duration : the time point when intensity of pruritus was of the same degree as before treatment.

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Effectiveness of Ondansertron on Treatment of Cholestatic Pruritus in Advanced Cirrhotic Patients

Abstract

The objective of the present study was to determine the effect of ondansetron, a specific serotonin type 3 (5-HT_3) receptor antagonist, to relieve cholestatic pruritus in patients resistant to conventional antipruritic therapy. In a placebo-controlled study the acute effect of an intravenous injection of ondansetron or placebo (normal saline) was tested in 12 cirrhotic patients (mean age 61 ± 8.8 yr) with cholestatic itch. Each patient received ondansetron (8 mg and 4 mg) and placebo infusion consequently. The intensity of pruritus was assessed by a visual rating scale from 0 to 10 (most severe pruritus). A successful treatment was regarded when the intensity was reduced by 50% or more within 2 hours after injection of ondansetron. During the following 24 hours, the patients were assessed and the time point recorded when the intensity of pruritus relapsed into the same degree as pre-treatment. Intravenous application of ondansetron abolished pruritus within 60 min by a 50% reduction of the intensity of itching.

The effect of ondansetron on itching intensity showed significant difference ($p < 0.001$) from placebo during a controlled observation period from 30 to 120 minutes. The onset of a successful treatment (18.34 ± 6.22 vs 36.82 ± 21.35 min, $p < 0.05$) and the duration (8.33 ± 1.30 vs 4.00 ± 0.95 hours, $p < 0.01$) were significantly earlier and longer at a high dose. No side effects occurred during treatment. Our findings suggest that the 5-HT3 receptor antagonist may be a novel therapeutic alternative for the treatment of cholestatic pruritus.

Introduction

Pruritus is a distressing and frequent complication of hepatic cholestasis that is often difficult to manage. Cholestatic pruritus may not only interfere with normal activity but also lead to sleep deprivation and suicidal attempts [1]. Because the pathogenesis and etiology of cholestatic pruritus is not well understood, several hypothesis have been proposed: (1) accumulation of toxic bile salts in the skin which excite cutaneous nerve endings; (2) destruction of hepatic cell membranes by a high concentration of bile salts which results in the release of an unidentified substance that causes pruritus; (3) alter metabolism of bile acids in the gut lumen resulting in the production of an pruitogenic compound; and (4) accumulation of endogeneous opioids in the cholestatic liver disease [2, 3]. Gastroenterologists confronted with the problem often find themselves impotent and frustrated by the inadequacy of the options available to provide a patient with substantial relief.

Treatments of cholestatic pruritus consist mainly of bile acid chelating agents (e.g., cholestyramine), antihistamines, hepatic enzyme inducers (phenobarbitone, rifampin), opioid receptor antagonist (naloxone), anabolic steroids, and propofol in subhypnotic dose [1-3]. Heroic measures such as charcoal hemoperfusion and partial external diversion of bile have also been tried. None of these conventional antipruritic treatments are consistently efficacious.

Ondansetron, a serotonin (5-hydroxytryptamine) type 3 ($5\text{-}HT_3$) receptor antagonist, is used as a very effective anti-emetic drug in chemotherapy and radiation induced emesis [3-5]. Preliminary studies suggested ondansetron may ameliorate the pruritus of cholestasis [4-8]. Because of the absence of prospective controlled trials of ondansetron in the treatment of cholestatic pruritus in Taiwan, we designed this placebo-controlled study to check the effectiveness of ondansetron in the amelioration of pruritus.

Patients and Methods

Twelve cirrhotic patients (8 men, 4 women; aged 61± 8.8 years, range 46-74 years) associated with a cholestatic liver disease due to advanced hepatocellular carcinoma were studied (Table 1). In each case, causes of pruritus other than cholestasis were excluded by taking a comprehensive medical history, doing a full physical examination, and obtaining results of laboratory tests and procedure relevant to each patient's medical status. Exclusion criteria for the trial were the presence of ascites or hepatic encephalopathy during the previous 3 months. The duration of pruritus was present for at least 1 month before study entry (range 1-3 months), and treated under conventional antipruritic therapy (e.g., cholestyramine and antihistamines). The severity of the pruritus was considered intractable if severe sleep deprivation or interference with regular activities occurred. All patients gave informed consent before treatment.

Characteristics of serum biochemical profiles on each patient were consistent with cholestasis and are shown in table 1. Therapy with all other antipruritic medications was discontinued 5 days before study. Ondansetron was tested in all patients at consequent doses of 8 mg and 4 mg followed by placebo treatment. Ondansetron (1 amp with 4 ml contains 8 mg) was added to physiologic sodium chloride (NACL) solution at 10 ml and slowly intravenous infusion into an arm vein.

Placebo treatment consisted of 10 ml of physiological NACL solution injected the same way. Ondansetron and placebo treatment were not tested on the same day. Placebo treatment was administered 2 days before (4 mg) and after (8 mg) application of ondansetron.

Patients were asked to assess the intensity of their pruritus on a visual rating scale (from 0 = no pruritus to 10 = the strongest itching to the patient). The patients had also estimated their intensity of itching before treatment. After application of ondansetron or placebo, the patients were asked at regular point (15, 30, 60, and 120 minutes) about their itching on a visual rating scale as well as adverse effects. During the following 24 hours, the patient were assessed when the intensity of itching relapsed to the same degree before treatment. A successful treatment of pruritus was recognized when the intensity of itching was reduced by 50% or more within 2 hours after intravenous administration of the drug.

Statistical analysis was performed by one-way ANOVA. All reported p values are two-sided and expressed as mean ± SD. A p value of less than 0.05 was considered statistically significant. Statistical tests were applied with the Statistical Package for the Social Sciences..

Results

The effect of ondansetron (8mg and 4mg) on itch intensity was significantly different ($p < 0.001$) from placebo during observation within two hours (Table 2). Intravenous administration of 8mg of ondansetron abolished the intensity of pruritus within 30 min in all 12 patients (Table 2). The duration of antipruritic effect of 8 mg ondansetron was significantly longer than that of 4 mg ondansetron (mean: 8.33 ± 1.30 hours vs 4.00 ± 0.95 hours, $p < 0.01$). The duration of antipruritic effect lasted for at least 7 hours. In one patient, this antipruritic effect lasted up to 11 hours. Intravenous administration of 4mg of ondansetron abolished the intensity of pruritus within 30 min in 9 patients, and up to 60 min in other three patients. The onset of a successful treatment was earlier at the higher dose than at the lower dose (18.34 ± 6.22 minutes vs 36.82 ± 21.35 minutes, $p < 0.05$). The administration of ondansetron was well tolerated by all patients. No severe adverse effects were reported by the patients nor by the physicians during treatment.

Discussion

The use of ondansetron, a specific serotonin type 3 (5-HT_3) receptor antagonist, is well established in patients with nausea and vomiting associated with cancer therapy, radiotherapy, anesthesia and surgery [9]. The wide distribution of the 5-HT_3 receptors in the body and the role of these receptors have provided the rationale for investigation of ondansetron in novel applications [10, 11]. From our present knowledge of ondansetron, it is evident that this drug is a highly specific receptor antagonist at the 5-HT_3 receptor. No affinities of ondansetron to receptors of other serotonic types, dopamine, muscarine, gamma-aminobutyric acid, benzodiazepine receptors, histamine or opioid receptors are known [10].

The 5-HT_3 receptors are present in the peripheral, autonomic and central nervous system [11]. They are also found on sensory neurons and the area postrema with the chemoreceptor trigger zone. The effectiveness of ondansetron on the intensity of pruritus suggests that the serotonin, acting via the 5-HT_3 receptors, is involved in the sensation and/ or generation of pruritus. Ondansetron, It is known that the pain-producing and pain-enhancing effects of serotonin are mediated via activation of 5-HT_3 receptor on sensory nerve endings. The effects are abolished by the 5-HT_3 receptor antagonist [3, 10, 11]. It cannot be excluded from the present data that the pruritogen formed during cholestasis may have affinity to the 5-HT_3 receptor [3, 8, 12].

To our best knowledge, there are no data available about the role of 5-HT in cholestatic disease. The pruritogen generated in the cholestatic liver disease is associated with Met- and Leu-enkelphen synthesized by the liver itself [12]. Preliminary reports have shown that ondansetron has clinical benefits in in patient with pruritus [3-8]. It is well-known that pain and itching are closely related to sensory apparatus. Both are transmitted through C fibers of polymodal nociceptors. The 5-HT plays an important role in regulating transmission of nociceptive information at various levels of the peripheral and central nervous system [10, 11]. Like the opioid, the serotonin system has been reported to modulate nociception (the perception of pain) in rats, and, hence, may also modulate the perception of pruritus [13].

The observation of the present data demonstrates that ondansetron can relive cholestatic pruritus in patients resistant to conventional antipruritic therapy. The effect of ondansetron was relatively rapid in onset. Significant amelioration of itching was reported by patients within 30 to 60 minutes. Although the degree of itching sensation is subjective and the study is not a double-blind trial, we still believe that the antipruritic effect is not due to the placebo effect. The following facts support our results as a real antipruritic effect of ondansetron on the intensity of cholestatic pruritus. First, in contrast to placebo treatment, ondansetron treatment caused complete or nearly complete relief of itching.

Second, the duration of the antipruritic action seemed to be dose dependent. Intravenous application of 8 mg of ondansetron effectively reduced the intensity of itching within 30 min in twelve patients, whereas 4mg relieved pruritus within 30 min in only nine of twelve patients. Compared with previous studies, our findings advocate the same result of acute onset of anti-pruritic effect of ondansetron [4-8]. The reported sides effects such as constipation, headache, sensation of flushing or a warm feeling, and transient asymptomatic increase in aminotransferases did not occur in our patients during the injection or in the third day follow-up after treatment [2-5].

For the pharmacokinetic reasons of ondansetron is metabolized mainly in the liver with a half-life of 3 hours, patients with poor hepatic reserve like ascites and hepatic encephalopathy were excluded. Treatment of patients with cholestatic pruritus, especially in patients with primary biliary cirrhosis, with opiate receptor antagonists (such as naloxone and nalmefene) may lead to a relief of pruritus but can induce an opioid withdraw syndrome [13-16]. No sign of withdrawal syndrome or known adverse effects could be observed under treatment with ondansetron.

In conclusion, the 5-HT_3 receptor antagonist, ondansetron, is effective in the relief of cholestatic pruritus. It is safe with rare adverse effects. Further studies are needed to investigate whether there are differences in the response of various forms of pruritus to the 5-HT_3 receptor antagonist.

Furthermore, it is worth studying whether the oral administration of ondansetron is also effective or not . However, based primarily on the cost and inconvenience associated with the intravenous administration of this drug, it is reasonable to use this drug in intractable pruritus after failure of conventional antipruritic treatment.

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