LETTER TO THE EDITOR

Pain Medicine 2017; 18: 2515–2517
doi: 10.1093/pm/pnx119

8% Capsaicin Patch as Analgesia for Severe Treprostinil Infusion Site Pain

Dear Editor,

Pulmonary arterial hypertension (PAH) is a progressive, often fatal disease characterized by abnormal remodeling of the pulmonary vasculature, increased pressure in the pulmonary arteries, and right ventricular failure [1]. Parenteral prostacyclins, such as epoprostenol and treprostinil, remain the treatment of choice for patients with a high-risk phenotype; this therapy improves exercise tolerance, reduces breathlessness, and probably increases survival [2–5]. Parenteral treprostinil has clear safety and convenience advantages, including a longer half-life of four hours and stability at room temperature and neutral pH, which make it suitable for both intravenous and subcutaneous (SQ) delivery. SQ infusion is bioequivalent and eliminates serious risks associated with IV delivery including sepsis, endocarditis, vascular thrombosis, and death [6,7]. When used subcutaneously, the drug is delivered with a microinfusion pump (CADD-MS 3) through a thread-like plastic catheter positioned under the skin. Most commonly, infusion sites are placed in the abdomen, although the flank area, back of the upper arm, or thigh can also be used. We have previously reported that patients can leave sites in place for as long as nine months before they deteriorate; as long as the site is benign and disease symptoms are stable, a "scheduled" change is not mandatory. In a prospective study of infusion site pain, we showed that 52% of infusion sites lasted more than four weeks [8]. Unfortunately, severe pain and irritation at the infusion site commonly occur due to prostacyclin-induced sensitization of cutaneous nociceptors (namely the transient receptor potential vanilloid receptor 1 [TRPV1]) [9,10]. This hyperalgesia is often severe and typically persists for up to a week following site changes; it does not appear to be dose related and varies significantly from patient to patient and even from site to site within a patient [8]. Current pain management strategies involve the use of oral and topical analgesics, anti-inflammatories, and infrequent site changes, though these methods provide suboptimal pain relief [8,11]. High-dose capsaicin, a TRPV1 agonist, provides intense nociceptor stimulation that induces retraction of nerve terminals to produce enduring but reversible reductions in neuronal responsiveness. As capsaicin directly impacts the same nociceptive pathways that mediate prostacyclin hyperalgesia [9,10], capsaicin is a logical approach to the management of SQ treprostinil pain.

A recent double-blind, single-center, randomized and placebo-controlled crossover study provided the first data on safety and efficacy of a single pre-application of the 8% capsaicin patch (Qutenza) in 11 PAH patients on SQ treprostinil [12]. Notably, the safety findings observed in this study match those seen in the trials for postherpetic neuralgia, for which the patch is FDA approved. While the primary efficacy end point was not met in that study, several subjects requested continued use of 8% capsaicin at the conclusion of the trial because of the significant analgesia that they perceived.

Contemporaneous to this blinded study, we conducted a longer, single-center, prospective, open-label study to gather preliminary data on the safety of pretreatment with the 8% capsaicin patch for reducing infusion site pain. We enrolled five SQ treprostinil users with severe site pain despite their maximal analgesic cocktail (enrollment required ratings $\geq$6 on two consecutive days on the visual analog scale [VAS]). While our primary goal was to assess safety, we explored the analgesic effects of capsaicin. During three to nine months of follow-up after quarterly capsaicin applications, research participants completed a two-week symptom diary each time they placed a new treprostinil infusion site, recording their daily pain experience, analgesic regimen, and associated relief. Diaries collected prior to capsaicin treatment served as a baseline for which to compare diaries completed after capsaicin intervention. We averaged pain scores for each participant's set of baseline and capsaicin diaries collected over the entire study period. For descriptive purposes, a paired *t* test was then used to compare the baseline and capsaicin pain scores.

There was a total of 13 capsaicin patch applications; four subjects successfully completed all three planned applications, and one subject completed a single treatment. Overall, the patch was well tolerated during the one-hour application; one subject experienced severe pain and mild hypertension that resolved the same day (Table 1). Aside from pain at the site and hypertension, no adverse events related to patch application were observed. Our safety data are nearly identical to those of Libri et al.

Cumulatively, we analyzed 22 "capsaicin" diaries and 45 "baseline" diaries. Regarding efficacy, we made several observations that suggest capsaicin provided a small but measurable benefit: 1) a reduction in average pain in the two weeks following placement of a new SQ treprostinil infusion site (4.2 vs 2.9, $P = 0.03$), 2) an insignificant reduction in maximal pain intensity (8.0 vs 6.4, $P = 0.06$), and 3) a trend toward improvement in the degree of relief provided by as-needed analgesics (1.7 vs 2.2, $P = 0.07$) (Figure 1, A–C). Moreover, at the individual level, there appeared to be two true "responders" who noted marked reduction in average pain and also reported much

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Table 1 Summary of demographics, diary submissions, patch application experience for each subject

Symbol	Age, y	Sex	Patches applied, No.	Baseline Diaries, No.	Capsaicin Diaries, No.	Pain During Patch Application						Blood Pressure During Patch Application					
						#1		#2		#3		#1		#2		#3	
						Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
▲	72	Female	3	2	5	0	0	4	4	0	0	149/66	142/68	121/65	134/65	149/67	141/72
●	50	Male	3	15	4	3	8	8	9	0	8	140/81	132/79	108/62	119/72	105/55	100/50
■	48	Female	3	7	4	3	4	0	0	0	0	127/63	137/76	128/64	115/63	102/49	102/56
⬢	77	Female	3	14	7	0	3	0	2	0	2	146/75	154/79	135/64	144/64	134/74	117/69
◆	56	Female*	1	7	2	0	8	N/A	N/A	N/A	N/A	104/69	147/64*	N/A	N/A	N/A	N/A

Safety was monitored by assessing pain on a 10-point visual analog scale and blood pressure before and after each patch application (maximum of 3). Patients with a 15 mmHg increase in systolic or diastolic blood pressure had repeat vital signs taken one hour later and at 60-minute intervals until pressures were within 15 mmHg of baseline.
* Subject only completed 40 minutes of the 60-minute patch treatment because of intolerable pain. Blood pressure after one hour was 98/57.

Figure 1 Capsaicin may decrease pain associated with new infusion sites. Each symbol represents the average data for a subject before and after treatment using a per-protocol analysis. Pain was measured on a 10 point visual analog scale with the word "none" above 0 and "agonizing" above 10. **A)** Average pain; measures pain over the entire two week diary period. **B)** Worst pain; maximum pain score recorded on any diary day. **C)** Pain relief after using as-needed analgesics (including narcotics); measured daily on a four-point scale (0 = no relief, 1 = a little, 2 = some, 3 = a lot, and 4 = complete relief).

less as-needed analgesic use (including the elimination of narcotics) (Figure 1, A–C, triangle and circle shapes).

While this study lacks a robust sample size and placebo-controlled observations, our findings are encouraging and support the design of a larger, controlled trial. The aforementioned blinded study by Libri was more rigorous in its placebo control, but our study offered more comprehensive data collection and confirmed safety over repeated applications. We are planning a blinded, multicenter, cross-over design study in which each participant will use a "placebo" patch with low-dose capsaicin (to preserve the blind) and an active 8% patch in randomly allocated order. They will use the two different sides of their abdomen to avoid carryover effect. As the blinded study just missed its efficacy end point with 11 participants, we are planning for 20 participants. We will use our same two-week diary tool to gather pain data and analgesic use for all infusion sites placed within a capsaicin-/placebo-treated area for a period of three months (i.e., the expected duration of the effects of one patch treatment). In summary, the 8% capsaicin patch appears to be safe and may be effective in alleviating more intense SQ treprostinil site pain, and we plan to establish efficacy in a subsequent study.

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