Analgesic Efficacy and Safety of Diclofenac Epolamine Topical Patch (Flector® Patch) by Location of Injury in Trials of Acute Pain: A Pooled Analysis of Five Trials

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ABSTRACT

Objectives: To evaluate the efficacy and safety of the diclofenac epolamine topical patch (DETP) by injury location during short-term treatment of pain associated with minor sports injuries or inflammatory pathologies.

Methods: The efficacy of the DETP was evaluated from the results of five clinical trials (three studies evaluated minor sports injuries and two evaluated inflammatory pathologies) based on injury location. Efficacy was summarized by treatment (the DETP or placebo) and by injury location into one of the following 10 categories: ankle, back, elbow, foot, arm/hand/wrist, knee, leg, neck, shoulder, and torso/other (abdomen, chest and side). Efficacy was analyzed by visual analog scale (VAS) scores for spontaneous pain, global response/efficacy evaluated by the patient and by the investigator. Safety was analyzed by tolerability analysis by both the patient and investigator, and adverse events (AEs) were recorded.

Results: Patients treated with the DETP experienced a statistically significant improvement in VAS pain scores for the back, elbow, and shoulder compared to the placebo group. For the investigator assessment of global response/efficacy, there were statistically significant differences in patients treated with the DETP for the back, elbow, shoulder, and foot compared to patients treated with placebo. When tolerability was assessed by investigator, there was a statisti-

***Table 1**: Summary of Demographic Information by Injury Location*

Injury Location	Treatment	N	Age (years)		Gender (%)		
			Mean ± SD	P-value[a]	Male	Female	P-value[a]
ANKLE	DETP	119	30.06 ± 9.92	0.14	63.03	36.13	0.84
	Placebo	115	32.19 ± 12.06		60.00	39.13	
ARM/HAND/ WRIST	DETP	58	33.41 ± 12.38	0.33	60.34	34.48	0.90
	Placebo	62	35.69 ± 12.34		61.29	35.48	
BACK	DETP	37	46.63 ± 10.90	0.10	43.24	54.05	0.15
	Placebo	43	41.80 ± 14.46		39.53	60.47	
ELBOW	DETP	37	41.58 ± 11.71	0.93	59.46	40.54	1.00
	Placebo	31	41.86 ± 12.66		61.29	38.71	
FOOT	DETP	47	39.72 ± 16.62	0.67	53.19	46.81	0.68
	Placebo	47	41.23 ± 17.73		57.45	40.43	
KNEE	DETP	81	34.41 ± 12.94	0.24	54.32	44.44	0.46
	Placebo	93	36.75 ± 13.09		62.37	35.48	
LEG	DETP	101	34.97 ± 14.50	0.41	50.50	47.52	0.90
	Placebo	79	36.82 ± 15.13		53.16	45.57	
NECK	DETP	8	43.95 ± 16.80	0.57	75.00	25.00	1.00
	Placebo	9	49.51 ± 21.96		66.67	33.33	
SHOULDER	DETP	84	41.35 ± 14.59	0.38	52.38	45.24	0.60
	Placebo	94	39.35 ± 14.85		44.68	52.13	
OTHER/ TORSO[b]	DETP	7	31.84 ± 10.17	0.43	100	0	0.52
	Placebo	13	35.37 ± 8.78		84.62	15.38	

DETP=Diclofenac Epolamine Topical Patch; SD=standard deviation.
[a] P-value derived from Student t-test for age, and from Fisher's exact test for gender.
[b] Category includes abdomen, chest, and side

cally significant difference in tolerability in patients when the DETP was applied to the leg, compared to patients who received placebo. There were no differences in the types or numbers of AEs reported by both the DETP and placebo patients.

Conclusions: The DETP demonstrated efficacy in reducing pain from acute injuries and has proven to be a safe, tolerable, and effective treatment for acute pain arising from injuries of the back, elbow, shoulder, and foot.

INTRODUCTION

Acute pain is defined as pain that begins suddenly, is generally time-limited, and serves as an alert to the body after an injury. Acute pain can be caused by soft tissue damage, infection, or inflammation. Minor soft tissue damage resulting from sport-related injuries such as sprains, strains, and contusions is a major source of acute pain. During 2005, an estimated 115.3 million visits were made to hospital emergency departments of which the most frequently reported injury-related diagnoses were strains/sprains (22%), contusions (17%), and fractures (12%).[1] The inflammatory response to tissue damage from these injuries results in pain and swelling, which can limit mobility. In adults, the sites most often affected include the ankle, knee, and wrist joint structures.[1]

Currently, the oral non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib, and naproxen, which provide analgesia and relief from inflammation, are used to treat patients with acute pain from minor soft tissue damage. Although effective, oral NSAIDs use can lead to serious adverse reactions associated with the upper gastrointestinal (GI) tract, renal, cardiovas-

***Table 2**: VAS Pain Scores by Injury Location*

Injury Location	Treatment	N	Day 0 (mean ± SD)\	Day 14 (mean ± SD) \	Difference (mean ± SD)	P-value
ANKLE	DETP	109	6.59 ± 1.23	1.66 ± 2.07	4.93 ± 1.97	0.98[a]
	Placebo	109	6.70 ± 1.28	1.84 ± 2.33	4.86 ± 2.09	
ARM/HAND / WRIST	DETP	56	6.62 ± 1.24	1.46 ± 2.06	5.16 ± 2.21	0.28[a]
	Placebo	51	6.84 ± 1.25	2.40 ± 2.76	4.44 ±2.62	
BACK	DETP	36	6.47 ± 1.97	2.35 ± 2.74	4.12 ± 2.63	0.02[a]
	Placebo	39	6.06 ± 2.23	3.31 ± 2.90	2.75 ± 2.68	
ELBOW	DETP	37	6.71 ± 1.58	1.60 ± 1.94	5.11 ± 2.16	0.02[b]
	Placebo	31	6.86 ± 1.92	2.95 ± 2.74	3.91 ± 2.62	
FOOT	DETP	47	6.97 ± 1.12	2.16 ± 2.41	4.81 ±2.50	0.99[a]
	Placebo	41	6.39 ±1.76	2.37 ± 2.63	4.02 ± 2.77	
KNEE	DETP	75	6.68 ± 1.59	2.09 ± 2.49	4.59 ± 2.24	0.15[a]
	Placebo	82	6.35 ± 1.57	2.28 ± 2.46	4.07 ± 2.31	
LEG	DETP	93	6.05 ± 1.84	1.19 ± 1.89	4.86 ± 2.15	0.46[a]
	Placebo	77	6.62 ± 1.73	2.00 ± 2.34	4.61 ± 2.48	
NECK	DETP	8	3.49 ± 1.67	0.95 ± 1.20	2.54 ± 1.71	0.29[b]
	Placebo	7	2.71 ± 1.60	1.29 ± 2.14	1.43 ± 1.13	
SHOULDER	DETP	82	6.91 ± 1.71	2.39 ± 2.57	4.52 ± 2.49	0.01[a]
	Placebo	87	7.13 ± 1.72	3.48 ± 3.19	3.64 ± 2.83	
OTHER/ TORSOc	DETP	7	6.14 ± 1.35	1.71 ± 1.25	4.43 ± 1.51	0.59[b]
	Placebo	13	7.20 ± 1.63	1.62 ± 2.17	5.58 ± 2.26	

ANCOVA=analysis of covariance; DETP=Diclofenac Epolamine Topical Patch; SD=standard deviation; VAS=visual analog scale.
[a]: P-values derived from rank-based analysis of variance stratified by study.
[b]: P-values derived from ANCOVA with changes as response variable, day 0 VAS score as covariate, and treatment as fixed effect.
[c] Category includes abdomen, chest and side

cular, and respiratory systems, mainly due to their ability to inhibit cyclooxygenase enzymes and resultant reduced prostaglandin production.[2-5]

One way to potentially bypass the systemic adverse effects of oral NSAIDs while maintaining therapeutic effect is through the use of topical NSAIDs applied directly at the site of injury. Topical application of NSAIDs results in continuous and localized drug delivery to the pain site while minimizing systemic levels of drug (0.2% to 8% of the oral equivalent),[6] thereby effecting a reduced local inflammatory reaction while avoiding GI adverse events (AEs).[6,7]

The diclofenac epolamine topical patch (DETP) is an NSAID topical patch used for the therapeutic treatment of acute pain due to minor strains, contusions, and sprains. In patients treated with the diclofenac patch for knee joint effusion, diclofenac could be detected in the synovial fluid, reaching the tissue immediately under the patch and providing a topical mode of action.[8, 9] A recent review demonstrated rapid onset of efficacy with reduction of pain relative to placebo occurring before detection of systemic diclofenac.[9] Throughout the period of application, systemic plasma concentrations remain approximately 100 times lower than concentrations observed after a single dosage of oral diclofenac at the lowest effective dose.[9]

When examining the safety and efficacy of a topical formulation, it is important to look at injury location in order to determine where the drug can be most effective. In this current study, the efficacy and safety of the DETP by injury location during short-term treatment of pain associated with minor

***Table 3**: Summary of Global Response/Efficacy Evaluated by Patient by Injury Location*

Injury Location	Treatment	N	None	Poor	Average	Good	Excellent	P-value[a]
ANKLE	DETP	70	10.0%	1.4%	27.1%	34.3%	27.1%	0.48
	Placebo	68	4.4%	4.4%	26.5%	35.3%	29.4%	
BACK	DETP	33	6.1%	12.1%	18.2%	33.3%	30.3%	0.002
	Placebo	36	33.3%	13.9%	16.7%	16.7%	19.4%	
FOOT	DETP	20	10.0%	10.0%	5.0%	20.0%	55.0%	0.02
	Placebo	21	23.8%	19.1%	23.8%	19.1%	14.3%	
ELBOW	DETP	26	3.9%	3.9%	15.4%	26.9%	50.0%	0.015
	Placebo	17	11.8%	11.8%	29.4%	47.1%	0	
ARM/ HAND/ WRIST	DETP	36	5.6%	13.9%	22.2%	13.9%	44.4%	0.33
	Placebo	32	9.4%	6.3%	18.8%	31.3%	34.4%	
KNEE	DETP	45	8.9%	4.4%	13. 3%	46.7%	26.7%	0.55
	Placebo	53	11.3%	9.4%	24.5%	17.0%	37.7%	
LEG	DETP	66	9.1%	10.6%	12.1%	31.8%	36.4%	0.40
	Placebo	47	12.8%	8.5%	21.3%	29.8%	27.7%	
NECK	DETP	8	12.5%	12.5%	0	12.5%	62.5%	0.63
	Placebo	7	28.6%	0	0	0	71.4%	
SHOULDER	DETP	42	7.1%	11.9%	16.7%	26.2%	38.1%	0.001
	Placebo	51	33.3%	5.9%	15.7%	25.5%	19.6%	
OTHER/ TORSO[b]	DETP	7	0	0	28.6%	57.1%	14.3%	0.09
	Placebo	9	11.1%	0	11.1%	44. 4%	33.3%	

CMH= Cochran-Mantel-Haenszel; DETP=Diclofenac Epolamine Topical Patch.
[a] P-value derived from CMH test controlling for study.
[b] Category includes abdomen, chest, and side

sports injuries or inflammatory pathologies was evaluated based on the results from five clinical studies.

METHODS

Clinical Trials Evaluated

In this current study, the results from five clinical trials were integrated into a database to examine the safety and efficacy of the DETP by injury location. Three of the studies evaluated patients with minor sports injuries,[10,11,12] and two studies evaluated patients with inflammatory pathologies.[13,14] All five clinical trials were placebo-controlled, double blinded studies in which patients were treated with the DETP or placebo twice daily for 14 days.

Efficacy

Analysis of Spontaneous Pain

Spontaneous pain was measured in all five clinical trials at different time intervals using differing versions of a visual analog scale (VAS). Three of the clinical trials used a continuous line scale to measure spontaneous pain,[10, 13,14] and two used an ordinal, numerical scale.[11,12] All of the VAS scores were normalized to a 0 to 10 cm continuous scale, where 0 = no pain and 10 = severe pain. In this study, the mean change in VAS scores from day 0 to day 14 was calculated for each injury location.

Patient Assessment of Global Response

Global response/efficacy evaluated by patient at exit from four clinical trials were used for this analysis. One study (Galeazzi and Marcolongo, 1993) used a slightly different scale from the other three studies, which used a 5-point scale.14 The scale from this study was therefore converted to a 5-point scale. Percentages were then calculated based on the number of non-

***Table 4**: Summary of Global Response/Efficacy Evaluated by Investigator by Injury Location*

Injury Location	Treatment	N	None	Poor	Average	Good	Excellent	P-value[a]
ANKLE	DETP	111	5.4%	8.1%	18.9%	37.8%	29.7%	0.21
	Placebo	108	9.3%	3.7%	25.9%	40.7%	20.4%	
BACK	DETP	36	11.1%	2.8%	13.9%	36.1%	36.1%	0.003
	Placebo	39	30.8%	0	30.8%	18.0%	20.5%	
FOOT	DETP	46	10.9%	8.7%	13.0%	37.0%	30.4%	0.04
	Placebo	44	9.1%	22.7%	25.0%	31.8%	11.4%	
ELBOW	DETP	37	2.7%	13.5%	10.8%	24.3%	48.7%	0.002
	Placebo	31	9.7%	25.8%	29.0%	32.3%	3.2%	
ARM/ HAND/ WRIST	DETP	56	3.6%	14.3%	12.5%	37.5%	32.1%	0.99
	Placebo	55	10.9%	10.9%	12.7%	34.6%	30.9%	
KNEE	DETP	76	5.3%	18.4%	9.2%	36.8%	30.3%	0.18
	Placebo	82	15.9%	8.5%	22.0%	24.4%	29.3%	
LEG	DETP	92	13.0%	7.6%	14.1%	22.8%	42.4%	0.35
	Placebo	76	9.2%	13.2%	17.1%	34.2%	26.3%	
NECK	DETP	8	12.5%	0	12.5%	12.5%	62.5%	0.37
	Placebo	7	28.6%	0	14.3%	14.3%	42.9%	
SHOULDER	DETP	82	3.7%	13.4%	24.4%	31.7%	26.8%	0.001
	Placebo	88	20.5%	13.6%	19.3%	28.4%	18.2%	
OTHER/ TORSO[b]	DETP	7	0	0	28.6%	57.1%	14.3%	0.74
	Placebo	13	15.4%	0	46.2%	15.4%	23.1%	

CMH= Cochran-Mantel-Haenszel; DETP=Diclofenac Epolamine Topical Patch.
[a] P-value derived from CMH test controlling for study.
[b] Category includes abdomen, chest, and side

missing patients in each treatment group. A Cochran-Mantel-Haenszel (CMH) test was used to determine the association between treatment and global response/efficacy evaluated by patient controlling for study.

Investigator Assessment of Global Response

Global response/efficacy was evaluated by the investigator in all five clinical trials. Global response/efficacy evaluated by investigator at exit was available across five clinical trials and was used for analysis. The scales were converted to a 5-point scale. Percentages were calculated based on the number of non-missing patients in each treatment group. A CMH test was used to assess the association between treatment and global response/efficacy evaluated by investigator.

Safety Analyses

Analyses of Adverse Events

In this current study, all AEs were mapped using MedDRA, version 10.1. The AEs were grouped according to system organ class (SOC). Percentages of AEs were reported with respect to the total study population as well as the treatment group being summarized. Frequencies represented the number of patients who experienced AEs; however, some patients may have reported more than one AE. Overall descriptive summaries of the number of patients who experienced AEs were tabulated by treatment group.

Analyses of Tolerability

Only three of the five clinical studies had data for the tolerability analysis. Tolerability was evaluated by patient and investigator using the scale listed above for assessment of global response. The association between

Table 5: *Summary of Tolerability Evaluated by Patient at Exit by Injury Location*

Injury Location	Treatment	N	None	Poor	Average	Good	Excellent	P-value[a]
ANKLE	DETP	111	0	1.8%	5.4%	36.0%	56.8%	0.10
	Placebo	107	0.9%	3.7%	8.4%	37.4%	49.5%	
BACK	DETP	20	0	5.0%	15.0%	25.0%	55.0%	0.34
	Placebo	20	0	5.0%	10.0%	50.0%	35.0%	
FOOT	DETP	33	3.0%	0	15.2%	24.2%	57.6%	0.67
	Placebo	26	0	7.7%	3.9%	42.3%	46.2%	
ELBOW	DETP	43	0	0	16.3%	46.5%	37.2%	0.83
	Placebo	40	0	10.0%	5.0%	35.0%	50.0%	
ARM/ HAND/ WRIST	DETP	56	1.8%	0	16.1%	30.4%	51.8%	0.76
	Placebo	51	0	3.9%	13.7%	35.3%	47.1%	
KNEE	DETP	74	1.4%	2.7%	8.1%	31.1%	56.8%	0.41
	Placebo	77	0	0	19.5%	33.8%	46.8%	
LEG	DETP	83	0	2.4%	9.6%	31.3%	56.6%	0.04
	Placebo	73	2.7%	1.4%	17.8%	35.6%	42.5%	
NECK	DETP	2	0	0	50.0%	0	50.0%	
	Placebo	1	0	0	0	0	100%	
SHOULDER	DETP	60	0	3.3%	15.0%	43.3%	38.3%	0.88
	Placebo	73	1.4%	5.5%	13.7%	35.6%	43.8%	
OTHER/ TORSO[b]	DETP	7	0	28.6 %	0	14.3%	57.1%	0.80
	Placebo	13	0	7.7%	15.4%	38.5%	38.5%	

CMH= Cochran-Mantel-Haenszel; DETP=Diclofenac Epolamine Topical Patch.
a P-value derived from CMH test controlling for study.
b Category includes abdomen, chest, and side
Note: There was a notable amount of missing data for back (> 40%) and P-value was not reported for neck because more than 80% of data were missing.

tolerability assessment and treatment was evaluated by CMH test controlling for study.

Statistical Analysis

The integrated dataset from the five clinical studies was categorized by injury location. Injuries located at arm, hand, and wrist were grouped together as "arm/hand/wrist," at leg, upper leg, lower leg, and hip were grouped together as "leg," and at abdomen, chest, and side were grouped together as "Torso/ Other." The number of subjects assessed differed by injury location and data was not assessed if the number of subjects per group was less than 10 patients.

The VAS scores were evaluated using an analysis of covariance (ANCOVA) model where change from baseline to day 14 was the response variable. The baseline value was the covariate, and treatment was the fixed effect. If the assumptions of ANCOVA were violated, a rank based analysis of variance method was used, stratifying by study. A Cochran-Mantel-Haenszel (CMH) test was used to determine the association between treatment and global response and efficacy evaluated by patient or investigator controlling for study. A descriptive frequency table of global response/efficacy by treatment was presented for the available data. Fisher's exact test was used to compare the frequencies of AEs between the DETP and placebo treatments. In addition, odds ratios were computed where appropriate to assess the odds of a patient experiencing an AE for a given group.

RESULTS

Demographic Information by Injury Location

This pooled analysis dataset consisted of 1,165 patients and there were no statisti-

***Table 6**: Summary of Tolerability Evaluated by Investigator at Exit by Injury Location*

Injury Location	Treatment	N	None	Poor	Average	Good	Excellent	P-value[a]
ANKLE	DETP	110	0	0	5.5%	29.1%	65. 5%	0.09
	Placebo	107	0	0.9%	8.4%	34.6%	56.1%	
BACK	DETP	20	0	10.0%	5.0%	45.0%	40.0%	0.63
	Placebo	19	0	5.3%	10.5%	36.8%	47.4%	
FOOT	DETP	33	0	6.1%	6.1%	15.2%	72.7%	0.90
	Placebo	26	0	3.9%	3.9%	26.9%	65.4%	
ELBOW	DETP	43	2.3%	4.7%	2.3%	51.2%	39.5%	0.45
	Placebo	40	0	5.0%	2.5%	45.0%	47.5%	
ARM/ HAND/ WRIST	DETP	56	0	3.6%	7.2%	28.6%	60.7%	0.42
	Placebo	51	0	3.9%	15.7%	21.6%	58.8%	
KNEE	DETP	74	1.4%	2.7%	6.8%	29.7%	59.5%	0.98
	Placebo	78	0	1.3%	9.0%	35.9%	53.9%	
LEG	DETP	83	0	3.6%	7.2%	21.7%	67.5%	0.02
	Placebo	72	2.8%	0	15.3%	36.1%	45.8%	
NECK	DETP	2	0	0	0	50.0%	50.0%	
	Placebo	1	0	0	0	0	100%	
SHOULDER	DETP	61	0	3.3%	14.8%	31.2%	50.8%	0.37
	Placebo	73	1.4%	6.9%	12.3%	38.4%	41.1%	
OTHER/ TORSO[b]	DETP	7	0	14.3%	14.3%	14.3%	57.1%	0.97
	Placebo	13	0	0	23.1%	23.1%	53.9%	

CMH= Cochran-Mantel-Haenszel; DETP=Diclofenac Epolamine Topical Patch.
[a] P-value derived from CMH test controlling for study.
[b] Category includes abdomen, chest, and side

cally significant differences between patients treated with the DETP or for the placebo group in any category of injury location, according to age or gender (Table 1). Slight differences were observed in some categories with regard to pathology (injury vs. inflammation). However, these differences were not statistically significant (data not shown).

Efficacy

Spontaneous Pain

In patients treated with the DETP, compared to patients treated with placebo, there were statistically significant differences in the mean change in VAS scores between baseline and day 14 in injuries located at the back (p = 0.02), elbow (p = 0.02), and shoulder (p = 0.01) (Table 2). There were no statistically significant differences between the DETP and placebo groups in the other injury locations.

Patient Assessment of Global Response/ Efficacy

Using a 5-point scale, the global response/ efficacy as evaluated by patient for each injury location for the DETP and placebo groups is summarized in Table 3. This data was collected on study day 14 in four of the five clinical trials. Statistically significant differences were observed in injuries located at the back (p=0.002), foot (p=0.02), elbow, (p=0.015), and shoulder (p=0.001) for patients treated with the DTEP compared to patients treated with placebo.

Investigator Assessment of Global Response/Efficacy

On study day 14, global response/efficacy, by injury location, was also evaluated by the investigator in all five clinical trials (Table 4). In patients treated with the DETP, statistically significant differences were observed

***Table 7**: Summary of Adverse Events by System Organ Class*

System Organ Class	DETP N=579 N (%)	Placebo N=586 N (%)
Any AE	149 (25.73)	157 (26.79)
Cardiac disorders	0	2 (0.34)
Eye disorders	1 (0.17)	2 (0.34)
Gastrointestinal disorders	29 (5.01)	25 (4.27)
General disorders and administration site conditions	28 (4.84)	39 (6.66)
Immune system disorder	1 (0.17)	0
Infections and infestations	6 (1.04)	4 (0.68)
Injury, poisoning and procedural complications	3 (0.52)	1 (0.17)
Metabolism and nutrition disorders	0	1 (0.17)
Musculoskeletal and connective tissue disorders	4 (0.69)	8 (1.36)
Nervous system disorders	28 (4.84)	20 (3.41)
Psychiatric disorders	6 (1.04)	3 (0.51)
Renal and urinary disorders	1 (0.17)	0
Respiratory, thoracic and mediastinal disorders	2 (0.35)	2 (0.34)
Skin and subcutaneous tissue disorders	40 (6.91)	50 (8.53)

AE=adverse event; DETP=Diclofenac Epolamine Topical Patch.
Note: All patients who received at least one dose of the DETP or placebo were included in the analysis for AEs.

***Table 8**: Adverse Events by Injury Location*

Injury Location	Treatment	N	AE N (%)
ANKLE	DETP	119	25 (21.01)
	Placebo	115	33 (28.70)
BACK	DETP	37	5 (13.51)
	Placebo	43	3 (6.98)
FOOT	DETP	47	9 (19.15)
	Placebo	47	7 (14.89)
ELBOW	DETP	37	12 (32.43)
	Placebo	31	6 (19.35)
ARM/HAND /WRIST	DETP	58	13 (22.41)
	Placebo	62	15 (24.19)
KNEE	DETP	81	19 (23.46)
	Placebo	93	21 (22.58)
LEG	DETP	101	14 (13.86)
	Placebo	79	20 (25.32)
NECK	DETP	8	0
	Placebo	9	0
SHOULDER	DETP	84	16 (19.05)
	Placebo	94	24 (25.53)
OTHER /TORSOa	DETP	7	1 (14.29)
	Placebo	13	3 (23.08)

AE=adverse event; DETP=Diclofenac Epolamine Topical Patch.
Note: All patients who received at least one dose of the DETP or placebo were included in the analysis for AEs
[a] Category includes abdomen, chest, and side

in injuries located at the back (p=0.003), foot (p=0.04), elbow (p=0.002), and shoulder (p=0.001) compared to patients in the placebo group.

Swelling as Assessed by Patient and Investigator

Three of the five clinical studies analyzed contained relatively complete sets of data on swelling. No statistically significant difference in swelling was observed between the DETP and placebo groups as assessed by either patient or investigator (data not shown).

SAFETY

Adverse Events and Tolerability

No statistically significant difference in tolerability was observed between patients in the DETP and placebo groups at any injury location as assessed by the patient (Table 5). When tolerability was assessed by investigator, there was a statistically significant difference in tolerability in patients when the DETP was applied to the leg, compared to patients who received placebo (Table 6). In all other injury location categories assessed by investigator, no statistically significant difference in tolerability was seen between the DETP and placebo groups.

Adverse events for both the DETP or placebo groups are listed by SOC in Table 7 and by location in Table 8. No statistically significant difference in the frequency of AEs was observed between placebo and treatment groups. The overall frequency of AEs was 25.7% (149/579) among DETP treated patients, and 26.8% (157/586) among placebo treated patients. The number of GI-related AEs reported by patients receiving the DETP (5.0%) or placebo (4.3%) was similar.

DISCUSSION

The results of this pooled analysis of five clinical trials indicate that the DETP is more efficacious than placebo in treating acute pain of the back, elbow, and shoulder. In patients treated with the DETP, VAS pain scores by injury location revealed significant improvement over placebo in the back, elbow, and shoulder injury categories. These results suggest that the DETP can be effective in maintaining pain reduction over a 2 week period.

The results of this pooled analysis also indicate that the DETP was safe and well tolerated regardless of the site of application. Tolerability did not differ between treatment and placebo at any injury location as evaluated by subject. When tolerability was evaluated by investigator, no significant differences were seen in any location other than the leg, wherein, the DETP was significantly better tolerated. However, it should be noted that tolerability assessment data was not available from two studies that contributed a large number of patients to the overall study population. A notable amount of data for some injury locations (>40% for back, >80% for neck) was not included in the tolerability analysis. Therefore, p-value for back should be interpreted with caution. Only a descriptive frequency table of tolerability evaluation by treatment for the available data was presented for neck.

The occurrence of AEs did not differ between patients who received the DETP or placebo at any injury location. These results suggest that the DETP is a safe option for treatment of pain regardless of location.

In addition, this pooled analysis suggests that the DETP provides an effective and safe alternative to oral NSAIDs in treatment of acute pain in the back, elbow, and shoulder. Other pain patches that have been examined for safety and efficacy in the treatment of acute pain include lidocaine and ketoprofen.[15, 16]

An open label study on the use of lidocaine patches in the treatment of lower back pain demonstrated significant improvement in average daily pain scores from baseline in subjects treated with a 5% lidocaine patch for 2 to 6 weeks. However, because this study was not placebo-controlled, it is not clear if patients would have demonstrated significantly less improvement without treatment. Furthermore, 19% of the 131 patients enrolled in the study experienced

adverse events thought to be related to study drug.[15] In a study examining the efficacy of the ketoprofen patch in the treatment of ankle sprain, almost 31% of the 81 patients enrolled in the study experienced complications due to treatment.[16] Several of these reported adverse events were GI- and CNS-related (each 6.2% of the ketoprofen-treated population). By contrast, GI and CNS-related AEs were comparable between the DETP and placebo in the 5 studies included in this analysis (Table 7). In addition, no cardiovascular AEs were observed in the DETP group in any of the 5 studies examined.

This meta-analysis has several limitations. Since reductions in spontaneous pain are affected by both time and treatment, it is possible that clinically significant differences between treatment and placebo may have existed at earlier time points for some injury locations. For example, if pain due to injury or inflammation was completely resolved before the end of study, then differences in VAS score between placebo and treatment may have been minimal or non-existent by the end of study. It is important to note that, in such an instance, a lack of significance at the end of study would not necessarily mean that no significant differences occurred at any time point in the study.

Subjects who heal appreciably before institution of treatment could also substantially reduce the mean VAS score of a particular injury group. These studies limit or remove this possibility by allowing enrollment within a time frame including the period where allodynia and hyperalgesia would generally be at their peak.

CONCLUSION

In this meta analysis of five placebo-controlled clinical trials, the DETP demonstrated efficacy and safety in reducing pain from acute injuries while remaining a safe, tolerable, and effective treatment for acute pain arising from injuries of the back, elbow, shoulder, and foot.

CONFLICT OF INTEREST STATEMENT

Drs. Jillmarie Yanchick was an employee of Alpharma Pharmaceuticals, LLC, a wholly owned subsidiary of King Pharmaceuticals, Inc., which markets DETP in the United States, at the time of this work. Dr. Arturo Lanzarotti is an employee of Institut Biochimique SA, which sponsored the DETP studies described herein. Dr. Zhao was and Ms. Pierchala is an employee of MMS Holdings, Inc. Funding for the statistical analyses and reporting of this project was provided by Alpharma Pharmaceuticals, LLC.

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