

**Bon Secours Richmond
Pharmacy & Therapeutics Committee
Lidocaine and Tetracaine (Synera[®]) Transdermal Patch
February 2007**

Recommendations:

Synera patch is recommended for addition to SMH formulary, to be made available for relief of pain for superficial venous access and dermatologic procedures; restricted to pediatric patient use.

Findings:

- Indicated for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatologic procedures in adults and children at least 3yrs of age.
- Synera was developed under the name S-Caine[™] Patch; is a combination of lidocaine 70mg and tetracaine 70mg per each patch.
- Contains a thin layer of a local anesthetic formulation integrated with an oxygen-activated heating element. The heating element enhances the delivery of the local anesthetics into the skin. When removed from its storage pouch, the patch begins to heat, warming the skin after application. *see page 2*
- Compared to EMLA cream, our formulary dermal anesthetic agent, Synera patch:
 - achieves effective anesthesia for minor dermatologic procedures in 30 minutes, 20-30 minutes for vascular access procedures in adults and children vs. 60-90minutes for EMLA
 - heating component helps to reduce pain and vasoconstriction
- Efficacy, as compared to EMLA cream, based on one randomized, controlled, cross-over study. Synera patch was shown to produce greater anesthesia when applied 10, 20 or 30 minutes prior to procedure – however not at 60minutes prior to procedure; greater pain relief also reported in patients receiving the patch 20-30 minutes prior to procedure, compared to EMLA. *see page 4*
- Additional data from randomized, double-blind trials showing that use of the patch was significantly more effective than placebo for reducing pain associated with superficial dermatologic procedures in adults and the elderly (age, > 65 years), as assessed by visual analog scale (VAS) scores (median score, adults, 5 vs. 31; elderly, 10 vs. 23) *see page 6*
 - Similar results were observed in two adult studies and one geriatric study of the patch's analgesic efficacy relative to placebo for venipuncture (median VAS score, 1 vs. 9; 5 vs. 28; 8 vs. 14).
 - Additional pediatric trials demonstrated the patch's efficacy across all age groups for reducing pain associated with lidocaine injection
 - Significant anesthesia achieved in 20-30 minutes (adult trial); VAS scores were reduced compared to placebo (adult and elderly); Oucher Scale scores indicated greater pain relief compared to placebo (children)
- Safe and well tolerated, as demonstrated in all clinical trials; no evidence of systemic toxicity
 - Compared to EMLA cream, methemoglobinemia has not been reported with either lidocaine or tetracaine (20-30% incidence of methemoglobinemia in infants and children following excessive applications of EMLA cream)
 - Adverse effects occurred in less-than 10% of patients; most common adverse effects were mild and transient local skin reactions (erythema, edema and blanching)
 - Contraindicated in patients with known history of sensitivity to lidocaine, tetracaine, local anesthetics of the amide or ester type, or any other component of the product and in patients with para amionbenzoic acid (PABA) hypersensitivity
 - Keeping a patch on longer than recommended or applying multiple patches simultaneously or sequentially could result in systemic absorption sufficient to result in serious adverse effects typical to lidocaine and tetracaine
 - Systemic toxicity potential is negligible. Tetracaine is metabolized (dermal route) by nonspecific esterases, is retained and released slowly from the stratum corneum and cleared rapidly by pseudocholinesterases; lidocaine absorption through intact skin of children remains well below levels considered toxic.
 - Use with caution in patients who may be more sensitive to the systemic effects of lidocaine and tetracaine, including the acutely ill, the debilitated, and patients with hepatic dysfunction.

- Use with caution in patients receiving Class I antiarrhythmics and/or other local anesthetics, as systemic toxic effects may be additive and potentially synergistic with the action of lidocaine and/or tetracaine
- The heating component contains iron powder – Synera patch must be removed before MRI procedures

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

Chemistry, Pharmacology, Pharmacokinetics, Indication, Dosing and Price

	SYNERA PATCH	EMLA CREAM (SMH formulary)
Drug class	Anesthetic combination components: lidocaine and tetracaine	Anesthetic combination components: lidocaine 2.5% and prilocaine 2.5%
Mechanism of action	Lidocaine is an amide-type local anesthetic agent and tetracaine is an ester-type local anesthetic agent. Both agents provides for local anesthesia by blocking sodium ion channels necessary for the initiation and conduction of neuronal impulses. The oxygen-activated heating component of the lidocaine and tetracaine patch enhances the delivery of the local anesthetics and improves the analgesic effects	Provides dermal analgesia by release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and by accumulation in vicinity of dermal pain receptors and nerve endings. Lidocaine and prilocaine, as anesthetic agents, stabilize neuronal membranes by inhibiting ionic fluxes required for initiation and conduction of impulses.
Metabolic pathway	Lidocaine: liver, via CYP1A2 (minor 3A4) Tetracaine: blood, via hydrolysis by plasma esterases	Lidocaine: liver, via CYP1A2 (minor 3A4) Prilocaine: liver and kidney
Active metabolite	Lidocaine: monethylglycinexylidide (MEGX) Glycinexylidide (GX) Tetracaine: para-aminobenzoic acid (PABA) diethylaminoethanol	Lidocaine: monethylglycinexylidide (MEGX) Glycinexylidide (GX) Prilocaine : ortho-toluidine and N-n-propylanine
Route of elimination	Lidocaine: kidney, greater than 98% of absorbed dose recovered in urine as metabolites or parent drug Less-than 10% excreted unchanged Approximately 20% of lidocaine is excreted unchanged in neonates Tetracaine: note established	Lidocaine: 98% of absorbed dose recovered in the urine as metabolites or parent drug
Elimination half-life	Intravenous lidocaine = 1.8hrs Tetracaine = not established (hydrolysis in plasma is rapid) Cardiac and hepatic dysfunction: lidocaine half-life increased Severe hepatic disease and pseudocholinesterase deficiency: lidocaine and tetracaine metabolism impaired; greater risk for developing toxicity	Intravenous lidocaine: 10-150minutes (prolonged in elderly) Prilocaine: NA
Volume of distribution (L/kg)	0.8-1.3L/kg (intravenous lidocaine) VD not determined for tetracaine due to rapid hydrolysis in plasma	0.8-1.3L/kg (intravenous lidocaine) VD not available for prilocaine
Protein binding	75% of lidocaine, approximately PB not determined for tetracaine due to rapid hydrolysis in plasma Crosses blood brain barrier and placenta via passive diffusion CNS toxicity may be observed around 5000mg/mL of lidocaine	70% lidocaine, via alpha-1-acid glycoprotein 55% prilocaine Both cross placental and blood brain barrier, presumed by passive diffusion
Time to Peak Concentration	1.7 hours	2-3 hours Persists 1-2 hours after removal
Onset of action	20-30 minutes	1 hour after application
FDA approved indication (s)	Topical anesthetic to skin for superficial dermatologic procedures Topical local anesthetic to skin, for superficial venous access	Indicated for local analgesia of normal, intact skin Superficial, minor surgery and pretreatment for infiltration anesthesia for genital mucosa membranes
Adverse effects (incidence %)	Transient local reactions: erythema (71%), edema (12%) blanching (12%); Application site reactions: contact dermatitis, rash, skin discoloration (<4%) Delayed skin reaction	Transient, local blanching followed by transient, local redness or erythema Ototoxicity has resulted (animal studies) when instilled into the middle ear Not for use in patients with congenital or idiopathic methemoglobinemia or patients under 12months receiving treatment with methemoglobin-inducing agents
Contraindications	Known history of sensitivity to lidocaine or tetracaine; or amide- or ester-type local anesthetics Known history of sensitivity to other product components Known para-aminobenzoic acid (PABA) sensitivity	Known history of sensitivity to local amide anesthetics

Drug interactions	<ul style="list-style-type: none"> ▪ class I antiarrhythmic agents (i.e. tocainide, mexilitine) ▪ local anesthetics (potential for additive/synergistic effects) ▪ CYP3A4 inhibitors (protease inhibitors, macrolides, azole antifungals, amiodarone) ▪ amiodarone, metoprolol and nadolol: inhibits and/or attenuates lidocaine metabolism ▪ cholinesterase inhibitors (i.e. anticholinergics, cyclophosphamide, echothiophate, isofluorophate): may inhibit metabolism of tetracaine 	<ul style="list-style-type: none"> ▪ class I antiarrhythmic agents (i.e. tocainide, mexilitine) ▪ 20-30% of infants and children have developed significant methemoglobinemia following excessive applications of EMLA; therefore drugs that may induce methemoglobin (such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthaline, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, phenobarbital, phenytoin, primaquine, quinine).
Dosage and Administration	For adults and pediatrics (greater-than 3rs) Apply to intact skin 20-30min prior to procedure, venipuncture or IV cannulation Simultaneous or sequential application of multiple patches is not recommended	Apply under occlusive dressing for at least 1hour (clinical procedures such as IV catheter placement and venipuncture) Apply under occlusive dressing for at least 2hours (split skin graft harvesting)
Cost	10 patches for \$ 123.12; or \$12.31/ 1-patch application	EMLA 2.5% cream = \$3.89/5g tube (1 application)
SMH USE 2006	NA	150 units of EMLA January – December 2006

Reference: Synera® product package insert, Endo Pharmaceuticals 1/2006; EMLA® product package insert, AstraZeneca 5/2005

Anesthesiology. 2004;101:A1123.

The lidocaine/tetracaine patch versus EMLA® for topical anesthesia before a vascular access procedure: a randomized controlled trial. A Randomized, Double-blind, Crossover Study Comparing the S-Caine™ Patch to EMLA® Cream for Induction of Local Dermal Anesthesia for Vascular Access Procedures in Adult Subjects

Sawyer J, Salvatore Febrarro, MD

OBJECTIVES: To compare the clinical effectiveness of the S-Caine™ patch to EMLA® cream in providing clinically useful local dermal anesthesia for vascular access procedures in adult subjects and to monitor the nature and frequency of AEs associated with the use of the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, paired study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP plus an oxygen-activated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period of time (2 h). EMLA cream is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%. EMLA cream was applied to a localized area and occluded according to the product's instructions, using a plastic template the same size of the S-Caine™ patch to ensure uniformity of the treatment across subjects and to maintain blinding of the investigator. Subjects who met study criteria received concurrent applications of both treatments, with application location randomized between the left and right antecubital surfaces. Subjects were further randomized to a 10-, 20-, 30- or 60-minute application group. After removal of the study medication, the investigator evaluated the skin area for erythema, edema, blanching, and other skin reactions before performing a vascular access procedure at the right and left antecubital surfaces, respectively. Erythema and eschar formation were jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema and blanching were independently evaluated (5-point categorical scale: none through severe/extreme). Following insertion, the investigator recorded the difficulty of the puncture using a 5-point categorical scale (1=insertion at first attempt through 5=unable to insert). Post-procedure efficacy evaluations included subject ratings of procedural pain (100-mm VAS where 0 mm=no pain and 100 mm=worst pain imaginable), investigator ratings of the subject's pain (4-point categorical scale: no pain, slight pain, moderate pain, severe pain), and subject and investigator ratings of the adequacy of the anesthetic (yes, no). Before discharge from the study site, subjects were given a handout describing potential onset of delayed reactions and instructed to inspect the application sites over the next 24 to 48 hours and to call the study site if a skin reaction developed.

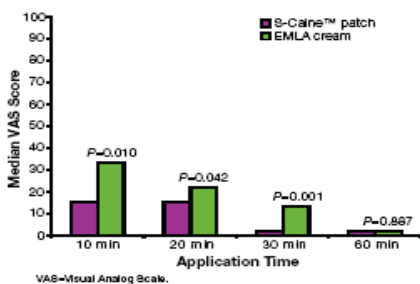
PATIENTS: Planned enrollment was 80 subjects. Adults ≥18 years of age without known allergies or sensitivities to lidocaine, tetracaine, or other local anesthetics and who had never used EMLA cream were eligible for participation. Subjects were excluded if they had taken concomitant prescription analgesic medication during the previous 24 hours; had damaged, denuded, or broken skin at the designated patch site; or were pregnant or breastfeeding. All participants provided written informed consent. **STATISTICAL ANALYSIS:** Demographic, history, and

examination variables were summarized using descriptive statistics. Between-group comparisons of age, height, body weight, and pretreatment vital signs were evaluated using 1-way ANOVA. Race, sex, and concomitant medication use were compared between groups using chi-square tests. Skin type was compared between groups using a Kruskal-Wallis test. Procedure duration was analyzed using repeated measures ANOVA, with the grouping factor of application time and the repeated measure of treatment type. Vascular access difficulty was compared between treatments using a sign test. Because differences in efficacy and safety outcomes were expected with different application times for the 2 treatments, the study was powered to analyze application time groupings separately for these outcome variables. The subject's VAS score, investigator pain ratings, and erythema/eschar evaluation and blanching were compared between treatments for each application period separately using Wilcoxon signed rank tests. Edema was compared similarly using sign tests. The subject and investigator assessment of the elimination of pain and whether the subject would use the patch again were compared between treatments using McNemar chi-square tests for each application time separately. Exploratory comparisons of S-Caine™ patch VAS scores by application time were performed using pairwise Mann-Whitney tests. AEs were presented descriptively.

RESULTS: A total of 82 subjects were randomized: 20 subjects each to the 10-, 20-, and 60-minute application time groups, and 22 subjects to the 30-minute group. 2 subjects initially randomized to the 30-minute group received each treatment for only 20 minutes; data from these subjects were included in the 30-minute intent-to-treat group. To compensate, 2 additional subjects were added to the 30-minute treatment group, which resulted in the treatment group sample of 22 subjects. 1 subject in the 10-minute group received both treatments but refused the second vascular access procedure (EMLA arm) and was withdrawn from the study. All baseline variables, including skin type, were similar across all treatment groups. The S-Caine™ patch was more effective than EMLA cream for 10- and 20-minute applications, but the most highly significant difference was seen for 30-minute application. The efficacy of EMLA cream was comparable with that of the S-Caine™ patch only for 60-minute application (Figure 5, Table 5). Exploratory comparisons of VAS scores with the S-Caine™ patch across the 4 application times found no significant differences between the 10- and 20-minute ($P=0.978$) or between the 30- and 60-minute ($P=0.701$) application times; however, significant differences were seen between 10 or 20 minutes and 30 or 60 minutes ($P<0.001$ except for 10 min vs 60 min, which was significant at $P=0.005$). A single 10-, 20-, 30-, or 60-minute application of the S-Caine™ patch was generally well tolerated. 2 subjects experienced nausea and faintness during the vascular access procedure, 1 of whom was withdrawn from the study. The investigator considered the AEs to be moderate in severity and unlikely related to study treatment. Subjects experienced more erythema with the S-Caine™ patch than with EMLA cream at 20, 30, and 60 minutes ($P^20.041$) and more blanching with EMLA cream than with the S-Caine™ patch at 30 and 60 minutes ($P^20.027$). No subject experienced a severe dermal reaction to the patch.

CONCLUSIONS: The S-Caine™ patch was more effective than EMLA cream for 10-, 20-, and 30-minute applications, with the most highly significant difference observed with the 30-minute application. EMLA cream was comparable in efficacy to the S-Caine™ patch only for the 60-minute application. Both treatments were safe and well tolerated. Significantly more cases of erythema occurred with the S-Caine™ patch, and significantly more cases of blanching occurred with EMLA cream.

Figure 5. SC-40-02 Median VAS Scores for Procedural Pain.



Randomized, Double-blind, Placebo-controlled Study Evaluating an S-Caine™ Patch to Induce Local Anesthesia of the Skin Prior to a Vascular Access Procedure in Pediatric Patients

Bari Cunningham, MD

David Fivenson, MD

OBJECTIVES: To compare the clinical effectiveness of the S-Caine™ patch (developmental formulation) to a placebo patch in providing clinically useful dermal anesthesia in pediatric patients having a vascular access procedure and to monitor the nature and frequency of adverse events (AEs) associated with the safety of the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, placebo-controlled study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine base United States Pharmacopoeia (USP) and 70 mg tetracaine base USP plus an oxygen-activated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period of time (2 h). The placebo formulation contained olive oil National Formulary (NF) in place of the active ingredients and an identical heating element. Patients who met the study criteria were randomized to receive either the S-Caine™ patch or a placebo patch. Each patient received a 30-minute administration of the study patch immediately before undergoing the procedure. Following patch removal, the investigator evaluated the skin area under the patch for erythema, edema, and other skin reactions. Erythema and eschar formation were jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema and blanching were independently evaluated (5-point categorical scale: none through severe/extreme). The vascular access procedure was then performed on the designated patch site. Post-procedure efficacy evaluations included patient ratings of procedural pain (100-point Oucher® Scale), guardian, investigator and independent observer ratings of the patient's pain (4-point categorical scale: no pain through severe pain); guardian, investigator, and independent observer ratings of whether the treatment provided adequate analgesia (yes/no); and guardian assessment of whether they would use the treatment again on their child (yes/no). Safety and tolerability were evaluated based on the frequency of AEs and on the occurrence of local reactions to treatment. Patients were dismissed from the study once the vascular access procedure and pain evaluations were completed.

PATIENTS: Planned enrollment was 60 patients. Children between 7 and 18 years of age who required a vascular access procedure and had no known allergies or sensitivities to lidocaine, tetracaine, or other local anesthetics were eligible to participate. Patients were excluded if they had damaged, denuded, or broken skin at the designated patch site; were pregnant or breast-feeding; or had been exposed to an investigational drug or device within the previous 30 days. All participants or their guardians provided written informed consent.

STATISTICAL ANALYSIS: Demographic and background variables were summarized using descriptive statistics and compared between treatment groups stratified by study site using analysis of variance (ANOVA) for continuous variables and Mantel-Haenszel summary chi-square tests for categorical data. Assessment scales for efficacy and evaluation of skin reactions and the incidence of clinical responses to pain impression questions were compared between groups stratified by study site using Mantel-Haenszel summary chi-square tests. Oucher pain scale results were compared using Mann-Whitney tests. AEs were tabulated by type, onset, duration, severity, outcome, and relationship to treatment.

RESULTS: A total of 60 patients were enrolled: 30 in each treatment group. All patients completed the study. Mean age was 12.5 years in the S-Caine™ group and 12.9 years in the placebo group. Groups were well matched with regard to sex, ethnic background, and medical history. The S-Caine™ patch was effective in providing clinically useful local anesthesia for vascular access procedures in pediatric patients. Median Oucher scores of procedural pain were 0 for the S-Caine™-treated group versus 35 for the placebo-treated group ($P<0.001$). Guardian, investigator, and independent observer ratings of pain and anesthetic efficacy consistently favored the S-Caine™ patch over placebo (Table 1), although not all differences in guardian evaluations achieved statistical significance. S-Caine™-treated patient experienced a rash considered to be moderate in severity and related to study drug. The AE resolved in approximately 2 hours with no intervention. As expected with local anesthesia, patients in the active treatment group experienced significantly more erythema (83% vs 27%, $P<0.001$) and edema (30% vs 10%, $P=0.033$) than patients in the placebo group. No patient experienced a severe dermal reaction to the patch.

CONCLUSIONS: The S-Caine™ patch was effective in providing clinically useful local anesthesia for vascular access procedures in pediatric patients. Patient, investigator, and independent observer efficacy evaluations significantly favored active treatment over placebo for all assessments performed. Guardian efficacy evaluations also favored active treatment, although the differences in evaluations were statistically significant for only 1 assessment. The S-Caine™ patch was safe and well tolerated.

Table 1. SC-09-99 Efficacy Outcomes

	S-Caine™ (n=30)	Placebo (n=30)	P Value
Patient ratings			
Median Oucher score	0	35	<i>P</i> <0.00†
Guardian ratings, %			
Pain Evaluation			
No pain	70	47	
Slight pain	20	27	
Moderate pain	10	23	<i>P</i> =0.050†
Severe pain	0	3	
Patch provided adequate anesthesia	80	57	<i>P</i> =0.10†
Would use patch again	83	67	<i>P</i> =0.238†
Investigator evaluation of pain, %			
No pain	73	30	
Slight pain	20	37	
Moderate pain	7	33	<i>P</i> =0.00†
Severe pain	0	0	
Independent observer evaluation of pain, %			
No pain	70	43	
Slight pain	20	23	
Moderate pain	7	30	<i>P</i> =0.019†
Severe pain	3	3	

†Mann-Whitney statistic.
‡Mantel-Haenszel summary chi-square.

A Randomized, Double-blind, Placebo-controlled Study Evaluating the S-Caine™ Patch, When Applied for Twenty Minutes, for Induction of Local Anesthesia of the Skin Prior to a Vascular Access Procedure in Pediatric Patients

Bari Cunningham, MD

Annette Wagner, MD

OBJECTIVES: To compare the clinical efficacy of the S-Caine™ patch (developmental formulation) to a placebo patch in providing clinically useful dermal anesthesia in pediatric patients having a vascular access procedure and to monitor the nature and frequency of AEs associated with the safety of the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, placebo-controlled study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP plus an oxygen-activated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period of time (2 h). The placebo formulation contained olive oil, NF in place of the active ingredients and an identical heating element. Patients who met the study criteria were randomized to receive either the S-Caine™ patch or a placebo patch. Each patient received a 20-minute administration of the study patch immediately before undergoing the procedure. Following patch removal, the investigator evaluated the skin area under the patch for erythema, edema, and other skin reactions and performed a preassessment of the child's behavior. Erythema and eschar formation were jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema was independently evaluated (5-point categorical scale: none through severe). The vascular access procedure was then performed on the designated patch site. Postprocedure efficacy evaluations included patient ratings of procedural pain (Oucher Scale: 0–100 numeric scale or 0–6 photographic scale), investigator and independent observer ratings of the patient's pain (4-point categorical scale: no pain through severe pain), and investigator and independent observer ratings of whether the treatment provided adequate analgesia (yes/no). Safety and tolerability were evaluated based on the frequency of AEs and on the occurrence of local reactions to treatment. Patients were dismissed from the study once the vascular access procedure and pain evaluations were completed.

PATIENTS: Planned enrollment was 60 patients. Children between 7 and 17 years of age who required a vascular access procedure and had no known allergies or sensitivities to lidocaine, tetracaine, or other local anesthetics were eligible to participate. Patients were excluded if they had damaged, denuded, or broken skin at the designated patch site; were pregnant or breast-feeding; or had been exposed to an investigational drug or device within the previous 30 days. Participants (when applicable) and their guardians provided written informed consent.

STATISTICAL ANALYSIS: Demographic and background variables were summarized using descriptive statistics and compared between treatment groups stratified by study site using 2-way ANOVA for continuous variables and Mantel-Haenszel summary chi-square tests for categorical variables. Preassessment behavior scales, investigator and observer's evaluations, and skin reactions were compared between groups stratified by study site using Mantel-Haenszel summary chi-square tests. Procedure duration and the numeric Oucher Scale results were compared between treatment groups using 2-way ANOVA with the factors of treatment, center, and treatment by center. A Mann-Whitney test was performed on the Oucher Scale results combined over centers. AEs were tabulated by type, onset, duration, severity, outcome, and relationship to treatment.

RESULTS: A total of 60 patients were enrolled: 30 in each treatment group. All patients completed the study and were analyzed for safety and efficacy. The mean age was 13.5 years in the S-Caine™ group and 13.3 years in the placebo group. Groups were well matched with regard to sex, ethnic background, and medical history. Because only 2 patients used the Photographic Oucher Scale, only data from the 58 patients using the numeric scale were included in the analysis of patient assessment of pain. The S-Caine™ patch was effective in providing clinically useful local anesthesia for vascular access procedures in pediatric patients. Median Oucher scores of procedural pain were 0 for the S-Caine™-treated group versus 20 for the placebo group (*P*<0.001). Investigator and independent observer ratings of pain and anesthetic efficacy consistently favored the S-Caine™ patch over placebo (Table 2). The S-Caine™ patch was generally well tolerated. 3 patients—all in the placebo group—experienced an AE during the study. 2 patients had mild skin tears that were related to the patch adhesive, and 1 patient reported a burning sensation that was mild in severity and possibly related to the study drug. As expected with local anesthesia, patients in the S-Caine™ treatment group experienced significantly more erythema than patients in the placebo group (90% vs 43%, *P*<0.001). No severe dermal reactions were observed or reported.

CONCLUSIONS: A 20-minute application of the S-Caine™ patch was effective in providing clinically useful anesthesia for vascular access procedures in pediatric patients. Patient, investigator, and independent observer efficacy evaluations significantly favored S-Caine™ treatment over placebo. The S-Caine patch was well tolerated.

Table 2. SC-10-00 Efficacy Outcomes

	S-Caine™ (n=30)*	Placebo (n=30)*	P Value
Patient ratings			
Median Oucher score	0	20	<i>P</i> <0.00†
Investigator evaluation of pain, %			
Pain Evaluation			
No pain	83	20	
Slight pain	17	67	
Moderate pain	0	13	<i>P</i> <0.00†
Severe pain	0	0	
Patch provided adequate anesthesia	90	27	<i>P</i> <0.00†
Independent observer evaluation of pain, %			
Pain Evaluation			
No pain	87	23	
Slight pain	10	63	
Moderate pain	0‡	10	<i>P</i> <0.00†
Severe pain	0	3	
Patch provided adequate anesthesia	93	37	<i>P</i> <0.00†

*N=29 per group for Oucher scale results.

†Mann-Whitney statistic.

‡Mantel-Haenszel summary chi-square.

§1 subject (0.3%) had moderate pain.

Anesthesiology. 2005 Feb;102(2):403-8.

A randomized controlled trial to evaluate S-Cain patch for reducing pain associated with vascular access in children.

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OBJECTIVES: To compare the clinical efficacy of the S-Caine™ patch to a placebo patch in providing clinically useful dermal anesthesia in pediatric patients having a vascular access procedure and to monitor the nature and frequency of AEs associated with the safety of the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, placebo controlled, clinical study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP plus an oxygen-activated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period of time (2 h). The placebo formulation contained olive oil NF in place of the active ingredients and an identical heating element. Patients who met the study criteria were stratified into 2 age groups: (1) aged 3 to 6 years; and (2) aged 7 to 17 years. Patients were randomized (2:1) to receive a 20-minute application of either the S-Caine™ patch or a placebo patch before undergoing a vascular access procedure. Following patch removal, the investigator evaluated the area under the patch for erythema, edema, and other skin reactions and performed a preassessment of the child's behavior using a 3-point scale (1=calm, 2=slightly frightened, 3=frightened). Erythema and eschar formation were jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema and blanching were independently evaluated (5-point categorical scale: none through severe/extreme). The vascular access procedure was then performed on the designated patch site. Efficacy evaluations were performed after the vascular access procedure was completed. The primary efficacy evaluation consisted of patient rating of procedural pain using the Oucher Scale (0–100 numeric scale or 0–6 photographic scale). Other efficacy evaluations included investigator and independent observer ratings of the patient's pain (4-point categorical scale: no pain through severe pain) and investigator ratings of whether the treatment provided adequate analgesia (yes/no). Safety and tolerability were evaluated based on the frequency of AEs and on the occurrence of local reactions to treatment. Patients were dismissed from the study once the vascular access procedure and pain evaluations were completed. Before leaving the study site, parents received a handout and verbal explanation of possible delayed skin reactions and were instructed to call the study site if any delayed skin reaction developed at the patch site.

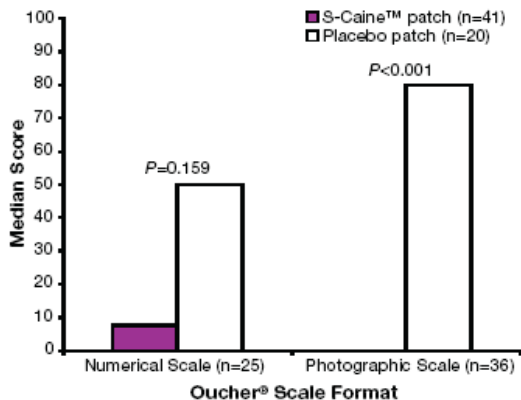
PATIENTS: Planned enrollment was 60 patients. Children between the ages of 3 and 17 years who required a vascular access procedure and had no known allergies or sensitivities to lidocaine, tetracaine, other local anesthetics, or components of the test materials were eligible to participate. Patients were excluded if they had taken concomitant prescription-strength analgesic medication during the previous 24 hours; had damaged, denuded, or broken skin at the designated patch site; had active atopic dermatitis; were pregnant or breast-feeding; had known multiple allergies that could indicate hypersensitive skin; or had severe cognitive impairment. Patients or their guardians provided written informed consent.

STATISTICAL ANALYSIS: Demographic, history, and examination variables were summarized using descriptive statistics. Comparability of treatment groups on age, height, body weight, and vital signs were evaluated using 2-way ANOVA, with the factors of treatment group and center, plus treatment by center. Sex, race, concomitant medication use, and previous topical anesthetic use were compared between treatments using Mantel-Haenszel summary chi-square tests, stratified by center, and between centers using chi-square tests. Skin type, pre-assessment behavior, and procedure duration were compared between centers using Mann-Whitney tests and between treatment groups using Mantel-Haenszel chi-square tests for ordered categories, stratified on center. Numerical and photographic Oucher Scale results were analyzed separately. For each scale, a 2-way ANOVA was used to confirm the absence of treatment-by-center interactions, and then scores combined over centers were compared using Mann-Whitney tests. Additionally, in an attempt to combine data from the 2 scales, the proportions of patients with no pain on each scale were calculated and compared using a Mantel-Haenszel chi-square test stratified by scale used. Cochran's test was used to assess the homogeneity of results across stratifications before computing the combined significance test. Erythema/eschar and edema evaluations and investigator and observer evaluations were compared between treatment groups using Mantel-Haenszel summary chi-square tests for ordered or dichotomous categories, stratified by center.

RESULTS: 65 patients entered the study and were randomized to treatment: 43 to the S-Caine™ group (22 patients aged 3 to 6 years and 21 patients aged 7 to 17 years) and 22 to the placebo group (11 patients in each age group). 1 subject in the placebo group withdrew before undergoing any study procedures. 61 patients completed the study—41 in the S-Caine™ group and 20 in the placebo group—and were included in the efficacy analyses using Oucher pain scores. 1 child refused to undergo venipuncture after patch application, and site staff determined that venipuncture was not necessary in 2 children. Demographic and baseline characteristics generally were comparable between the treatment groups, although significantly more patients in the S-Caine™ group had skin type IV, V or VI. The S-Caine™ patch was more effective than placebo in younger children (ie, those who used the photographic version of the Oucher Scale) as evidenced by statistically significantly lower median Oucher scores (0.0 vs 80.0, $P<0.001$). Median Oucher scores for older patients were 7.5 for the S-Caine™ patch and 50 for placebo, but the difference was not statistically significant ($P=0.159$) (Figure 1). Investigator and independent observer ratings of procedural pain supported the efficacy of the S-Caine™ patch: the investigator rated 76% of S-Caine™-treated patients as having no pain compared with 20% of patients who received placebo ($P=0.001$), and the independent observer rated 76% of patients who received S-Caine™ as having no pain compared with 15% of patients who received placebo ($P<0.001$). The investigator felt that the local anesthetic produced adequate anesthesia in the majority of patients in both the S-Caine™ and placebo groups (80% vs 70%, $P=0.556$). A 20-minute application of S-Caine™ patch was well tolerated. No AEs were noted in either group. As expected with local anesthesia, patients in the S-Caine™ treatment group experienced slightly more erythema than patients in the placebo group; however, this difference was not statistically significant. No severe dermal reactions were observed or reported.

CONCLUSIONS: The S-Caine™ patch was significantly more effective than placebo in younger children and was clinically more effective in older children. Investigator and independent observer ratings showed significant pain relief with the S-Caine™ patch as compared with placebo. The S-Caine patch was safe and well tolerated in this pediatric population.

Figure 1. SC-20-01 Median Oucher Scores for Procedural Pain.



A Randomized, Double-blind, Placebo-controlled Study Evaluating the S-Caine™ Patch for Induction of Local Anesthesia for Lidocaine Injection in Pediatric Patients

Moise Levy, MD, Bari Cunningham, MD, Bernard Cohen, MD, Elaine Siegfried, MD, Toivo Rist, MD, Alicia Barba, MD

OBJECTIVES: To evaluate the clinical efficacy of the S-Caine™ patch in providing clinically useful local anesthesia in pediatric patients undergoing a lidocaine injection for a minor dermatologic procedure and monitor the nature and frequency of AEs associated with the safety of the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, placebo-controlled study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine USP and 70 mg tetracaine USP plus an oxygenactivated heating element that generated a controlled level of heating (39°C–41°C) for the application period. The placebo formulation contained olive oil NF in place of the active ingredients. Eligible patients were randomly assigned to receive a 30-minute application of S-Caine™ or placebo patch before receiving a lidocaine injection for a minor dermatologic procedure. After removal of the patch, the investigator assessed the patient's behavior using a 3-point scale (1=calm, 2=slightly frightened, 3=frightened) and evaluate the skin area under the patch for erythema, edema, and other skin reactions. Erythema and eschar formation were jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema and blanching were independently evaluated (5-point categorical scale: none through severe/extreme). Moderate to severe cases of erythema or edema were also recorded as AEs. The lidocaine injection was then performed on the designated patch site. Efficacy evaluations were performed immediately following the injection, and included patient ratings of procedural pain (Oucher Scale: 0–100, 11-point numeric scale or 1–100, 6-point photographic scale), investigator and independent observer ratings of the patient's pain (4-point categorical scale: no pain through severe pain), and investigator ratings of whether the treatment

provided adequate analgesia (yes/no). Safety and tolerability were evaluated based on the frequency of AEs and on the occurrence of local reactions to treatment. Patients were dismissed from the study once the injection, pain assessments, and dermatologic procedures were completed. Patients and parents received a handout and verbal explanation of potential delayed skin reactions and were contacted within 24 to 48 hours of the procedure to determine if any reactions had developed.

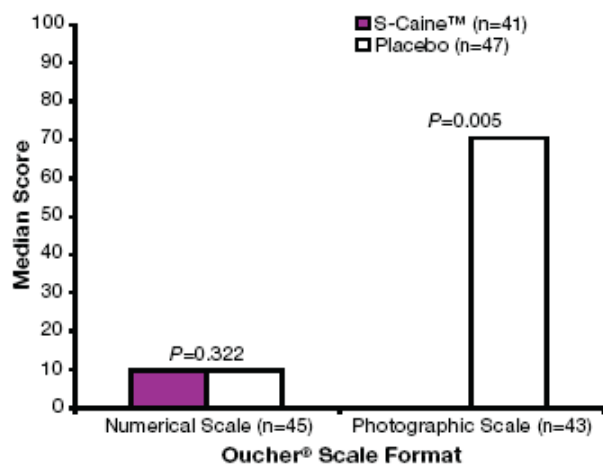
PATIENTS: Planned enrollment was 80 patients. Children between 3 and 17 years of age who required a lidocaine injection and had no known allergies or sensitivities to lidocaine, tetracaine, other local anesthetics, or any components of the test materials were eligible to participate. Patients were excluded if they had damaged, denuded, or broken skin at the designated patch site; were pregnant or breast-feeding; or had taken prescription-strength analgesic medication during the past 24 hours. Participants (when applicable) and their guardians provided written informed consent.

STATISTICAL ANALYSIS: Demographic, history, and examination variables were summarized using descriptive statistics. Comparability of treatment groups on age, height, body weight, and vital signs were evaluated using 2-way ANOVA, with the factors of treatment group and center, plus the treatment-by-center interaction. Sex, race, concomitant medication use, and previous topical anesthetic use were compared between treatments using Mantel-Haenszel summary chi-square tests; stratified by center, and between centers using chi-square tests. Skin type and preassessment behavior were compared among centers using Kruskal-Wallis ANOVA and between treatment groups using Mantel-Haenszel chi-square tests for ordered categories, stratified on center. Time from patch removal to injection was analyzed using 2-way ANOVA. A square root transformation was applied before analysis to temper the effect of large values. Numeric and Photographic Oucher Scale results were compared separately between treatments using Mann-Whitney tests (no adjustments by center were made because of small numbers for some of the centers and stratifications). To corroborate findings from the patient scores, investigator and witness evaluations were also performed separately for Oucher scale groups using Mann-Whitney tests for pain evaluations and Fisher exact test for assessment of adequate anesthesia. Erythema and eschar evaluation, edema evaluation, blanching, and investigator and witness evaluations were compared between treatment groups using Mantel-Haenszel summary chi-square tests for ordered or dichotomous categories, stratified by center.

RESULTS: 88 patients were enrolled: 41 to the S-Caine™ group (20 patients aged 3 to 6 years and 21 patients aged 7 to 17 years) and 47 to placebo (22 patients aged 3 to 6 years and 25 patients aged 7 to 17 years). All patients completed the study and were included in efficacy and safety analyses. Treatment groups were well matched for age, height, weight, race, and skin type. Among children who used the photographic version of the Oucher Scale, the median pain score was 0.0 with the S-Caine™ patch versus 70.0 with placebo ($P=0.005$) (Figure 2). The data from older patients using the numeric version of the Oucher Scale demonstrated that 70% of S-Caine™-treated patients had an Oucher score of ≥ 10 compared with 52% of placebo-treated patients, but these results were not statistically significant. Overall, investigator and independent witness ratings were not different for S-Caine™ and placebo. However, when these ratings were evaluated by the version of Oucher Scale used, the findings were similar to the patient ratings: for younger patients using the photographic scale, investigator ratings were significantly better for the S-Caine™ patch than placebo ($P=0.005$), and differences in independent witness ratings approached statistical significance ($P=0.057$). The S-Caine™ patch was well tolerated by pediatric patients undergoing lidocaine injection. 2 patients—both in the S-Caine™ group—experienced an AE during the study. 1 patient had moderate erythema that was definitely related to the study drug and resolved in 1 hour. 1 patient had moderate edema that was definitely related to the study drug and resolved within a day without treatment. Patients in the S-Caine™ treatment group experienced significantly more erythema (46% vs 23%, $P=0.006$) and edema (22% vs 0%, $P=0.003$) than patients in the placebo group. None of the patients experienced a severe dermal reaction to the patch.

CONCLUSIONS: The S-Caine™ patch was significantly more effective than placebo for younger children who used a photographic version of the Oucher Scale. Although the S-Caine™ patch appeared to show efficacy in the older group of children, treatment group differences were not statistically significant. The patch was safe and well tolerated in pediatric patients undergoing lidocaine injection.

Figure 2. SC-21-01 Median Oucher Scores for Procedural Pain



A Randomized, Double-blind, Placebo-controlled Study Evaluating an Integrated Transdermal Drug Delivery Local Anesthetic System Containing an Integrated S-Caine™ Patch and a Controlled Heat-Aided Drug Delivery (CHADD™) Patch to Induce Local Anesthesia of the Skin for Minor Dermatological Procedures in Pediatric Patients

David Rodriguez, MD, Daniel Stewart, MD

OBJECTIVES: To evaluate the efficacy of the S-Caine™ patch (developmental formulation) versus a matched placebo in providing clinically useful dermal anesthesia in pediatric patients undergoing minor dermatologic procedures, and to monitor the nature and frequency of AEs associated with the use of S-Caine™ and placebo.

STUDY DESIGN: Randomized, double-blind, placebo-controlled study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP plus an oxygen-activated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period. The placebo patch contained olive oil NF in place of the active ingredients and delivered the same level of heat as the S-Caine™ patch. Eligible patients were randomized to receive either an S-Caine™ or a placebo patch for 60 minutes before undergoing a minor dermatologic procedure (eg, shave or punch biopsy, removal of a superficial benign or malignant tumor, seborrhea or actinic keratosis lesion, nevus, or skin tag removal). After removal of the patch, the investigator assessed the patient's behavior using a 3-point scale (1=calm, 2=slightly frightened, 3=frightened) and evaluated the skin area under the patch for erythema, edema, and other skin reactions. Erythema and eschar formation were jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema was independently evaluated (5-point categorical scale: none through severe). The investigator then verified dermal anesthesia at the patch site using a pinprick test. If the patient was without sensation in the area treated, the treatment was considered an initial success and the dermatologic procedure was initiated. If there was sensation in the treated area, the treatment was considered a failure and a rescue lidocaine injection was administered before initiating the dermatologic procedure. Subject pain ratings were not evaluated. The protocol stipulated that subject efficacy evaluations would not be performed in treatment failures on the pinprick test. Because most subjects in the placebo group were treatment failures, there were not enough subjects to allow for a meaningful analysis. Other post-procedure efficacy evaluations included investigator and parental ratings of the patient's pain (4-point categorical scale: no pain through severe pain) and investigator ratings of whether the treatment provided adequate analgesia (yes/no). Parents were also asked if they would use this type of anesthesia for their child again. Safety and tolerability were evaluated based on the frequency of AEs and on the occurrence of local reactions to treatment. Patients were dismissed from the study once the dermatologic procedure and pain evaluations were completed.

PATIENTS: Planned enrollment was 60 patients. Children between the ages of 4 and 16 years who required local anesthesia for a minor dermatologic procedure and had no known sensitivities to lidocaine, tetracaine, other local

anesthetics, or any components of the test materials were eligible for inclusion. Exclusion criteria included pregnancy, breastfeeding, or a history of having taken prescription-strength analgesic medication during the past 24 hours. Participants (when applicable) and their guardians provided written informed consent.

STATISTICAL ANALYSIS: Demographic, history, and examination variables were summarized using descriptive statistics. Comparability of treatment groups on age, height, body weight, and vital signs were evaluated using 2-way ANOVA, with the factors treatment group, center, and treatment by center. Sex was compared between groups using Mantel-Haenszel summary chi-square tests, stratified by center. No comparison of race was conducted, because most patients at each center were of the same race. Skin type, pre-assessment behavior, erythema/eschar evaluation, edema evaluation, and the parent's and investigator's evaluations of pain were compared between treatment groups using Mantel-Haenszel summary chi-square tests for ordered categories, stratified by center. Incidence of anesthesia, rescue lidocaine use, parent's assessment of whether the patch would be used again, and investigator's evaluation of adequate anesthesia and patient acceptance were analyzed using Mantel-Haenszel summary chi-square tests, stratified by center.

RESULTS: 60 patients were enrolled: 30 in the S-Caine™ group and 30 in the placebo group. Demographic and baseline variables were similar across treatment groups. All 60 patients were included in efficacy and safety analyses. Adequate anesthesia was achieved in 87% of S-Caine™-treated patients versus 17% of the placebo group ($P<0.001$), and the investigator rated 67% of patients who received S-Caine™ as having no pain compared with 10% of patients who received placebo ($P<0.001$). The parents of 97% of patients who received S-Caine™ indicated that they would choose this form of anesthesia for their child again, compared with 43% of patients who received placebo treatment ($P<0.001$). The S-Caine™ patch was well tolerated by pediatric patients undergoing minor dermatologic procedures. Only 2 patients—both from the S-Caine™ treatment group—experienced AEs during the study. Both patients reported a burning sensation at the patch application site. Both events were rated as mild in severity and resolved in less than an hour with no action taken. Patients who received S-Caine™ experienced significantly more erythema (83% vs 53%, $P<0.001$) and edema (17% vs 0%, $P=0.014$) than patients who received placebo. None of the patients experienced a severe dermal reaction to the patch.

CONCLUSIONS: The S-Caine™ patch was effective in providing clinically useful local anesthesia for minor dermatologic procedures in pediatric patients. Investigator and parent efficacy ratings significantly favored S-Caine™ over the placebo formulation for all assessments. The patch was generally well tolerated in this population.

Randomized, Double-blind, Placebo-controlled, Crossover Study Evaluating an S-Caine™ Patch to Induce Local Anesthesia of the Skin Prior to a Vascular Access Procedure in Normal, Healthy, Adult Volunteers

Ruth Zimmer, MD, Lazzare Ogden, MD

OBJECTIVES: (1) Evaluate the efficacy of the S-Caine™ patch (developmental formulation) in providing clinically useful dermal anesthesia for a vascular access procedure in healthy adult volunteers; (2) determine if lidocaine and tetracaine levels in plasma are detectable by standard clinical laboratory methods following a single administration of the S-Caine™ patch, and (3) monitor the nature and frequency of AEs associated with use of the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, placebo-controlled, 2-period crossover study in healthy volunteers. Subjects were to receive both an S-Caine™ patch and a placebo patch at separate treatment visits. The S-Caine™ patch was composed of a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP plus an oxygen activated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period of time (2 h). The placebo patch contained olive oil NF plus an oxygenactivated heating element identical to the S-Caine™ patch. A hep-lock intravenous (IV) catheter was inserted into the antecubital vein on the arm not being used for vascular access. A baseline blood sample was drawn for lidocaine and tetracaine plasma level analysis immediately before the study patch was applied. The patch was placed directly over the antecubital vein for 30 minutes. Thirty minutes following the patch application, a second blood sample was obtained and the investigator removed the S-Caine™ or placebo patch. Following patch removal, the investigator evaluated the skin area under the patch for erythema, edema, and any other adverse skin reaction. Vascular access was then performed on the designated patch site, and the investigator recorded the difficulty of the puncture using a 5-point categorical scale (1=insertion at first attempt through 5=unable to insert catheter). Post-procedure efficacy evaluations included subject ratings of procedural pain (100-mm Visual Analog Scale [VAS], where 0 mm=no pain and 100 mm=worst pain imaginable), investigator ratings of the subject's pain (4-point categorical scale: no pain, slight pain, moderate pain, severe pain), and subject and investigator ratings of the adequacy of the anesthetic (yes, no). Additional blood

samples were taken at 60, 120, 180, and 240 minutes following the patch application. A minimum of 1 week later, the subject returned to the study site and received the alternative treatment. The application procedure, efficacy evaluations, and blood sampling procedures were identical to those followed in the first arm of the study. Following collection of the final blood sample (4 h after the patch application), subjects were dismissed from the study.

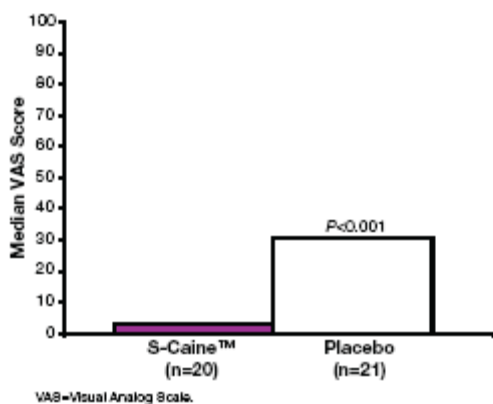
PATIENTS: Planned enrollment was 20 subjects. Healthy men or women 18 to 70 years of age who had adequate bilateral antecubital veins and no known allergies or sensitivities to lidocaine, tetracaine, or other local anesthetics were eligible to participate. Subjects were excluded if they had taken concomitant analgesic medication during the previous 24 hours; had damaged, denuded, or broken skin at the designated patch site; were pregnant or breast-feeding; or had multiple allergies that could indicate hypersensitive skin. All participants signed a written informed consent.

STATISTICAL ANALYSIS: Demographic and background variables were summarized using descriptive statistics and compared between administration groups using *t* tests or rank sum tests for continuous variables and chi-square or exact tests for categorical data. VAS results were compared using ANOVA for a crossover design, with the factors treatment, group (order of administration), and period. Assessment scales for dermal anesthesia, evaluation of therapy, and evaluation of skin reactions were compared between treatments using Wilcoxon signed rank tests and sign tests. Vital signs were summarized descriptively and compared between treatments using ANOVA for a crossover design with repeated measurements. The plasma concentrations for lidocaine and tetracaine were to be summarized descriptively for the S-Caine™ patch. However, because all concentrations were below the limit of quantitation (LOQ), none of the planned pharmacokinetic calculations were performed. AEs were tabulated by type, onset, duration, severity, outcome, and relationship to treatment. Incidence of individual events was to be compared between treatments using sign tests, and total number of events was compared using crossover ANOVA.

RESULTS: 22 subjects enrolled. 1 subject experienced an AE before the application of the first patch and was withdrawn from the study. IV access for blood sampling could not be accomplished for another subject: no samples were collected during the first treatment arm, and this subject did not receive the second assigned patch. 21 subjects were included in efficacy analyses, 20 subjects were included in pharmacokinetic analyses, and all subjects were included in safety analyses. The S-Caine™ patch was effective in providing clinically useful local anesthesia for vascular access procedures: the median VAS score for procedural pain was 2.0 mm for S-Caine™ treatment compared with 30.0 mm for placebo treatment ($P<0.001$) (Figure 3). 90% of subjects reported adequate anesthesia following S-Caine™ treatment compared with 24% of subjects following placebo treatment ($P=0.001$), and 95% of subjects receiving the S-Caine™ patch indicated that they would use this type of local anesthesia again compared with 14% of subjects receiving placebo ($P<0.001$). The investigators rated 55% and 10% of subjects as having no pain with S-Caine™ and placebo treatment, respectively ($P=0.006$). The investigator felt that the local anesthetic provided adequate anesthesia in 85% of subjects following S-Caine™ treatment compared with 14% of subjects following placebo treatment ($P<0.001$). Plasma concentrations of lidocaine and tetracaine were below the LOQ (100 ng/mL for lidocaine and 5 ng/mL for tetracaine) for all samples collected from subjects after application of the S-Caine™ patch, indicating that systemic exposure to these 2 agents is low. The S-Caine™ patch was well tolerated, with no unexpected AEs reported. Subjects experienced worse erythema following S-Caine™ treatment compared with placebo, but this difference was not statistically significant ($P=0.058$). None of the subjects experienced a severe dermal reaction to the patch.

CONCLUSIONS: The S-Caine™ patch was effective in providing clinically useful local anesthesia for vascular access procedures in healthy adults. For all subjects, plasma concentrations of lidocaine were <100 ng/mL or less than 1/10 the levels associated with antiarrhythmic activity and less than 1/50 the levels associated with central nervous system toxicity. Plasma levels of tetracaine were <5 ng/mL, or less than 1/40 the levels associated with toxic effects. The S-Caine™ patch was safe and well tolerated in this adult population.

Figure 3. SC-05-99 Median VAS Scores for Procedural Pain.



A Randomized, Double-blind, Placebo-controlled Crossover Clinical Study Evaluating the S-Caine™ Patch for Induction of Local Anesthesia of the Skin Prior to Vascular Access Procedures in Adult Subjects

Toivo E. Rist, MD

OBJECTIVES: To compare the clinical effectiveness of the S-Caine™ patch versus a placebo patch in providing clinically useful dermal anesthesia for vascular access procedures in adult volunteers and to monitor the nature and frequency of AEs associated with use of the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, placebo-controlled, crossover study. The S-Caine™ patch was composed of a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP plus an oxygen-activated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period of time (2 h). The placebo patch contained olive oil NF plus an oxygen-activated heating element identical to the S-Caine™ patch. Subjects meeting study criteria were randomized to receive the S-Caine™ patch on either the right or left antecubital surface and a placebo patch on the alternate arm. Each subject received a 20-minute administration of the 2 study patches immediately before undergoing the procedures. Following removal of the patches, the investigator evaluated the skin area under the patches for erythema, edema, and other skin reactions. Vascular access procedures were then performed on the designated patch sites. Postprocedure efficacy evaluations included subject ratings of procedural pain (100-mm VAS where 0 mm=no pain and 100 mm=worst pain imaginable), investigator and independent observer ratings of the subject's pain (4-point categorical scale: no pain, slight pain, moderate pain, severe pain), and subject and investigator ratings of the adequacy of the anesthetic (yes, no).

PATIENTS: Planned enrollment was 20 subjects. Healthy adults ≥ 18 years of age without known allergies or sensitivities to lidocaine, tetracaine, or other local anesthetics were eligible to participate. Subjects were excluded if they had taken concomitant prescription-strength analgesic medication during the previous 24 hours; had damaged, denuded, or broken skin at the designated patch site; had active atopic dermatitis; were pregnant or breast-feeding; or had multiple allergies that could indicate hypersensitive skin. All participants provided written informed consent.

STATISTICAL ANALYSIS: Demographic and background variables were summarized using descriptive statistics, and subject VAS scores were compared between patches using a Wilcoxon signed rank test. The subject assessments of pain and whether he or she would use the patch again were compared between patches using McNemar chi-square tests. Investigator and witness evaluations of pain were compared between patches using Wilcoxon signed rank tests, and the investigator assessment of adequate anesthesia was compared using a McNemar chi-square test. AEs were tabulated by type, onset, duration, severity, outcome, and relationship to treatment.

RESULTS: 21 subjects enrolled and received both S-Caine™ and placebo treatment; all 21 were analyzed for safety and efficacy. The median VAS score for procedural pain with S-Caine™ treatment was 1 mm, compared with 9 mm for the placebo treatment ($P=0.004$) (Table 3). 81% of subjects reported adequate anesthesia following S-Caine™ treatment compared with 24% of subjects following placebo treatment ($P=0.003$). Following S-Caine™ treatment, 76% of subjects indicated that they would use this type of local anesthesia again compared with 14% of subjects following placebo treatment ($P<0.001$). The investigator rated 90% of subjects as having no pain with S-Caine™ compared with 24% of subjects with placebo ($P=0.001$), and the same percentage of subjects in each group

were noted to have adequate anesthesia ($P<0.001$). The independent observer rated 86% of subjects as having no pain with S-Caine™ compared with 29% of placebo-treated subjects ($P=0.003$). The S-Caine™ patch was well tolerated. No AEs were reported in the study, although significantly more subjects experienced erythema following application of the S-Caine™ patch than placebo (29% vs 0%, $P=0.031$), as expected with local anesthesia. None of the subjects experienced a severe dermal reaction to the patch.

CONCLUSIONS: The S-Caine™ patch was effective in providing clinically useful local anesthesia in adult subjects when applied for 20 minutes before conducting vascular access procedures. Efficacy evaluations by subjects, the investigator, and an independent observer significantly favored active treatment over placebo for all assessments performed. The S-Caine™ patch was safe and well tolerated, with no AEs observed or reported.

Table 3. SC-11-01 Efficacy Outcomes

	S-Caine™ (n=21)	Placebo (n=21)	P Value
Subject ratings			
Median VAS score	1	9	0.004*
Patients reporting elimination of pain, %	81	24	0.003†
Patients reporting they would use patch again, %	78	14	<0.001†
Investigator evaluation of pain, %			
No pain	90	24	
Slight pain	10	67	<0.001†
Moderate pain	0	10	
Independent observer evaluation of pain, %			
No pain	86	29	
Slight pain	14	57	<0.003*
Moderate pain	0	14	

*Wilcoxon signed rank test.
†McNemar chi-square test.

A Randomized, Double-blind, Placebo-controlled, Crossover Clinical Study Evaluating the S-Caine™ Patch for Induction of Local Anesthesia Prior to Vascular Access Procedures in Adult Subjects

Saundra Curry, MD, Julia Finkel, MD

OBJECTIVES: To compare the effectiveness of the S-Caine™ patch to placebo in providing clinically useful local anesthesia for vascular access procedures in adult subjects and to monitor the nature and frequency of AEs associated with the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, placebo-controlled, crossover study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP plus an oxygen activated heating element that generated a controlled level of heating (39°-41°C) for a consistent period of time (2 h). The placebo formulation contained olive oil NF in place of the active ingredients and an identical heating element. Subjects received simultaneous applications of the S-Caine™ patch and a placebo patch 20 minutes before undergoing vascular access procedures. The application sites were randomized 1:1 between the right and left antecubital surfaces. After removal of the study patches, the investigator evaluated the skin area for erythema, edema, and other skin reactions. The occurrence of erythema and eschar formation was jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema was independently evaluated (5-point categorical scale: no edema through severe edema). Each subject then underwent a vascular access procedure in both the right and left antecubital veins. Following insertion, the investigator recorded the difficulty of the puncture using a 5-point categorical scale (1=insertion at first attempt through 5=unable to insert catheter). Postprocedure efficacy evaluations included subject ratings of procedural pain (100-mm VAS where 0 mm=no pain and 100 mm=worst pain imaginable), investigator and independent observer ratings of the subject's pain (4-point categorical scale: no pain, slight pain, moderate pain, severe pain), and subject and investigator ratings of the adequacy of the anesthetic (yes, no). Subjects returned to the study center within 24 to 48 hours for a second

posttreatment skin assessment evaluating erythema, edema, and AEs. Safety and tolerability were evaluated based on the frequency of AEs and on the assessment of skin reactions following removal of the study patch.

PATIENTS: Planned enrollment was 40 subjects. Adults ³18 years of age who presented to the study sites for a vascular access procedure and with no known allergies or sensitivities to lidocaine, tetracaine, or other local anesthetics were invited to participate in the study. Subjects were excluded if they had taken concomitant prescription analgesic medication during the previous 24 hours; had damaged, denuded, or broken skin at the designated patch site; or were pregnant or breast-feeding. All participants provided written informed consent.

STATISTICAL ANALYSIS: Demographic, background, and procedure variables were summarized descriptively by center and overall. Age, height, weight, and preprocedure vital signs were compared between centers using ANOVA, with the factors of center and randomization group. Race, sex, and the use of medications were compared between centers using Mantel-Haenszel summary chi-square tests, adjusting for randomization. Skin type was compared between centers using Mantel-Haenszel tests for ordered categories. Medical history and physical exam results were tabulated descriptively by center. Treatment variables were tabulated by treatment type and center. Subject VAS scores and investigator and observer pain evaluations were compared between treatments using Wilcoxon signed rank tests. Adequacy of anesthesia and whether the treatment would be used again were compared between treatments using McNemar chi-square tests. Erythema and edema ratings were compared between treatments using Wilcoxon signed rank tests or sign tests when the results were dichotomous.

RESULTS: 20 subjects initially were enrolled at each study site. Demographic and baseline characteristics were similar for subjects enrolled at both centers, although the mean age was significantly higher for the subjects at center 2 (31 vs 40 y, $P=0.009$). Because 1 site erroneously applied the study patches for 30 minutes instead of the protocol-specified 20 minutes, an additional 20 subjects were enrolled. A total of 39 subjects received simultaneous 20-minute applications of the S-Caine™ and placebo patch. 1 subject received a 20-minute application of the S-Caine™ patch, but not a placebo patch. All 40 subjects who received a 20-minute treatment were included in the efficacy analyses. All 60 subjects enrolled were included in the safety analyses. The median VAS score for procedural pain with S-Caine™ treatment was 5 mm versus 28 mm for placebo treatment ($P<0.001$, Figure 4). 49% of subjects had lower VAS scores with S-Caine™ than placebo, and 17% of subjects had lower VAS scores with placebo ($P<0.001$). 73% of subjects reported elimination of pain following S-Caine™ treatment compared with 31% of subjects following placebo treatment (Table 4). 59% of subjects indicated adequate pain relief with S-Caine™ and not placebo, and 15% indicated adequate pain relief with placebo and not S-Caine™ ($P=0.002$). 70% of subjects indicated that they would use the S-Caine™ patch again, and 33% indicated they would use the placebo patch again; 51% of subjects indicated they would use S-Caine™ but not placebo, and 15% indicated they would use the placebo and not S-Caine™ ($P=0.006$). The investigators rated 63% of subjects as having no pain with S-Caine™ treatment compared with 33% of subjects with placebo treatment. Investigators considered 46% of subjects to have less pain with S-Caine™ than placebo and 15% of subjects to have less pain with placebo than S-Caine™ ($P=0.021$). The investigators noted adequate anesthesia in 60% of patients receiving S-Caine™ treatment compared with 23% of patients receiving placebo treatment, and considered 54% of subjects to have adequate anesthesia with S-Caine™ and not placebo and 15% of subjects to have adequate anesthesia with placebo and not S-Caine™ ($P=0.004$). The independent observer rated 68% of subjects as having no pain with S-Caine™ treatment compared with 38% of subjects with placebo treatment. The independent observers considered 46% of subjects to have less pain with S-Caine™ than placebo and 15% of subjects to have less pain with placebo than S-Caine™ ($P=0.015$). The S-Caine™ patch was generally well tolerated. 2 subjects reported AEs following the 20-minute S-Caine™ treatment: itching (2 subjects) and erythema (1 subject). All AEs were rated by the investigator as mild in severity and possibly or probably related to study treatment. All AEs resolved without treatment. As expected with local anesthesia, S-Caine™ treatment was associated with slightly more erythema than placebo (62% vs 42%, $P=0.018$). No subject experienced edema or a delayed skin reaction to the patch. **CONCLUSIONS:** The S-Caine™ patch was effective in providing clinically useful local anesthesia for vascular access procedures in adults. Subject, investigator, and independent observer efficacy evaluations significantly favored S-Caine™ treatment over placebo. The S-Caine™ patch was safe and well tolerated.

Table 4. SC-24-01 Efficacy Outcomes

	S-Caine™ (n=40)	Placebo (n=39)	P Value
Subject ratings			
Median VAS score	5	28	<0.001*
Patients reporting elimination of pain, %	73	31	0.002†
Patients reporting they would use patch again, %	70	33	0.006†
Investigator evaluation of pain, %			
No pain	63	33	
Slight pain	30	54	0.021*
Moderate pain	8	13	
Independent observer evaluation of pain, %			
No pain	68	38	
Slight pain	28	46	0.015*
Moderate pain	5	15	

*Wilcoxon signed rank test.
†McNemar chi-square test.

Table 5. SC-40-02 Efficacy Outcomes

	10 min (n=20)*	20 min (n=20)	30 min (n=22)	60 min (n=20)
Subject ratings				
Subjects reporting elimination of pain, %				
S-Caine™ patch	65	90	95	95
EMLA cream	42	60	64	95
P value†	0.059	0.014	0.020	1.00
Subjects reporting they would use patch again, %				
S-Caine™ patch	80	95	100	90
EMLA cream	47	70	64	95
P value†	0.008	0.025	0.005	0.317
Investigator evaluation of pain				
No pain, %				
S-Caine™ patch	10	10	23	40
EMLA cream	0	10	0	30
Slight pain, %				
S-Caine™ patch	80	80	68	60
EMLA cream	84	80	91	70
Moderate pain, %				
S-Caine™ patch	10	10	9	0
EMLA cream	16	10	9	0
Overall P value (S-Caine™ vs EMLA)‡	0.046	1.000	0.059	0.317

*1 subject dropped out before EMLA evaluation
†McNemar chi-square test
‡Wilcoxon signed rank test

A Randomized, Double-blind, Placebo-controlled, Pharmacokinetic Study Evaluating the S-Caine™ Patch for Induction of Local Anesthesia Prior to Vascular Access Procedures in Geriatric Subjects

Alan K. Copa, PharmD

OBJECTIVES: To compare the effectiveness of the S-Caine™ patch to placebo in providing clinically useful local anesthesia before vascular access procedures in subjects >65 years of age, to characterize the pharmacokinetic profile of a 20-minute S-Caine™ patch application in subjects >65 years of age, and to monitor the nature and frequency of AEs associated with the use of the S-Caine™ patch in this population. **STUDY DESIGN:** Randomized, double-blind, placebo-controlled study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP plus an oxygen-activated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period of time (2 h). The placebo formulation contained olive oil NF in place of the active ingredients and an identical heating element. Subjects who met the study criteria were randomized to receive a 20-minute administration of the S-Caine™ patch to 1 antecubital surface and a placebo patch to the other. Following removal of the patches, the investigator evaluated the skin area under each for erythema, edema, blanching, and other skin reactions before performing a vascular access procedure at the right and left antecubital surfaces, respectively. Erythema and eschar formation were jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema and blanching were independently evaluated (5-point categorical scale: none through severe/extreme).

Postprocedure efficacy evaluations included subject ratings of procedural pain (100-mm VAS where 0 mm=no pain and 100 mm=worst pain imaginable), investigator and independent observer ratings of the subject's pain (4-point categorical scale: no pain, slight pain, moderate pain, severe pain), and subject and investigator ratings of the adequacy of the anesthetic (yes, no). The 30 subjects who were not undergoing blood sampling were dismissed from the study. The remaining 10 subjects also were evaluated for delayed skin reactions. For the 10 subjects participating in the pharmacokinetic section of the study, blood samples were collected at baseline and 0.5, 1, 2, 3, 4, and 8 hours postdose. Subjects returned to the study site between 24 and 30 hours postdose for an additional sample collection and for evaluation of delayed skin reactions. Maximum plasma concentration, time of maximum plasma concentration, area under the plasma concentration versus time curve from 0 to 4 hours, and plasma half-life were calculated if measurable levels of either lidocaine or tetracaine were detected in blood samples (LOQ=0.9 ng/mL for both lidocaine and tetracaine).

PATIENTS: Planned enrollment was 40 subjects, with 10 subjects for pharmacokinetic analysis. Adults \leq 65 years of age who had adequate veins for the study procedures were eligible provided they had no known allergies or sensitivities to lidocaine, tetracaine, or other local anesthetics. Subjects who were currently taking anticoagulant therapy (except aspirin \leq 81 mg), had a history of chronic prednisone use, or had received antiarrhythmic medications within 30 days were not eligible for inclusion. Subjects were excluded if they had taken concomitant prescription-strength analgesic medication during the previous 24 hours or had damaged, denuded, or broken skin at the designated patch site. All participants provided written informed consent.

STATISTICAL ANALYSIS: Demographic and background variables were summarized descriptively by administration time group and overall. Age, height, weight, and baseline vital signs were analyzed between groups using *t* tests. Race, sex, use of medications, and previous anesthetic history were compared between groups using Fisher exact tests. Skin type was compared between groups using a Mann-Whitney test. Medical history and physical exam results were tabulated descriptively. The treatment variable of time to injection was tabulated by patch type and compared using a Wilcoxon signed rank test. VAS scores were analyzed using Wilcoxon signed rank tests because the data exhibited skewness. Investigator and observer pain scales were analyzed using Wilcoxon signed rank tests. Assessment of adequate anesthesia by the patient and investigator and whether the subject would use the patch again were analyzed by McNemar chi-square tests. Because none of the blood samples had measurable lidocaine or tetracaine, no statistical evaluations were performed for the pharmacokinetic parameters. Because no AEs occurred, no statistical evaluations were performed for AEs. Evaluations of the skin reactions for erythema were compared between patch types using Wilcoxon signed rank tests. Vital signs collected at the times of blood sampling were summarized descriptively and compared over time using ANOVA for a repeated measures design, with the grouping factor of randomization assignment.

RESULTS: 40 subjects entered the study. Treatment groups were generally well matched, although the number of subjects with skin type 1 (always burns/rarely tans) was significantly higher in the group receiving S-Caine™ on the right arm ($P=0.032$), and more women than men received S-Caine™ on the right arm (difference approaching significance, $P=0.096$). Median VAS scores for the S-Caine™ and placebo treatments were 8.0 mm and 13.5 mm, respectively (Table 6, Figure 6). 65% of subjects had lower scores with the S-Caine™ patch compared with 28% of subjects with the placebo patch ($P=0.039$). There were no significant differences between the S-Caine™ and placebo patches in other subject evaluations and investigator and independent observer ratings, likely because the low pain level associated with the procedure was not sufficient for discrimination between treatments.

There were no blood samples with measurable levels of either lidocaine or tetracaine. A single, 20-minute application of the S-Caine™ patch was well tolerated. No AEs were noted with either the S-Caine™ or placebo treatment. As expected with local anesthesia, subjects experienced slightly more erythema with S-Caine™ than with placebo (53% vs 35%, $P=0.022$). There were no reports of severe or delayed dermal reactions. **CONCLUSIONS:** Based on subject-reported pain, a 20-minute application of the S-Caine™ patch was effective in providing clinically useful local anesthesia for a vascular access procedure in elderly subjects. The levels of lidocaine and tetracaine in the systemic circulation were <0.9 ng/mL. The S-Caine™ patch was safe and well tolerated with no AEs reported in this population.

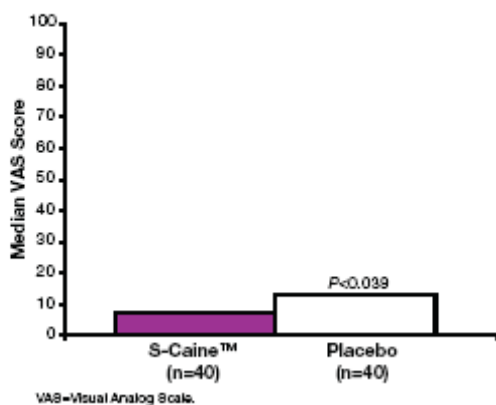
Table 6. SC-31-01 Efficacy Outcomes

	S-Caine™ (n=40)	Placebo (n=40)	P Value
Subject ratings			
Median VAS score	8	13.5	<i>P</i> =0.039*
Patients reporting elimination of pain, %	85	75	<i>P</i> =0.206†
Patients reporting they would use patch again, %	85	75	<i>P</i> =0.206†
Investigator evaluation of pain, %			
No pain	90	83	
Slight pain	5	18	<i>P</i> =0.739*
Moderate pain	5	0	
Independent observer evaluation of pain, %			
No pain	90	85	
Slight pain	7.5	15	<i>P</i> =0.782*
Moderate pain	2.5	0	

*Wilcoxon signed rank test.

†McNemar chi-square test.

Figure 6. SC-31-01 Median VAS Scores for Procedural Pain.



A Randomized, Double-blind, Pilot Study to Obtain Preliminary Information on the Variability and Magnitude of Effect of Heat, Application Time, and Stimulus Intensity on the Efficacy of the S-Caine™ Patch (Lidocaine and Tetracaine Topical Patch) 70 mg/70 mg

Richard Wasnich, MD, Thomas Garland, MD, Stephen Halpern, MD, Denis Mee-Lee, MD

OBJECTIVES: To obtain preliminary information on the variability and magnitude of the effect of heat, application time (20 or 30 min), and stimulus intensity (16- or 18-gauge catheter) on the efficacy of the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, multicenter pilot study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine USP and 70 mg tetracaine USP. The active patch included an oxygen-activated heating element that generated a controlled level of heating (37°C–41°C) for the application period. The comparator patch contained all of the components of the active patch except the heating element. Eligible patients were randomly assigned to 1 of 8 treatments with the S-Caine™ patch. Groups 1-4 received the heated patch and Groups 5-8, the unheated patch. Groups 1, 2, 5, and 6 received a 20-minute application and Groups 3, 4, 7, and 8 received a

30-minute application of the patch. A 16-gauge needle was used in the odd numbered groups and an 18-gauge needle in the even numbered groups. Postprocedure efficacy evaluations included subject ratings of procedural pain (100-mm VAS where 0 mm=no pain and 100 mm=worst pain imaginable). Subjects were also asked if the anesthetic provided adequate pain relief and if they would use this form of anesthetic again. Safety and tolerability were evaluated based on the frequency of AEs and on the assessment of skin reactions following removal of the study patch. Upon completion of the subject pain evaluations, the investigator examined the treatment site for erythema, edema, and other skin reactions. The occurrence of erythema and eschar formation was jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema and blanching were independently evaluated (5-point categorical scale: none through severe/extreme). Subjects were instructed to inspect the treatment site 24 to 48 hours following drug removal and to contact the study site if any reaction developed.

PATIENTS: Planned enrollment was 80 subjects. Adults ³18 years of age with no known sensitivities to lidocaine, tetracaine, or other local anesthetics were invited to participate in the study. Subjects were excluded if they had taken concomitant prescription-strength analgesic medication during the previous 24 hours; had damaged, denuded, or broken skin at the designated patch site; had contact dermatitis; had multiple allergies that indicated hypersensitive skin; or were pregnant or breast-feeding. All participants provided written informed consent.

STATISTICAL ANALYSIS: Baseline and demographic data were summarized descriptively. Because the study was designed to estimate the variability among treatment groups rather than to compare efficacy among groups, no inferential statistics were reported for VAS scores or overall impression of the S-Caine™ patch. To estimate variability, log-transformed scores were analyzed using 1-way ANOVA with fixed term for treatment group.

RESULTS: 88 patients were enrolled and all were analyzed for efficacy and safety. The number of subjects in each group is included in Table 7. Demographic and baseline variables were similar across treatment groups. Because the study was designed to estimate variability rather than efficacy among treatment groups, no efficacy conclusions can be drawn from this study. The results (Table 7) were used to aid in the design of the definitive study. A single application of the S-Caine™ patch, either heated or unheated, was well tolerated by subjects undergoing vascular access procedures. A total of 7 subjects experienced erythema and 1 subject reported a bitter taste. No other AEs occurred. As expected with topical anesthetics, localized skin reactions were common. Erythema occurred more frequently in those who received the heated (93%) compared with the unheated patches (67%). No subject experienced a severe dermal reaction to the patch.

CONCLUSIONS: This pilot study provides information regarding the influence of controlled heat, needle size, and application time on VAS score following application of the S-Caine™ patch. This information was used to design a subsequent study evaluating the effect of heat on the efficacy of the S-Caine™ patch.

Table 7. SC-53-04 Visual Analog Scale Scores

	Mean (SD)	Median	Geometric Mean*	Min/Max
Heated Patches				
20 min/16-gauge (n=10)	17.0 (18.5)	9	11.2	0/63
20 min/18-gauge (n=9)	10.2 (14.6)	4	6.1	1/40
30 min/16-gauge (n=13)	16.7 (16.0)	14	11.0	0/52
30 min/18-gauge (n=11)	13.8 (16.8)	9	7.8	0/53
Unheated Patches				
20 min/16-gauge (n=8)	34.0 (17.5)	32	31.2	15/65
20 min/18-gauge (n=11)	24.0 (31.3)	11	9.6	0/97
30 min/16-gauge (n=8)	28.9 (26.7)	23	20.3	4/81
30 min/18-gauge (n=10)	10.1 (15.3)	5	5.8	0/51

SD=standard deviation

*Antilog of the mean of log (VAS+1)

A Randomized, Double-blind, Study Comparing an S-Caine™ Patch (Lidocaine and Tetracaine Topical Patch) 70 mg/70 mg With Heat to an S-Caine™ Patch Without Heat Prior to Vascular Access

Jon Ruckle, MD, Thomas Garland, MD, Stephen Halpern, MD, Denis Mee-Lee, MD

OBJECTIVES: To compare the efficacy of an S-Caine™ patch with heat to and S-Caine™ patch without heat in providing local dermal anesthesia for vascular access in healthy adults and to monitor the nature and frequency of AEs associated with the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, parallel-design study. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine USP and 70 mg tetracaine USP. The active patch included an oxygen-activated heating element that generated a controlled level of heating (36°C–40°C) for the application period. The comparator patch contained all of the components of the active patch except the heating element. Eligible patients were randomly assigned to receive a 20-minute application of the S-Caine™ patch with or without the heating element before vascular access. Postprocedure efficacy evaluations included subject ratings of procedural pain (100-mm VAS where 0 mm=no pain and 100 mm=worst pain imaginable). Subjects were also asked if the anesthetic provided adequate pain relief and if they would use this form of anesthetic again. Safety and tolerability were evaluated based on the frequency of AEs and on the assessment of skin reactions following removal of the study patch. Upon completion of the subject pain evaluations, the investigator examined the treatment site for erythema, edema, and other skin reactions. The occurrence of erythema and eschar formation was jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema was independently evaluated (5-point categorical scale: no edema through severe edema). Subjects were instructed to inspect the treatment site 24 to 48 hours following drug removal and to contact the study site if any reaction developed.

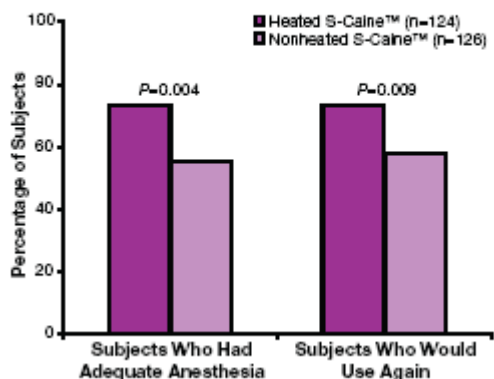
PATIENTS: Planned enrollment was 250 subjects. Adults ³18 years of age with no known sensitivities to lidocaine, tetracaine, or other local anesthetics were invited to participate in the study. Subjects were excluded if they had taken concomitant prescription-strength analgesic medication during the previous 24 hours; had damaged, denuded, or broken skin at the designated patch site; had contact dermatitis; had multiple allergies that indicated hypersensitive skin; or were pregnant or breast-feeding. All participants provided written informed consent.

STATISTICAL ANALYSIS: Baseline and demographic data were summarized descriptively by treatment. For continuous variables, treatments were compared using a Fisher Exact test for unordered categories and a Wilcoxon test for ordered categories. The primary efficacy analysis of VAS scores used a 2-sample *t* test comparing scores between treatments. Secondary efficacy variables were analyzed using Fisher's Exact test comparing treatments. An exploratory analysis was conducted to compare centers, consistency among centers, and treatments within each center. This analysis included descriptive statistics by center and treatment; a 2-way ANOVA for continuous variables with fixed terms for center, treatment, and center by treatment interaction, including unadjusted pairwise least-square means to compare centers and treatments within each center; a Fisher Exact test for categorical variables for each center to compare treatments, a Cochran Mantel Haenszel test stratified by center to compare treatments, a Fisher Exact test on combined treatments to compare centers, and a logistic regression with terms for treatment, center, and treatment by center. All tests were 2-sided with an unadjusted significance level of 0.05. Adverse events were summarized descriptively by treatment.

RESULTS: 250 patients were enrolled: 124 in the heated S-Caine™ patch group and 126 in unheated patch group. Demographic and baseline variables were similar across treatment groups. All 250 patients were included in efficacy and safety analyses. The heated S-Caine™ patch produced significantly lower VAS scores than the unheated patch (geometric means 14.2 vs 20.5 mm, $P=0.006$). Furthermore, significantly more subjects who received the heated patch reported adequate anesthesia (71% vs 53%, $P=0.004$) and said they would use the product again (71% vs 55%, $P=0.009$) compared with those who received the unheated patch (Figure 7). A single application of the S-Caine™ patch, either heated or unheated, was well tolerated by subjects undergoing vascular access procedures. A total of 7 subjects reported AEs following the 20-minute S-Caine™ treatment: 5 who received the heated patch and 2 who received the unheated patch. 6 of the 7 subjects experienced skin reactions that were mild in severity. The other subject (in the heated patch group) experienced hematoma at the vascular access site, which was considered mild in severity and unrelated to study treatment. S-Caine™ treatment was associated with moderate erythema (4 and 2 subjects receiving the heated and unheated patch, respectively). No subject experienced a severe dermal reaction to the patch.

CONCLUSIONS: The heated S-Caine™ patch provided significantly better anesthesia compared with the unheated patch prior to vascular access procedures in adults. Both patches were safe and well tolerated.

Figure 7. SC-55-04 Anesthesia With Heated vs Nonheated S-Caine™ Patches



Dermatol Surg. 2005;31(2):135-138

A Randomized, Double-blind, Placebo-controlled Study Evaluating the S-Caine™ Patch for Induction of Local Anesthesia Prior to Minor Dermatological Procedures in Adult Patients

Brian Berman, MD, PhD, Javier Flores, MD, David Pariser, MD

OBJECTIVES: To compare the efficacy of the S-Caine™ patch to a matched placebo in providing clinically useful dermal anesthesia in adult patients undergoing minor dermatologic procedures and to monitor the nature and frequency of AEs associated with use of the S-Caine™ patch. **STUDY DESIGN:** Randomized, multicenter, double-blind, placebo-controlled study. This trial evaluated the efficacy and safety of the S-Caine™ patch for induction of local dermal anesthesia for minor dermatologic procedures such as skin tag removal, superficial excisions, electrodesiccation, keloid injection, and shave biopsies. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP with an oxygenactivated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period of time (2 h). The placebo patch contained olive oil NF and the same heating element as the S-Caine™ patch. Patients were randomized to receive a 30-minute application of either the S-Caine™ or placebo patch immediately before undergoing the dermatologic procedure. After patch removal, the investigator evaluated the area under the patch for erythema, eschar formation, and edema. Erythema and eschar formation were jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema was independently evaluated (5-point categorical scale: none through severe). Rescue medication (lidocaine injection) was provided in the event of breakthrough pain during the procedure. Postprocedure efficacy evaluations included subject ratings of procedural pain (100-mm horizontal VAS where 0 mm=no pain and 100 mm=worst pain imaginable); investigator and independent observer ratings of the subject's pain (4-point categorical scale: no pain, slight pain, moderate pain, severe pain); and subject and investigator ratings of the adequacy of the anesthetic (yes, no). Patients were also asked if they would use this form of anesthesia again (yes, no). Patients who received a lidocaine injection were instructed to rate the pain of the procedure before the lidocaine injection. Safety and tolerability were evaluated based on the frequency of AEs and on the evaluation of skin reactions following removal of the study patch. Each patient was given a handout describing potential onset of delayed skin reactions and was asked to report onset of any delayed skin reaction between 24 and 48 hours following treatment.

PATIENTS: Planned enrollment was 90 patients. Patients 18 years or older who presented to the study site for a minor dermatologic procedure were eligible to participate. Exclusion criteria included known allergy or sensitivity to lidocaine, tetracaine, or other local anesthetic; pregnancy or breastfeeding; and known sensitivity to any components of the test materials. Patients could also be excluded if they had taken a prescription-strength analgesic during the 24-hour period before the dermatologic procedure or had damaged, denuded, or broken skin at the treatment site. All patients provided written informed consent.

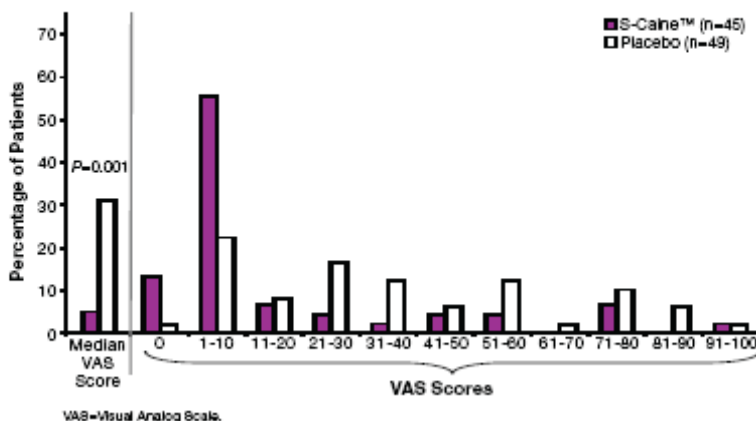
STATISTICAL ANALYSIS: Demographic, background, and procedure variables were summarized descriptively by center and overall. To assess the comparability of treatment groups and study centers, age, height, weight, and preprocedure vital signs were compared between centers using 2-way ANOVA, with the factors of center and

treatment. Race, sex, and the use of medications were compared between treatment groups using Mantel-Haenszel summary chi-square tests, adjusting for center. Skin type was compared between treatment groups using Mantel-Haenszel tests for ordered categories adjusted by center. Medical history and physical exam results were tabulated descriptively by treatment group and center. Treatment variables were tabulated by treatment type and center and compared between treatments using ANOVA or Mantel-Haenszel summary chi-square tests. Log-transformed patient VAS scores were compared among treatments using a 2-way ANOVA with the factors of treatment, center, and the treatment-by-center interaction. A Mann-Whitney test was used to assess final significance when results exhibited skewness and did not have a treatment-by-center interaction. An exploratory analysis of treatment differences in pain as a function of procedure type was performed grouping procedures with 10 or more patients separately and those procedures with fewer than 10 cases together. Individual treatment comparisons by procedure were performed using rank sum tests. Adequate anesthesia and whether the treatment would be used again were compared between treatments using Mantel-Haenszel summary chi-square tests. The investigator and witness pain evaluations were compared between treatments using Mantel-Haenszel summary chi-square tests for ordered categories, adjusted by center. AEs were presented descriptively. Erythema and edema ratings were compared between treatments using Mantel-Haenszel summary chi-square tests for ordered or dichotomous outcomes.

RESULTS: 94 patients were randomized: 45 to the S-Caine™ group and 49 to the placebo group. All patients completed the study. All baseline variables, including skin type, were similar across treatment groups. Rescue medication was administered to 22% of patients in the S-Caine™ group compared with 49% of patients in the placebo group ($P=0.008$). Median VAS scores were 5 mm for the S-Caine™ group and 31 mm for the placebo group ($P<0.001$) (Figure 8). 73% of patients who received S-Caine™ reported adequate anesthesia compared with 37% of patients who received placebo ($P<0.001$). The investigator rated 51% of patients in the S-Caine™ group as having no pain, compared with 10% of patients in the placebo group ($P<0.001$), and concluded that adequate anesthesia was achieved in 71% of S-Caine-treated patients versus 39% of patients who received placebo treatment ($P=0.004$). An independent observer rated 53% of patients in the S-Caine™ group as having no pain compared with 10% of patients in the placebo group ($P<0.001$). 1 S-Caine™-treated patient experienced an AE during the study: a burning sensation at the patch application site during the application period. The event was rated by the investigator as moderate in severity and definitely related to study drug. The AE resolved in 30 minutes with no intervention. Overall, patients in the S-Caine™ group experienced slightly more erythema and edema than patients in the placebo group, although the difference was not significant ($P=0.056$ for erythema and $P=0.273$ for edema). None of the patients experienced a severe dermal reaction or delayed skin reaction to the patch.

CONCLUSIONS: A 30-minute application of the S-Caine™ patch was effective in providing clinically useful local anesthesia for minor dermatologic procedures in adult patients. Patient, investigator, and independent witness efficacy evaluations significantly favored S-Caine™ treatment over placebo. The S-Caine™ patch was generally well tolerated in adult patients.

Figure 8. SC-23-01 VAS Scores for Procedural Pain



Randomized, double-blind, placebo-controlled study evaluating the lidocaine/tetracaine patch for induction of local anesthesia prior to minor dermatologic procedures in geriatric patients.

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OBJECTIVES: To compare the efficacy and safety of the S-Caine™ patch to placebo in providing clinically useful dermal anesthesia in geriatric patients undergoing a minor dermatologic procedure and to monitor the nature and frequency of AEs associated with the S-Caine™ patch.

STUDY DESIGN: Randomized, double-blind, placebo-controlled study of the efficacy and safety of the S-Caine™ patch for induction of local anesthesia for minor dermatologic procedures, including shave biopsy, electrodesiccation, keloid injection, skin tag removal, and superficial excision. The S-Caine™ patch contained a 1:1 eutectic mixture of 70 mg lidocaine base USP and 70 mg tetracaine base USP with an oxygenactivated heating element that generated a controlled level of heating (39°C–41°C) for a consistent period of time (2 h). The placebo patch contained olive oil NF and the same heating element as the S-Caine™ patch. Eligible patients were randomized (2:1) to receive a 30-minute application of either the S-Caine™ or placebo patch immediately before undergoing the procedure. Following patch removal, the investigator evaluated the area under the patch for erythema, eschar formation, and edema. Erythema and eschar formation were jointly evaluated (5-point categorical scale: no erythema through severe erythema to slight eschar formation), and edema was independently evaluated (5-point categorical scale: none through severe). Rescue medication (lidocaine injection) was provided in the event of breakthrough pain during the procedure. Postprocedure efficacy evaluations included subject ratings of procedural pain (100-mm horizontal VAS where 0 mm=no pain and 100 mm=worst pain imaginable); investigator and independent observer ratings of the subject's pain (4-point categorical scale: no pain, slight pain, moderate pain, severe pain); and subject and investigator ratings of the adequacy of the anesthetic (yes, no). Patients were also asked if they would use this form of anesthesia again (yes, no). Patients who received a lidocaine injection were instructed to rate the pain of the procedure before the lidocaine injection. Safety and tolerability were evaluated based on the frequency of AEs and on the evaluation of skin reactions following removal of the study patch. Each patient was given a handout describing potential onset of delayed skin reactions and was asked to report onset of any delayed skin reaction between 24 and 48 hours following treatment.

PATIENTS: Planned enrollment was 80 patients. Patients 65 years of age and older who required local anesthesia for a minor dermatologic procedure were eligible to participate. Exclusion criteria included known allergy or sensitivity to lidocaine, tetracaine, or other local anesthetic and known sensitivity to any components of the test materials. Patients could also be excluded if they had taken a concomitant prescription-strength analgesic during the 24-hour period before the procedure or had damaged, denuded, or broken skin at the treatment site. All patients provided written informed consent.

STATISTICAL ANALYSIS: Demographic, history, and examination variables were summarized by center and treatment group using descriptive statistics. Comparability of groups and study centers on age, height, body weight, and vital signs were evaluated using 2-way ANOVA with the factors of center and treatment group. Sex and concomitant medication use were compared between treatment groups stratified by center using Mantel-Haenszel summary chi-square tests. Centers were compared with chi-square tests. Skin type was compared between treatment groups using a Mantel-Haenszel ordered chi-square test stratified by center and among centers using a Kruskal-Wallis test. Patch location was compared among centers using a chi-square test. Erythema/eschar evaluation and edema were compared between treatments using Mantel-Haenszel summary chi-square tests stratified by center. Procedure type was compared among centers using a chi-square test and between treatments using a Mantel-Haenszel summary chi-square test. Procedure duration and depth were analyzed using a 2-way ANOVA with the factors of treatment and center. Rescue medication use, the patient and investigator's assessment of adequate anesthesia, and whether the patient would use the patch again were compared between treatments using Mantel-Haenszel summary chi-square tests stratified by center. Rescue medication use was also compared among centers using a chi-square test. VAS results were initially compared between treatments using 2-way ANOVA on logtransformed data. Values of zero were coded to 0.1 before transformation. When treatment-by-center interaction was determined to be nonsignificant, a Mann-Whitney test was used to assess final significance of the treatment comparison. Investigator and independent observer pain evaluations were compared between treatments using Mantel-Haenszel summary ordered chi-square tests, stratified by center. Exploratory analyses of VAS scores by procedure type and location were made using individual Mann-Whitney tests, grouping procedures with fewer than 10 total cases together.

RESULTS: 79 patients were enrolled and randomized: 54 to the S-Caine™ group and 25 to placebo. Demographic and baseline characteristics were similar across treatment groups. All patients completed the study: 79 were analyzed for safety, and 74 were analyzed for efficacy (5 patients were excluded from the efficacy analysis because of protocol violations). Median patient ratings of pain were significantly lower with S-Caine™ (9.5 mm) compared with placebo (22.5 mm, $P=0.041$) (Figure 9). Because 16 patients were enrolled at a study center that did not follow the assigned randomization schedule, analyses were performed excluding this group: median VAS scores were 7.0 mm for S-Caine™ and 24.5 mm for placebo ($P=0.020$). None of the secondary endpoints showed a statistically significant difference between S-Caine™ and placebo. No AEs were noted with either S-Caine™ or placebo treatment. S-Caine™-treated patients experienced slightly more erythema and edema than patients in the placebo group, but this difference did not reach statistical significance ($P=0.105$ for erythema and $P=0.074$ for edema). None of the patients experienced a severe dermal reaction to the patch.

CONCLUSIONS: The S-Caine™ patch was effective in providing clinically useful local anesthesia for minor dermatologic procedures in patients older than 65 years. The patch was well tolerated, with no AEs reported or observed.

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Topical anesthetics in children: agents and techniques that equally comfort patients, parents, and clinicians.

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Topical anesthetics are increasingly important, as the number of outpatient surgeries for dermatologic problems in infants and children is steadily growing. This noninvasive modality of anesthetic delivery in conjunction with a reassuring environment may minimize the discomfort of otherwise painful procedures. Since the 1880s, when cocaine was first used as a topical ophthalmologic anesthetic, many ester- and amide-based local anesthetics have been developed for a variety of simple and complex procedures. The pediatric dermatologist's arsenal of topical anesthetic preparations is increasing with the development of novel vehicles of transdermal delivery and the use of anesthetics in combination. Eutectic mixture of local anesthetics is currently the most frequently prescribed topical agent, though the use of ELA-max, another lidocaine-containing preparation, is gaining momentum, especially in the neonatal population. Amethocaine, tetracaine, iontophoresis, and the S-caine patch, a product on the horizon for use in the pediatric population, also are included in this discussion. PMID: 11717557 [PubMed - indexed for MEDLINE]

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Evaluating skin anesthesia after administration of local anesthetic system consisting of an S-Caine patch and a colled heat-aided drug delivery (CHADD) patch in volunteers.

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OBJECTIVE: The objective of this study was to evaluate the depth and duration of skin anesthesia after the administration of a local anesthetic system consisting of an S-Caine (Zars, Salt Lake City, UT) patch coupled with a controlled heat-aided drug delivery (CHADD; Zars) patch. **DESIGN:** The study design was a randomized, double-blind, placebo-controlled, two-period crossover trial. **PATIENTS:** Twelve healthy adult volunteers between the ages of 18 and 50 years were enrolled. **INTERVENTIONS AND OUTCOME MEASURES:** After administration of the study drug or placebo, vital signs (blood pressure, pulse, respiratory rate) were monitored and recorded, and depth and duration of anesthesia were determined and recorded at defined intervals for 10 to 120 minutes after treatment. Depth of anesthesia was measured with a 21-gauge short-bevel needle attached to a depth gauge, and duration was measured using a 0 to 2 (0 = no sensation, 1 = dull sensation, 2 = sharp scratching sensation) verbal report scale. **RESULTS:** Statistically significant differences were noted in both depth and duration of anesthesia between the

active and placebo groups. The posttreatment mean for anesthetic depth in the active group was 6.8 mm compared with 4.7 mm for control group ($p = 0.050$). The median anesthetic duration was greater than 120 minutes for the active group compared with less than 10 minutes for the placebo group ($p = 0.001$). CONCLUSIONS: The local anesthetic system consisting of a combination of S-Caine and CHADD patches provided a statistically significant dermal anesthesia effect compared with placebo in this volunteer study. If confirmed in other studies, this system has promise as a noninvasive method of producing dermal anesthesia for minor surgical procedures or intravenous insertion. PMID: 11014392 [PubMed - indexed for MEDLINE]