

Improper Potency and Impurities in Compounded Polidocanol

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ABSTRACT

Polidocanol is an FDA-approved sclerosant indicated for treating uncomplicated spider veins and reticular veins in the lower extremities. Despite restrictions against compounding drugs that are essentially copies of FDA-approved or commercially available products, polidocanol is also available from compounding pharmacies and outsourcing facilites. Compounded drug products are not FDA-approved and have not undergone premarket FDA review for safety, effectiveness, and quality. Seven samples of polidocanol were obtained from three compounding pharmacies and analyzed using high pressure liquid chromatography. None of the samples contained the labeled concentration of polidocanol and five contained excessive levels of impurities. Since the potency and purity of compounded polidocanol injection cannot be assured, physicians who use these products should consider FDA-approved products to ensure optimal safety and efficacy.

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INTRODUCTION

Varicose veins are enlarged superficial veins, most commonly found in the lower extremities. Risk factors include family history, advancing age, female gender, pregnancy, obesity and sedentary lifestyle.[1] Spider veins are similar, but they are smaller, more superficial and often red or blue. Some varicose veins become symptomatic and require treatment. Symptoms may include burning, throbbing, muscle cramping, itching, and edema. Depending on their size and severity, treatments for varicose veins include compression,[2] energy-based radiofrequency[3] and laser devices,[4] a variety of surgical procedures,[5] and sclerotherapy.[6] Sclerotherapy involves injecting a sclerosant into the lumen of a vein, resulting in fibrosis and eventual vein ablation.[7] Despite the increased popularity of new cutaneous laser devices, sclerotherapy remains the gold standard for treatment of reticular varicose and spider veins,[15,16] especially since FDA-approval of sclerosant agents in 2010.[19,20]

Available FDA-approved liquid sclerosing agents include sodium tetradecyl sulfate and polidocanol.[8] Polidocanol was first approved for use as a sclerosing agent in the United States in 2010 (Asclera® Injection, Merz North America, Raleigh NC).[9] Specifically, this drug product is indicated to sclerose uncomplicated spider veins (varicose veins ≤1 mm in diameter) and uncomplicated reticular veins (varicose veins 1 to 3 mm in diameter) in the lower extremities. Polidocanol is also an approved sclerosing agent in Europe (Aethoxysklerol®, Chemische Fabrik Kreussler & Co. GmbH, Wiesbaden, Germany). The safety and efficacy of polidocanol as a sclerosant have been demonstrated in large trials.[21]

Polidocanol is also available from certain compounding pharmacies and outsourcing facilities, despite government restrictions on compounding drugs that are "essentially copies" of FDA-approved or commercially available products.[10] Compounded drug products are not FDA-approved and have not undergone FDA premarket review for safety, effectiveness, and quality. Of note, polidocanol is manufactured according to strict FDA regulations for purity and potency throughout the entire manufacturing process. Unlike pharmaceutical companies, compounding pharmacies are not required to report adverse events to the FDA.[11] Despite FDA restrictions for compounding drugs, polidocanol remains available from compounding pharmacies and outsourcing facilities, potentially exposing patients to potentially serious health risks.

Previous investigations have demonstrated the inferiority of compounded sclerosants. Among compounded products in one study, three did not contain the labeled drug concentration: two were super-potent, one was sub-potent and all contained impurities.[12] These products were believed to be made by diluting the active substance from industrial chemical sources. In another study, five of six samples obtained from three pharmacies did not contain the labeled drug concentration, exceeding it by 20% to 300%, and all six contained impurities.[13] In a third study, chemical impurities were measured in eight of nine compounded samples from three pharmacies and some contained unknown particulate matter, while no impurities were detected in the original FDA-approved product.[14]

As compounded polidocanol for the treatment of varicose veins continues to be available from several pharmacies and outsourcing facilities in the United States, the objective of this study was to obtain and analyze samples of compounded polidocanol for potency and purity.

METHODS

Seven samples of polidocanol were purchased from three compounding pharmacies. Labeled concentrations of polidocanol ranged from 1.5% to 5%. Each sample was analyzed for potency of lauromacrogol 400 (polidocanol) and purity with reversed phase high pressure liquid chromatography (HPLC) with refractive index (RI) detection (Chemische Fabrik Kreussler & Co. GmbH, Wiesbaden, Germany). The results were compared with an FDA-approved polidocanol product (Asclera® Injection, Merz North America, Raleigh NC).

RESULTS

Results of the analysis are summarized in Table 1. Among the seven samples analyzed, six were sub-potent, containing 65.8 to 91.4% of the labeled concentration, and one was super-potent, containing 108.7% of the labeled concentration. Five contained a 10-fold excess of foreign fatty alcohol ethoxylate impurities and four exceeded the limit for unknown impurities. Overall, none of the tested samples were equivalent to the commercially marketed, FDA-approved product (Asclera) with respect to potency and purity.

DISCUSSION

Similar to previous studies,[12,13] compounded polidocanol solutions did not deliver the claimed potency in six of seven tested samples and five samples contained excessive contaminants. This inconsistency poses unacceptable risks, most importantly to the patient, but also medicolegal risks to the treating physician. In contrast, clinical trials have demonstrated FDA-approved polidocanol provides effective treatment of chronic venous insufficiency with low toxicity, minimal risk and few complications.[21]

Contaminants found in the tested compounded polidocanol samples in several publications included foreign fatty C-14 alcohol ethoxylate impurities, excessive formaldehyde and unknown impurities. Other reported contaminants in compounded sclerosants include carbitol,[12] tetradecanol, several isomers of 7-ethyl-2-methyl-undec-3/4 ene,[14] chlorobutanol (trichloro-2-methyl-2-propanol), benzaldehyde, and benzyl alcohol[13] (some samples contained multiple contaminants). Together, these results indicate the lack of purity of the ingredients and/or the absence of sufficient manufacturing controls used to compound these products.

In addition to frequently not meeting the labeled ingredient specifications for potency and purity, there is no requirement for compounded product labeling to include an approved shelf life. If the compounded product is not immediately used, there is no assurance that the product will remain potent and efficacious.

TABLE 1.

Analysis Results of Compounded Polidocanol for Sclerotherapy Injection

	Pharmacy #1	Pharmacy #1	Pharmacy #2	Pharmacy #2	Pharmacy #2	Pharmacy #3	Pharmacy #3	FDA-Approved Product Specification[c]	FDA-Approved Product Specification[c]
Labeled Polidocanol Concentration	1.5%	5%	1.5%	3%	5%	2%	3%	0.5%	1%
Actual Polidocanol Concentration	16.3 mg/mL (108.7%)	45.7 mg/mL (91.4%)	13.1 mg/mL (87.3%)	19.8 mg/mL (66.0%)	32.9 mg/mL (65.8%)	15.3 mg/mL (76.6%)	22.8 mg/mL (75.8%)	4.75-5.25 mg/mL 95.0-105.0%	9.5-10.5 mg/mL 95.0-105.0%
1-Dodecanol	0.63%	0.66%	0.50%	0.67%	0.74%	--[a]	--[a]	≤1.5%	≤1.5%
foreign fatty alcohol ethoxylate impurities	0.1%	0.1%	26.3%[b]	27.0%[b]	27.2%[b]	22.0%[b]	22.0%[b]	≤2%	≤2%
Formaldehyde	<0.2 ppm	<0.2 ppm	1.3 ppm	0.3 ppm	0.5 ppm	--[a]	--[a]	≤1 ppm	≤1 ppm
Acetaldehyde	<0.2 ppm	0.4 ppm	3.7 ppm	1.1 ppm	1.7 ppm	--[a]	--[a]	≤2 ppm	≤5 ppm
Unknown Impurities	0.05%	0.04%	0.67%	0.64%	0.70%	0.30%	0.40%	≤0.3%	≤0.3%

[a]Insufficient sample size. [b]Primarily foreign fatty alcohol ethoxylate impurities. Bold font denotes nonconforming results. [c]Asclera® Injection, Merz North America, Raleigh NC.

The Federal Food, Drug, and Cosmetic Act requires that all FDA-approved drugs must be safe and effective and manufactured according to current good manufacturing practices (GMPs) to ensure their identity, strength, quality, and purity;[22] however, some pharmacies are compounding drugs that are essentially copies of approved medications and doing so outside of GMPs. According to the FDA, "Compounding is a practice in which a licensed pharmacist, a licensed physician, or in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient." The FDA has created provisions to allow the practice of compounding for individual patient needs when a drug product is not commercially available. This is common in dermatology practice for therapies such as topical anesthetic (BLT) or an acne cream, but these provisions are not applicable for an injectable product for which the FDA-approved product is medically suitable for a patient. Compounding pharmacies are advertising for physicians to use or switch to compounding sclerosant(s) in lieu of FDA-approved polidocanol, but such promotional statements are prohibited if they are false or misleading, such as baseless statements that compounded products are superior or failing to disclose significant risks associated with unapproved uses that are promoted.

There are numerous cases of injury resulting from various improperly compounded medications.[11] An outbreak of meningitis in 2012 caused by a contaminated steroid injection intended for epidural injection made in a compounding pharmacy[23] affected 753 patients in 20 states with 64 deaths.[24] Subsequently, the United States Congress passed the Drug Quality and Security Act in November, 2013.[25] Among other requirements, the Act stipulates that pharmaceutical compounders are not allowed to essentially copy products that are already FDA-approved and commercially available, unless there is a manufacturing product shortage.[25] Serious patient illness and death associated with poor quality compounded drugs continue to occur.[26] This is also made clear under Section 503A of the Federal Food, Drug, and Cosmetic Act:[27]

> "The restrictions on making drugs that are essentially copies ensure that pharmacists and physicians do not compound drug products under the exemptions for patients who could use a commercially available drug product. Such a practice would create significant public health risks because patients would be unnecessarily exposed to drug products that have not been shown to be safe and effective and that may have been prepared under substandard manufacturing conditions. FDA has investigated serious adverse events in patients who received contaminated compounded drugs when a comparable approved drug, made in a facility subject to CGMP requirements, was available."

Since compounded drugs have not undergone FDA review to determine their safety and effectiveness, their potency and purity cannot be assured as demonstrated by the current analysis of several compounded polidocanol products. It has been recognized for many years that physicians who use these products may be at risk legally in the event of an adverse outcome.[28] A physician involved in litigation related to the use of a compounded sclerosant should be prepared to explain why an unapproved agent was used when an FDA-approved agent is available and whether a compounded product was used to increase profit.[29]

CONCLUSION

Compounded drug products have not undergone FDA review to establish safety and efficacy. An analysis of seven samples of compounded polidocanol injection found all of them to be outside the labeled concentration and five had excessive contaminant levels. Physicians who use these products should consider FDA-approved products to ensure optimal treatment outcomes.[29]

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DISCLOSURES

The authors have no further disclosures to report.

REFERENCES

1. National Heart Lung and Blood Institute; National Institute of Health. Varicose Veins. Available: https://www.nhlbi.nih.gov/health-topics/varicose-veins. Accessed: July 2019.
2. Attaran RR, Ochoa Chaar CI. Compression therapy for venous disease. *Phlebology.* 2017;32:81-88.
3. Woźniak W, Kielar M, Mlosek RK, Ciostek P. Comparative analysis of five-year outcomes of lower extremity varicose vein therapy using monopolar and segmental radiofrequency ablation. *Int Angiol.* 2018;37:457-464.
4. Wallace T, El-Sheikha J, Nandhra S, et al. Long-term outcomes of endovenous laser ablation and conventional surgery for great saphenous varicose veins. *Br J Surg.* 2018 105:1759-1767.
5. Kemp N. A synopsis of current international guidelines and new modalities for the treatment of varicose veins. Aust Fam Physician. 2017;46:229-233.
6. Duffy DM. Sclerosants: a comparative review. *Dermatol Surg.* 2010;36:1010-1025.
7. Zimmet SE. Sclerotherapy treatment of telangiectasias and varicose veins. *Tech Vasc Interv Radiol.* 2003;6:116-120.
8. Bush R, Bush P. Evaluation of sodium tetradecyl sulfate and polidocanol as sclerosants for leg telangiectasia based on histological evaluation with clinical correlation. P*hlebology.* 2017;32:496-500.
9. Asclera®(polidocanol) Injection [package insert]. Raleigh, NC: Merz North America, Inc: 2010.
10. United States Food and Drug Administration. Center for Drug Evaluation and Research, 2018. Guidance for Industry. Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act.
11. Gudeman J, Jozwiakowski M, Chollet J, Randell M. Potential risks of pharmacy compounding. *Drugs R D.* 2013;13:1-8.
12. Goldman MP. Sodium tetradecyl sulfate for sclerotherapy treatment of veins: is compounding pharmacy solution safe? *Dermatol Surg.* 2004;30:1454-1456.

13. Weiss RA, Voigts R, Howell DJ. Absence of concentration congruity in six compounded polidocanol samples obtained for leg sclerotherapy. *Dermatol Surg.* 2011;37:812-815.
14. Almeida JI, Raines JK. FDA-approved sodium tetradecyl sulfate (STS) versus compounded STS for venous sclerotherapy. *Dermatol Surg.* 2007;33:1037-1044.
15. Rabe E, Pannier F. Sclerotherapy of varicose veins with polidocanol based on the guidelines of the German Society of Phlebology. *Dermatol Surg.* 2010;36:968-975.
16. Weiss MA, Hsu JT, Neuhaus I, Sadick NS, Duffy DM. Consensus for sclerotherapy. *Dermatol Surg.* 2014;40:1309-1318.
17. Rabe E, Schliephake D, Otto J, Breu FX, Pannier F. Sclerotherapy of telangiectases and reticular veins: a double-blind, randomized, comparative clinical trial of polidocanol, sodium tetradecyl sulphate and isotonic saline (EASI study). *Phlebology.* 2010;25:124-131.
18. Weiss RA, Weiss MA, Goldman MP. Physicians' negative perception of sclerotherapy for venous disorders: review of a 7-year experience with modern sclerotherapy. *South Med J.* 1992;85:1101-1106.
19. Mann MW. Sclerotherapy: it is back and better. *Clin Plast Surg.* 2011;38:475-487.
20. United States Food and Drug Administration. Asclera (polidocanol) 0.5% and 1% Injection Approval Letter (NDA 021201) March 30, 2010. Available: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021201s000ltr.pdf. Accessed: May 2019.
21. Eckmann DM. Polidocanol for endovenous microfoam sclerosant therapy. *Expert Opin Investig Drugs.* 2009;18:1919-1927.
22. United States Food and Drug Administration. Code of Federal Regulations Title 21: Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals. 2012. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211 Accessed May 2019.
23. Cabaleiro J. New England Compounding Center indictment. *Int J Pharm Compd.* 2015;19:94-102.
24. Centers for Disease Control and Prevention. Multistate Outbreak of Fungal Meningitis and Other Infections – Case Count. October 29, 2015. Available: https://www.cdc.gov/hai/outbreaks/meningitis-map-large.html#casecount_table. Accessed: 17 May 2019.
25. Gabay M. The drug quality and security act. *Hosp Pharm.* 2014;49:615-676.
26. United States Food and Drug Administration. Compounding Risk Alerts. 2018. Available: https://www.fda.gov/drugs/human-drug-compounding/compounding-risk-alerts. Accessed: May, 2019.
27. United States Food and Drug Administration. Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act. Guidance for Industry 2018. Available: https://www.fda.gov/media/98973/download Accessed: May 2019.
28. McKenna KJ. Compounding sclerosing agents. Risks and consequences. *Vein Magazine.* 2008;March 31.
29. McKenna KJ. Compounded sclerosing agents: risks and consequences. *Vein Magazine.* 2015;April 1.

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