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Polidocanol for Endovenous Microfoam Sclerosant Therapy

David M. Eckmann, Ph.D., M.D.

Horatio C. Wood Professor of Anesthesiology and Critical Care, Professor of Bioengineering, University of Pennsylvania, 331 John Morgan Building/6112, 3620 Hamilton Walk, Philadelphia, PA 19104-4215, 215 349-5348 Office, 215 349-5078 Fax

Abstract

Background—Polidocanol is a liquid surfactant having endothelial cell lytic properties. In the form of a controlled, dispensed microfoam it is administered endovenously as a sclerosing agent in the treatment of varicose veins.

Objective—This review summarizes efficacy of polidocanol endovenous microfoam sclerotherapy using a proprietary dispensing system to control foam characteristics and gas content for treating varicose veins.

Methods—We reviewed in-vitro, Phase I, Phase II and limited Phase III data for polidocanol microfoam with a focus on controlled foam formulation in therapy

Results/conclusions—Clinical trials of controlled dispensing of polidocanol microfoam provide evidence of effective treatment of chronic venous insufficiency with low toxicity, minimal risk and few complications.

Keywords

foam; microfoam; polidocanol; sclerosant; sclerotherapy; varicose veins

1. Introduction

Chronic venous insufficiency of the lower extremities is commonplace in adults. The prevalence depends on a number of epidemiological factors including age, gender, family history, geographic location, pregnancy and obesity [1]. One study has shown nearly 30% of the population to have visible disease involving varicose veins or trophic changes of the legs, and 28% of the population to have functional disease of either the major superficial or deep leg veins [2]. Beyond the direct visibility of abnormal appearing veins, patients can suffer pain, alterations in skin pigmentation, inflammation, induration and skin ulceration as a result [3]. Clinical treatments are aimed at relieving presenting symptoms, preventing progression of disease, healing ulceration, improving cosmesis and improving quality of life. Treatment options have largely consisted of use of hosiery for compression, conventional surgical ligation or venous stripping, subfascial endoscopic perforator surgery, endovenous laser ablation, radiofrequency ablation, and chemical sclerotherapy [3,4].

Chemical sclerotherapy has been performed for over 70 years [5]. Vein sclerosing may be achieved by direct intravascular injection of either a liquid or a foamed agent to provoke endothelial cell damage within affected vessels and thereby stimulate transmural vessel wall damage [6,7]. Thrombus generation occurs locally with eventual transformation of the

Declaration of interest

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damaged veins into a fibrous cord, which subsequently cannot be recanalized [8]. Sclerotherapy with liquid compounds has been practiced for over 60 years [9,10], and foamed sclerosants have been used enthusiastically by phlebologists for nearly that long. At present, two agents are used commonly in clinical care: Sodium tetradecyl sulfate (Sotradecol®) and Polidocanol (Box 1). In 2004 the FDA approved the use of sodium tetradecyl sulfate by injection to treat small, uncomplicated varicose veins of the lower extremities that show simple dilation with competent valves. Polidocanol, the drug considered in this expert opinion, is the most commonly used foam sclerosing agent in Europe [11,12] and it is the only sclerosant approved by the Japanese Ministry of Health, Labor and Welfare [13]. The compound is not approved by the United States Food and Drug Administration (FDA), but it has been studied extensively in completed and ongoing Phase II and Phase III studies within and outside the United States. Despite the lack of regulatory approval for its use in treating vascular disease, phlebologists in the US use foamed polidocanol extensively in the clinical treatment of varicose veins. The foam formulation is considered to be “home made” since the foam is produced by a variety of relatively uncontrolled manual practices as is described below. Varisolve® (BTG International), also described in greater detail below, is a specifically formulated polidocanol microfoam for endovenous sclerosant therapy [14].

2. Introduction to the compound

Polidocanol (Laureth-9) is an alkyl polyglycol ether of Lauryl alcohol. It is chemically defined as an alcohol ethoxylate having an average alkyl chain of 12–14 carbon atoms (C₁₂–C₁₄) and an ethylene oxide chain of 9 ethylene oxide unites. Its average empirical formula, given its polymeric properties, is C₃₀H₆₂O₁₀, and its structural formula appears in Figure 1. It is a viscous liquid at room temperature, having a melting point of 15–21 °C. It is miscible in water, has a pH of 6.0–8.0 (1% in water) and has a density of 0.97 g/cm³ at room temperature, near that of water.

Polidocanol was first developed in 1931 and was originally sold as a local anesthetic agent. Subsequently it has been shown not to have any local anesthetic properties, but it has found extensive use in the manufacture of personal care products since the 1970s. It is used most commonly as a non-ionic emulsifier and surfactant in concentrations up to 4% in rinse off products such as hair conditioners and shampoos. It is also commonly used in concentrations up to 3% in leave on products including facial creams and body lotions. As a result it has undergone extensive evaluation for acute oral and dermal toxicity and dermal absorption in humans [15] related to its common use in topical cosmetics and lotions. Although it was first used as an endovenous sclerosant foam in the late 1960s [5,16], in general foam sclerotherapy did not become popular until the mid-1990's, by which time efficient methods for transforming liquid sclerosing solutions into foam were well described.

3. Chemistry and Formulation

3.1 Mechanism of Sclerosing Action

Polidocanol exerts its sclerosant effects by causing concentration dependent differential cell injury [6]. Cellular calcium signaling and nitric oxide pathways become activated by the administration of the sclerosant, followed by cell death. The timing of endothelial cell death is predictable based on sclerosant concentration during exposure. This ultimately results in cell lysis of endothelial cells but that can potentially also involve erythrocytes, platelets, and lead to platelet-derived microparticle formation [7]. Although hemolysis occurs experimentally in whole blood samples at polidocanol concentrations greater than 0.45% [7], erythrocyte lysis, platelet lysis and platelet-derived microparticle formation have not been a significant concern reported in any clinical trials of sclerosant therapy.

3.2 Foam Formulation

In recent years the use of foamed sclerosants has become increasingly popular, largely because foam instillation confers several specific advantages for clinical therapy. Since foam displaces the intravascular blood and is not diluted in it such as occurs with liquid sclerosant injection, the concentration of the sclerosing agent in the vessel is known and controlled. Foam instillation leads to a homogeneous distribution of the sclerosant within the vessel lumen, except in very large veins where gravitational effects maintain better contact between the upper venous wall and the foam, which is far less dense than blood. Foamed sclerosant provides a generous surface area of the therapeutic agent in contact with the endothelium. Foam can be produced to be sufficiently stable from breakdown so as to provide adequate therapeutic effects from relatively short times in which it is kept in contact with luminal surface of the vein [17]. In short, foam use permits delivery of a known drug concentration for a controllable duration to achieve sclerosis of affected venous segment.

A myriad of methods and mechanisms have been applied to mix and agitate liquid sclerosants with gas admixtures to create foams for clinical use. With the exception of one self-contained formulation, polidocanol microfoam for endovenous use (i.e. Varisolve®), foamed sclerosants are typically produced by cyclical mechanical agitation of the liquid agent in the presence of a gas to generate the froth used for intravascular injection. Commonly this is simply achieved by hand using room air as the gas and rapid, manual displacement of the mixture between two syringes joined by a stopcock [18] or between a syringe and a drug vial [19] to manufacture the foam. Such “home made” foams commonly employ ratios of gas to liquid ranging from 1:1 to 8:1, producing foams of varying densities and rheological properties. In any event, the result is a froth containing 79% nitrogen and 21% oxygen and having a characteristically wide bubble size distribution.

Varisolve® polidocanol microfoam is a pharmaceutical form of microfoam that emulates the foam originally produced and studied by Cabrera [20–22] in a standardized way. It is generated and dispensed using a proprietary pressurized canister mechanism depicted in Figure 2. The system contains the liquid agent and a gas mixture of oxygen and carbon dioxide with only trace (0.01–0.08%) nitrogen present. Passage of the gas and liquid under pressure through a microfoam producing mechanism yields a microstructurally consistent 1% polidocanol microfoam having reproducible rheological properties. Foam properties including stability are in general sensitive to materials and techniques used to produce foam [17,23]. In particular, the bubble size for Varisolve® foam is appreciably smaller than that resulting from manual foam production techniques, and the absence of nitrogen facilitates more rapid absorption of bubbles within the body [6,24–26]. Both these considerations are important to the safety profile, given the potential for gas embolism to occur with any type of foam sclerosant therapy.

4. Clinical efficacy

4.1 Phase I Studies

Despite many decades of use in sclerotherapy as well as in lotions and creams, there remains a paucity of accessible published data in the form of Phase I studies regarding polidocanol's safety profile in humans. Nonetheless, the very extensive worldwide practical clinical experience using both liquid and foamed polidocanol for sclerotherapy without identification of any associated mutagenesis, carcinogenesis or reproductive toxicity having been identified speaks to a relatively biologically inert compound having a distinct safety and tolerability profile related more generically to vein sclerosing as is described below.

There are no published Phase I studies specific to Varisolve® polidocanol microfoam. However, radiolabelled polidocanol has been used to investigate the compound's absorption, distribution and excretion following oral ingestion in human male volunteers [27]. Analysis

of blood, urine, feces and exhaled air collected for up to six days indicated that the majority (~75%) of the radioactivity was excreted via the urine within the first 24 hours post-treatment. Fecal and exhaled radioactive elimination constituted 5% and 4%, respectively at 24 hours. After 6 days, 89% of the total radioactivity was excreted by these three routes. Radioactivity was still detectable in the blood, but at less than 1% of the total dose [27].

Metabolism of polidocanol occurs by degradation of the ether linkage (Figure 1) as well as oxidation of the alkyl chain. This results in the formation of lower molecular weight polyethylene glycol-like compounds, carbon dioxide and water [27]. Those components of polidocanol having the longer alkyl chains give rise to a higher amount of carbon dioxide as an end product of metabolism and a lower amount of polyethylene glycol-like compounds being produced. This is reflected in the excretion in urine and in exhaled air. Metabolism does not appear to produce any known biologically active compounds.

Aqueous solutions of alcohol ethoxylates analogous to polidocanol have been studied for effects on skin irritation and skin sensitization [28–30]. Exposure to a either undiluted or a 25% compound solution under an occlusive patch for 4 hours a day on 3 alternate days produced only negligible skin irritation. A single 24 hour exposure to 10% solution yielded similar results [29]. In several series of human repeat insult patch tests of formulations having between 2.5% and 25% compound, there was no evidence of skin sensitization [28,30].

4.2 Phase II Studies

One of the earliest Phase II trials of polidocanol microfoam as a sclerosant was a retrospective observational follow-up study done 36–72 months following treatment of varicose great saphenous (originally referred to as “long saphenous” [31]) veins using 1–3% polidocanol frothed with carbon dioxide as the gas [22]. The main outcome measure was obliteration and subsequent disappearance of the treated veins. With three year follow-up of 500 treated lower limbs, the success rates were determined to be 81% for varicose great saphenous vein obliteration and 96.5% for superficial branch disappearance. Among the 81% of successful treatment cases reported, the number of injections required to obliterate the saphenous vein was one (86% of successful cases), two (10.5%) or three (3.5%). The study report indicates there were no major complications and only occasional localized segmented inflammatory reactions occurred. This trial clearly demonstrated both the quality and stability of outcomes possible using polidocanol microfoam and served as the precursor study to the advancement of Varisolve® as a precisely formulated microfoam.

In a follow-on study, 116 patients with more advanced venous disease involving leg ulcers received Cabrera’s early formulation of polidocanol microfoam as the primary mode of management [21]. Patients were injected serially with 0.27%–1% polidocanol microfoam every two to four weeks for up to 17 sessions until sufficient improvement occurred. All patients were evaluated after six months, and some were followed as long as four years. The main outcome measure was full ulcer healing, which was defined as complete reepithelialization of the wound without any residual drainage. Complete healing was achieved in 83% of subjects at six months, and 6% of patients were never cured. At 24 months, 6.3% of patients who experienced ulcer healing had a recurrence of disease. No significant adverse events were reported. Overall the study demonstrated polidocanol microfoam to be an effective treatment for more significantly advanced chronic venous insufficiency, although the healing of venous leg ulceration is closely related to the elimination of predisposing factors such as deep venous reflux.

There have been at least two trials conducted to compare directly the relative effectiveness of foamed polidocanol to liquid polidocanol in sclerotherapy in 75 or more patients [32,33]. These studies establish foam therapy to be superior to liquid sclerosing. In the first of these studies,

patients were randomized to receive either liquid polidocanol (concentration range 1%–2.5%, depending on diseased vein diameter) or polidocanol foam at half the concentration used for liquid sclerosing. The foam was “home made” using room air and two syringes joined at 90° by a three-way stopcock. The main outcome measures included clinical assessment of pain, inflammation and pigmentation) as well as ultrasound examination to determine both the diameter of the lumen and the length of the sclerosed vein. Complete sclerosis occurred in 94.4% of patients receiving foam and in 53% of those receiving liquid ($p < .001$) at 90 days. Clinically, pain, signs of inflammation and pigmentation did appear more often with foam sclerosis, and though the difference was significant, the degree of patient satisfaction was similar for both techniques [32]. In the second trial comparing foam to liquid, patients received 3% polidocanol as a liquid or a standardized mechanically produced air-based foam created using a mixing machine. Patients underwent up to three separate treatment sessions. The primary outcome measure was ultrasound determination that reflux measured 3 cm below the sapheno-femoral junction was eliminated three months after the last injection. Almost 70% of patients receiving foam were successfully treated, whereas the success rate was only 27% in patients treated with liquid sclerosant. Secondary endpoints including vein occlusion, reflux time, refilling time and patient satisfaction were also more significantly improved in the foam group. There were no differences in adverse drug reactions observed between the two treatment groups [33].

Although there are no published outcomes studies of Varisolve® comparing polidocanol concentrations, two studies have compared outcomes in sclerotherapy treatment of great saphenous vein reflux using air-based 1% and 3% polidocanol foam in either 80 [34] or 148 [35] patients. At long duration after treatment (one year or greater), both studies revealed equivalent efficacy for the two doses to abolish reflux. Side effects were similar between treatment groups in both studies. Patient satisfaction with cosmetic improvement was recorded in only one of the studies, with cosmesis statistically found to be no different between treatment groups [34].

A multi-center safety trial of 82 patients conducted with Varisolve® has now been completed [36]. The early results show that sapheno-femoral junction reflux was eliminated in 94% of patients and that the greater saphenous vein was occluded in 88% of participants. Adverse events in this study have been reported as mild and transient, consistent with other studies of Varisolve®.

4.3 Phase III Studies

No Phase III studies of Varisolve® have been concluded in the United States. An open-label, international (mostly French), multi-center prospective randomized Phase III study of 710 patients was conducted to compare the safety and efficacy of Varisolve® with alternative treatment (surgery or sclerotherapy with any marketed sclerosant administered as either liquid or foam) in the treatment of varicose veins and trunk vein incompetence [37]. The surgical or sclerotherapy approach used as an alternative to Varisolve® was not specified in the manuscript. The study endpoint was ultrasound-determination of occlusion of trunk veins and elimination of reflux, analyzed against a non-inferiority hypothesis. This study found non-inferiority to be demonstrated with 83.4% efficacy for Varisolve® and with 88.1% for alternative treatment at three months. At twelve months, the corresponding magnitudes were 78.9% and 80.4%. Overall, surgery was more efficacious than Varisolve®, which was more efficacious than sclerotherapy performed with the marketed sclerosants delivered in liquid or foamed form. Varisolve® treatment resulted in less pain and patients reported returning to normal more quickly. This study conforms to consensus guidelines for assessing efficacy in foam sclerotherapy [38].

The most recently reported Phase III data on outcomes with air-based polidocanol foam used to sclerose varicose veins come from a study comparing it to another sclerosing agent, sodium tetradecyl sulfate (Sotradecol®), and to a placebo, isotonic saline in 338 patients undergoing treatment of C1 varicose veins (i.e., telangiectases or reticular veins) [39]. Generally, foam would not be expected to show an advantage over liquid sclerosant in such veins. Polidocanol foam had a treatment success rate of 96% at 12 weeks and 95% at 26 weeks. These results were superior to those achieved with placebo (8% and 6% success at the same time points) but not statistically different from the results achieved with Sotradecol®. Patient satisfaction was higher with polidocanol treatment (88%, 84% at 12 and 26 weeks) than with Sotradecol® (64%, 63%) and placebo (13%, 11%). Polidocanol was well tolerated, and the incidence of side effects was significantly lower than that occurring in the Sotradecol® group.

4.4 Other Studies

There are forms of venous disease treatment other than varicosities and reflux in which sclerotherapy has been evaluated. In such cases, surgical intervention is often unsuccessful, radiological intervention with embolization has no well-defined role, and conventional sclerotherapy has provided little benefit. A variety of primary endpoints for studies of venous malformation treatment using polidocanol foam have been utilized, including cosmetic improvement, ulcer healing and pain elimination alone or in combination [40–42]. A retrospective analysis of polidocanol endovenous microfoam for 50 patients with congenital vascular malformations of venous predominance, including follow-up for over 8 years (mean, 30 months) has been conducted [20]. Nineteen patients had limited venous malformations, 16 had infiltrating venous malformations and 15 had Klippel-Trenaunay syndrome. Percutaneous sclerotherapy was performed using 0.25% to 4% polidocanol microfoam in one to 46 sessions (mean, 12 sessions). The primary efficacy end point assessed was venous malformation size reduction. Polidocanol microfoam was judged beneficial 92% of the cases. Among the 46 responders, 18 experienced disappearance of treated malformations and 15 showed at least a 50% size reduction in their malformations. Out of 39 patients who presented with pain, 25 reported complete pain resolution and 14 reported pain reduction. No patient reported any major adverse effects, though there were four cases of transient skin pigmentation and three episodes of skin necrosis.

5. Safety and tolerability

As mentioned above, patients report polidocanol to be extremely well tolerated when delivered either as a liquid or foamed sclerosant. There are both absolute and relative contraindications for its use [43] in any form. The absolute contraindications include known allergy, presence of acute superficial or deep vein thrombosis, advanced peripheral arterial occlusive disease, first trimester and late (post 36 weeks) pregnancy, and immobility. Relative contraindications include longstanding history of leg edema, hypercoagulable state, late stage diabetic complications, and asthma. In the absence of these, polidocanol generally has an acceptable, but not complication-free, profile [44].

Complications resulting from polidocanol foam sclerotherapy occur with a frequency of events that tends to be inversely proportional to the complication severity [45]. Complications can be readily categorized as 1) frequent but transient, 2) rare but self limited and 3) rare but major [44]. The frequent and transient complications include urtication, which is probably from local histamine release occurring with the vascular injury. Urtication is more prevalent with polidocanol than with other agents. Posclerotherapy hyperpigmentation occurs following polidocanol administration in 10%–30% of patients and can last over one year. The incidence is less than that occurring with sodium tetradecyl sulfate. Telangiectatic matting often occurs along the inner thigh as well as on the calves and ankles [46], but it usually resolves spontaneously in three to 12 months [47]. Among the rare but self limited complications are

transient chest tightness and visual disturbances. These symptoms are of heightened concern at present with foamed sclerosants in the context of pulmonary gas embolism or, in patients with a patent foramen ovale (PFO), the risk of paradoxical cerebrovascular gas embolism. The specific risk of gas embolism is discussed below in detail with particular attention given to the microfoam (gas and bubble size) formulated as Varisolve®. Finally, the rare and serious complications include cutaneous skin necrosis, development of deep vein thrombosis, and systemic allergic reactions. Sufficiently large population studies have not been conducted to demonstrate the occurrence rates of these complications to be different for Varisolve® than for other sclerosant formulations and preparations. Cutaneous skin necrosis most commonly results from extravasation and is accompanied by pain at the time of injection for other sclerosants, but is a complication of intraarterial injection for polidocanol. Polidocanol is less caustic than sodium tetradecyl sulfate to skin, and current guidelines require foamed sclerosants to be delivered under ultrasound guidance to confirm intravenous delivery [3,38]. Patients by and large do not experience pain on Varisolve® injection.

A study of the incidence of side effects associated with use of carbon dioxide (CO₂) foam compared with a historical control using air-based foam was conducted using foam prepared using the three-way tap technique to mix gas with 1% polidocanol [48]. Adverse events were recorded for 24 hours following the sclerotherapy procedure to treat segments of the great and small saphenous veins and their tributaries, with 49 patients in the air-based foam group and 128 patients in the CO₂ foam group. The major significant differences in findings between the two groups included the rates of visual disturbances experienced (3.1% vs 8.2% in the CO₂ and air groups respectively), incidence of chest tightness (3.1% vs 18%), dry cough (1.6% vs 16%), and dizziness (3.1% vs 12%). The percentage of patients describing side effects fell from 39% to 11% with CO₂ replacing air in the foam preparation.

Well-documented reports have appeared describing significant neurological events including major stroke, seizures and transient ischemic attacks in patients undergoing foam sclerotherapy [49,50]. The patients each were subsequently shown to have a PFO. Furthermore, two reports have shown that all individuals injected with foamed sclerosants had echocardiographic evidence gas bubbles within the right heart chambers, and some had bubbles appearing within the left heart [51,52]. An echocardiography study of intracardiac bubble presence and bubble durability showed gas emboli appeared in the right atrium within two to three minutes following Varisolve® injection in a leg vein. Bubbles were detectable for as long as 32 minutes after treatment [53]. This raises the specter that trans-PFO bubble passage could result in gas bubbles within the systemic arterial circulation, with cerebrovascular gas embolization being possible. In support of this notion, a recent analysis of 3259 patients who underwent ultrasound-guided foam sclerotherapy for the treatment of varicose veins revealed a clear association between PFO and adverse events including visual disturbances, migraines and chest discomfort [54]. Five of the seven (71.4%) of patients suffering adverse events at their first sclerotherapy session tested positive for PFO, but none had permanent symptoms.

Other recent evidence also indicates that bubbles derived from Varisolve® used in lower extremity venous sclerotherapy do enter the cerebral circulation and may be associated with neurological symptoms but do not cause any form of lasting cerebral injury [36,55]. In a study of 75 patients undergoing lower extremity polidocanol “home made” foam sclerotherapy, bubbles were detected by transcranial Doppler monitoring of the middle cerebral artery of over 30% of patients. Fewer than 7% of patients experienced headache, dizziness, dry cough, migraine, visual disturbances, nausea or limb paresthesias. All patients who reported migraine had intracerebral gas emboli [55]. In a separate study 57 of 82 patients had middle cerebral arterial gas emboli detected with transcranial Doppler monitoring. All underwent sensitive surveillance for brain, retinal and cardiac microinfarction. None of the subjects developed neurological or visual field abnormalities, none developed magnetic resonance imaging

evidence of new brain lesions and none had any alterations of cardiac markers [36]. In a combined review of 106 patients, 82 of whom were studied in [36] and 24 in [53], 58% had a known right-to-left intracardiac shunt while there was only a 0.9% total incidence of neurological or visual symptoms following Varisolve[®] injection to treat a great saphenous vein varicosity [56].

These studies focusing on neurological events and cerebrovascular gas embolism draw on the physiological advantages conferred by the ultra low nitrogen gas formulation used in Varisolve[®] and its engineered dispensing mechanism which produces a microfoam having a highly controlled and limited bubble size distribution. These two features are absent from other foam sclerotherapy formulations, which lack Varisolve[®]sR specifically manufactured properties to minimize its gas embolism potential [6,24-26].

6. Conclusion

Analysis of polidocanol endovenous microfoam (Varisolve[®]) trials as well as additional studies of both Varisolve[®] and other polidocanol liquid and foam sclerotherapy formulations suggests that Varisolve[®] is a safe and effective sclerosant for chronic venous insufficiency. The long history of polidocanol use outside the realm of governmental regulatory control has contributed to the minimal publication of Phase I data related to its intravascular use as a sclerosant. However, the practical experience over multiple decades has demonstrated it to have an excellent safety and toxicity profile at doses that provide the desired sclerosing effect.

More recent Phase II studies have brought the necessary critical focus onto the use of foamed polidocanol to treat venous insufficiency. The multiple clinical studies performed have revealed that foamed polidocanol is effective at 1% concentration, that it is at least as effective as foamed sodium tetradecyl sulfate but with fewer complications and side effects, and that patient satisfaction with their treatment results is rated very highly. The additional value of those studies of Varisolve[®] that have been published or reported to date has been to demonstrate its capacity to provide similar or improved outcomes, efficacy and patient satisfaction while also presenting a rationale for production of a microfoam engineered to yield a refined safety profile in light of the recognized risk of gas embolism accompanying the use of foamed sclerosants. Currently applications are extending its utilization into treatment of other vascular disease for which other treatment options have been profoundly limited or unsuccessful. Given the longstanding and pervasive use of polidocanol foam by phlebologists in Europe, there is very limited utility to pursuing any further trials in the United States except to those that may yet be required to permit Varisolve[®] to be studied in Phase III evaluations.

7. Expert opinion

Because foamed sclerosants are so effective in eradicating chronic venous insufficiency, so easy to administer clinically and so well tolerated by patients, they are already in widespread use despite a lack of regulatory approval for such preparations. The combined profiles of successful patient outcomes, reasonable costs of therapy compared to surgical alternatives and very high patient satisfaction with treatment currently drive a thriving market for this varicose vein intervention. However, the persistent and significant concerns regarding neurological events thought to represent cerebrovascular gas embolism resulting from transcatheter passage of foam bubbles has already resulted in published guidelines that suggest limiting the injectate volume as a risk reduction strategy. The literature makes it apparent that arterial bubble emboli are unavoidable during injection of foamed sclerosants, making the imperative be to promote formulation of an injectate that minimizes patient risk. Varisolve[®], by virtue of both its gas composition and bubble size distribution, represents a major therapeutic advance as a polidocanol endovenous microfoam. Importantly, Varisolve[®] presently confers a safety

advantage that no other foamed sclerosant formulation can claim. Although future drug evaluation is required to demonstrate its clinical efficacy in direct comparison to other accepted and practiced treatment modalities for chronic venous insufficiency, the published data favor the notion that Varisolve'sR unique combination of polidocanol as the sclerosant, ultra low nitrogen content of the gas and controlled microfoam as the dispensed injectate will both maximize the benefits and minimize the risk of undergoing sclerotherapy.

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Figure 1.
Chemical structure of polidocanol.

Figure 2.
The Varisolve® polidocanol endovenous microfoam generation and dispensing canister.

Table 1

Drug name	Polidocanol
Phase	Phase III
Indication	Venous insufficiency
Pharmacology description	Membrane integrity antagonist
Route of administration	Parenteral, intravenous
Chemical structure
Pivotal trial(s)	In a US Phase II trial in 82 patients with varicose veins, sapheno-femoral junction reflux was eliminated in 94% of patients and the greater saphenous vein was occluded in 88% of participants. In another US Phase II safety trial in 57 patients with varicose veins, no MRI lesions, neurological abnormalities or elevated cardiac markers were recorded. A multi-center European Phase III study of 710 patients having varicose veins and trunk vein incompetence showed non-inferiority of polidocanol endovenous microfoam compared to alternative (surgical intervention and sclerotherapy) treatment at three and twelve months.

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