Sodium Tetradecyl Sulfate for Sclerotherapy Treatment of Veins: Is Compounding Pharmacy Solution Safe?

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OBJECTIVE. **The objective was to determine the composition of three available solutions of sodium tetradecyl sulfate from compounding pharmacies in comparison to pharmaceutical-grade sodium tetradecyl sulfate, Fibrovein (STD Pharmaceuticals, Ltd.).**

METHODS. **Solutions of 3% sodium tetradecyl sulfate were obtained from three compounding pharmacies. An analysis of their composition was performed.**

RESULTS. **All samples of 3% sodium tetradecyl sulfate obtained had a different concentration of sodium tetradecyl sulfate than that stated on the bottle (range, 2.59%–3.39%). Significant concentrations of the contaminant carbitol were present in samples from all three sources (0.33%–4.18%).**

CONCLUSION. **The production of 3% sodium tetradecyl sulfate by these three compounding pharmacies appears to occur by simple dilution of a 27% industrial detergent solution that is not manufactured for use in humans. Physicians need to be aware that the stated concentration may not be correct and that along with sodium tetradecyl sulfate, potentially harmful contaminants may be present in the solution.**

ANALYSIS OF SODIUM TETRADECYL SULFATE SAMPLES WAS PAID FOR BY STD PHARMACEUTICALS, LTD., HEREFORD, ENGLAND.

SCLEROTHERAPY REFERS to the introduction of a foreign substance into the lumen of a vessel causing thrombosis and subsequent fibrosis. The mechanism of action for sclerosing solutions is that of producing endothelial damage (endosclerosis) that eventuates in endofibrosis. The extent of damage to the blood vessel wall determines the effectiveness of the solution. One class of sclerosing solutions commonly used is detergents. They produce endothelial damage through interference with cell surface lipids.[1]

Sclerotherapy has been proven to be a safe and effective means for treating varicose and telangiectatic leg veins. This treatment began with the introduction of the hypodermic syringe in the mid-1800s. A wide variety of solutions have been used to destroy unwanted veins. One of the most widely used, safest, and effective solutions is sodium tetradecyl sulfate.

Sodium tetradecyl sulfate is a synthetic, surface-active substance first described by Reiner [2] in 1946. It is composed of sodium 1-isobutyl-4-ethyloctyl sulfate plus 2% benzoyl alcohol (which may act as an anesthetic agent as well as having bactericidal properties) and phosphate buffered to a pH value of 7.6. It is recommended that solutions be protected from light. It is a long-chain fatty acid salt of an alkali metal with the properties of soap. The solution is clear and nonviscous, has a low surface tension, and is readily miscible with blood, leading to a uniform distribution after injection. [3] It primarily acts on the endothelium of the vein because, if diluted with blood, the molecules attach to the surface of red blood cells, causing hemolysis. On August 13, 1946, Elkins Sinn received approval to market sodium tetradecyl sulfate injection. During 2000, Elkin Sinn, a division of Wyeth-Ayerth, discontinued manufacture of this product.

Sodium tetradecyl sulfate is distilled from a compound manufactured as a high-grade detergent used to clean optical surfaces by Niacet in Niagara Falls, New York. The product name is Niaproof anionic surfactant 4, also known as NAS 4 and Niaproof 4. It is manufactured to have between 26 and 28% by weight sodium tetradecyl sulfate with 20% by weight maximum of diethylene glycol ethyl ether (carbitol) and 1% to 2% by weight sodium chloride. During the manufacture carbitol is added so that the final product is three parts sodium tetradecyl sulfate to two parts carbitol. This 27% parent compound is the same compound provided to each manufacturer of sodium tetradecyl sulfate for injection. Each manufacturer then may attempt to purify the active ingredient sodium tetradecyl sulfate. Fibrovein (STD Limited, Hereford, England; the only pharmaceutical manufacturing company to distill sodium tetradecyl sulfate) contains 0.02% to 0.045% (wt/vol) of carbitol.

Because the US manufacturer of sodium tetradecyl sulfate stopped production in 2000, physicians who

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want to use this sclerosing solution have turned to a variety of sources. One source is compounding pharmacies. This study examines the purity of sodium tetradecyl sulfate supplied by three compounding pharmacies.

Methods

We sent for analysis 3% sodium tetradecyl sulfate solution purchased from three compounding pharmacies that advertise to physicians treating varicose and telangiectatic leg veins (Central Avenue Pharmacy, Pacific Grove, CA; McGuff Company, Inc., Santa Ana, CA; and Kronos Compounding Pharmacy, Las Vegas, NV). It is presumed that their direct mail advertising list is obtained and/or copied from the American Society for Dermatologic Surgery and/or the American College of Phlebology.

Results

Table 1 details an analysis of the pH, percentage concentration of sodium tetradecyl sulfate, and carbitol content of STD Pharmaceutical's Fibrovein and three sodium tetradecyl sulfate solutions obtained from compounding pharmacies.

Discussion

Because the Food and Drug Administration of the United States has yet to approve the manufacture and distribution of sodium tetradecyl sulfate since Elkins Sinn discontinued the production of its brand of sodium tetradecyl sulfate, Sotradecol, in 2000, physicians are obtaining sodium tetradecyl sulfate from a variety of sources. Some physicians obtain sodium tetradecyl sulfate either from the Canadian and French manufacturer Omega Laboratories, as Trombovar, or from the British manufacturer STD Pharmaceuticals, as Fibrovein. Because of an increasing need for this sclerosing solution, many compounding pharmacies have also been supplying this solution. Various loopholes in federal and state regulations allow pharmacies to compound a variety of medications for use in humans. The Food and Drug Administration has no regulatory power over this "branch" of the pharmaceutical industry. Although the compounding pharmacy industry has voluntary standards, no organization exists to test the quality and accuracy of medications provided from the compounding pharmacies. These loopholes were recently exposed in a report in the *Wall Street Journal*.[4]

Table 1. Analysis of Sodium Tetradecyl Sulfate from Four Sources

Batch	pH Value	Percentage	Carbitol Content (%)
Fibrovein	7.5	3.0	0.045%
Central Avenue Pharmacy	7.89	2.59	1.79%
McGuff Company, Inc.	8.01	3.39	4.18%
Kronos Compounding Pharmacy	7.99	3.21	0.33%

Our analysis found a discrepancy in both the stated concentration and the actual concentration of sodium tetradecyl sulfate as labeled on the bottle form all three compounding pharmacies. The concentration of the sclerosing solution should be matched to the size and type of vein treated to produce the minimal sclerosing effect. This will prevent excessive inflammation or ineffective sclerosis.[1]

The reason for the difference in concentration may be related to the variability of the percentage of the bulk sodium tetradecyl sulfate industrial solution. In temperatures below 15°C, the product fractionates so that the concentration of sodium tetradecyl sulfate is greater than 27% at the bottom of the drum and below 27% at the top of the drum. An analysis of this 27% sodium tetradecyl sulfate solution by the Professional Compounding Centers of America (Houston, TX) performed in July 2003 found that the 27% sodium tetradecyl sulfate contained 27.94% sodium tetradecyl sulfate. No analysis of the carbitol component or any other component in the industrial solution was performed. The presence of impurities in any intravenous injection is worrisome.

Carbitol has about the same toxicity as ethylene glycol when ingested which has a mean lethal dose in humans of 3 to 4 oz.[5] The LD_{50} for intraperitoneal carbitol is 5.39 mL/kg in both rats and mice. The Ames test is very weakly mutagenic for *Salmonella typhimurium* and *Saccharomyces cerevisiae*. Carbitol is reported to be teratogenic in rats and mice.[6] Cutaneous contact to carbitol also can produce a dermatitis with both immediate and delayed hypersensitivity.[7,8] Therefore, it would appear that one should limit the amount of carbitol in the sclerosing solution.

The Food and Drug Administration has an onerous responsibility to protect the health of American people. This process is oftentimes bogged down in a bureaucratic maze. The Food and Drug Administration was made aware of the lack of an approved sclerosing solution available to treat American patients more than 3 years ago. Various foreign manufacturers have been working with the Food and Drug Administration to have their pharmaceutical-grade solution approved, but this is a long tedious process. In the meantime, compounding pharmacies, which do not fall under Food and Drug Administration scrutiny, have been supplying sclerosing solution to well-meaning physicians. Unfortunately, these compounding pharmacies have not taken the necessary steps to ensure that their

solutions are free of contaminants and even are of uniform concentration. It is hoped that this study will encourage the Food and Drug Administration to speed the process of approval of sodium tetradecyl sulfate in the United States. It is also hoped that appropriate legislation be initiated to ensure that the safety of the American public is not jeopardized by the compounding pharmacy industry.

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Commentary

This timely article underscores the dilemma facing American phlebologists whose source of this commonly used Food and Drug Administration approved sclerosant was abruptly terminated in 2000. At this time, Americans face legal obstacles in obtaining sodium tetradecyl sulfate produced under strict European standards and, accordingly, extemporaneous (and sometimes crudely manufactured) substitutes have begun to appear. This is the kind of issue that might prompt the establishment of testing programs for extemporaneous compounds, as well as hopefully provoke some movement in the approval process for polidocanol (aethoxysclerol), which is widely used in this country despite its lack of Food and Drug Administration approval. Hopefully political pressure from phlebologists, who desperately need safe and useful modern agents such as sotradecol and polidocanol, as well as the American College of Phlebology and prominent physicians such as Dr Goldman, will help clear the bureaucratic impasse that has produced this intolerable situation.

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