0099-2399/98/2404-0213$03.00/0
JOURNAL OF ENDODONTICS

Printed in U.S.A.
VOL. 24, NO. 4, APRIL 1998

SCIENTIFIC ARTICLES

Risk Assessment of the Toxicity of Solvents of Gutta-Percha Used in Endodontic Retreatment

Michael J. Chutich, DDS, MS, Edward J. Kaminski, PhD, Donald A. Miller, DDS, MS, and Eugene P. Lautenschlager, PhD

Three randomly assigned groups of single-canaled extracted teeth obturated with gutta-percha were retreated using controlled application of one of three organic solvents: chloroform, xylene, or halothane. Two additional groups of teeth served as positive and negative controls. Residual volume of solvent expressed through the apical foramen during retreatment was determined by the difference of pretreatment and posttreatment weights of hermetically sealed receptacles attached to the root surface of the teeth. Results indicate that the amount of solvent that has been determined to have leached out through the apical foramen is several orders of magnitude below the permissible toxic dose. Thus, it is proposed that the use of any of the aforementioned solvents used in the retreatment of root canals would pose negligible risk to the patient.

Chloroform has been the most popular gutta-percha solvent because it solubilizes gutta-percha rapidly, is stable, and has a long history of clinical use. However, due to the results of a positive animal carcinogenicity bioassay in 1976 (1), the Food Drug Administration banned the use of chloroform in drugs and cosmetics (2) and thereby cast a state of confusion upon the dental profession as to whether the use of chloroform in the practice of dentistry is considered safe or has been prohibited.

The weight of evidence indicates that chloroform acts through a nongenotoxic/cytotoxic mode. Tumor formation is thought to result from initiation and promotional events that are secondary to induced cytolethality and regenerative cell proliferation. No increased risk of tumors would be anticipated at doses that do not induce cytolethality (3). Toxicity, therefore, is dose-dependent.

Because of concerns of carcinogenicity of chloroform, clinicians and researchers have developed a renewed interest in finding alternative solvents (4–6). These studies have failed to identify a solvent with superior gutta-percha dissolving or softening capabilities. Proposed alternative solvents either offered no advantages over chloroform, required special precautions in handling or required further study to determine the safety and suitability of their use.

Of the possible suitable alternative solvents to chloroform, halothane, a fluorinated hydrocarbon used for induction anesthesia seems to be most promising due to its biocompatibility. It is nearly as effective as chloroform and about twice as effective as eucalyptol in dissolving gutta-percha (6, 9). Halothane, however, is not without drawbacks. Idiosyncratic hepatic necrosis is a potential side effect following repeated use of halothane-induced anesthesia. Idiosyncratic toxicities are a major concern, because they are difficult to predict and are usually not present until the patient has been previously exposed to the agent. They are host-dependent and dose-independent (11).

Recently, the cytoxicity of halothane and of turpentine was evaluated compared with that of chloroform. All solvents were found to be toxic, with halothane having the same level of toxicity as chloroform (12).

Paracelsus stated several centuries ago, "What is there that is not a poison? All things are poison and nothing (is) without poison. Solely the dose determines that a thing is not a poison. All substances can be remedies or poisons depending on the dose and mode of application" (13).

The purpose of this investigation was to determine how much of a particular solvent used may become available to the tissues surrounding the tooth structure, and if the controlled use and the amount of such solvent of gutta-percha poses a significant health risk to the patient.

MATERIALS AND METHODS

Fifty-five human single-canal, extracted human teeth with completely formed root apices were used for this investigation. An acrylic collar was fabricated around the coronal portion of the root of each tooth to fit into the mouth of a 1.5 ml polypropylene test tube (equipped with a hinged lid) receptacle. The teeth were secured to the receptacle via the acrylic collar using a gasket fabricated from rubber dam material to establish a hermetic seal between the acrylic collar and the inner walls of the polypropylene test tube (Fig. 1).

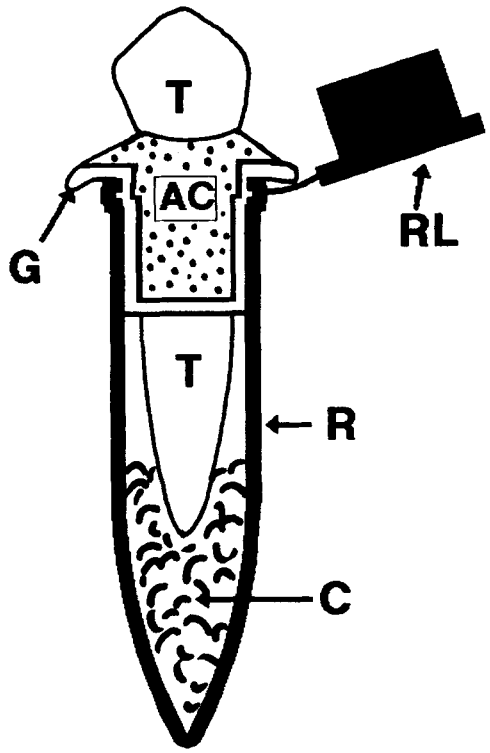

FIG 1. Cross-section view of the tooth secured to receptacle. *R*, receptacle; *RL*, receptacle lid; *T*, tooth; *G*, gasket; *C*, cotton; and *AC*, acrylic collar.

Canal Preparation

All canals were prepared to working length (1 mm short of the apical foramen) to a file size three sizes larger than the first file that bound at working length or to a minimum file size 40, whichever was larger, via a conventional step-back instrumentation technique using Flex-R files (Union Broach Co., Emigsville, PA) and copious irrigation with 5.25% sodium hypochlorite. Patency of the apical foramen was maintained by passing a #15 Flex-R file 2 mm beyond the apical foramen at the completion of each file size or bur used.

After canal preparation, 40 teeth were randomly selected for canal obturation, and the remaining 15 teeth for use as positive controls (used to establish the ability of solvent to pass through the apical foramen).

Obturation Procedure

Root canal obturation was completed by using lateral condensation of gutta-percha and Roth's root canal sealer (Roth's 801 Elite Grade; Roth Drug Co., Chicago, IL). Upon completion of obturation, the teeth were placed into a humidor at room temperature and 100% humidity to ensure the final set of the root canal filling material.

The obturated teeth were randomly selected for placement into one of the three experimental groups based on the solvent to be used to remove the gutta-percha or to the negative control group. Experimental groups consisted of a chloroform retreatment group (10 teeth), a halothane retreatment group (10 teeth), and a xylene retreatment group (10 teeth). The negative control group (used to establish a baseline unit of measure for statistical analysis) consisted of the remaining 10 teeth.

Gutta-Percha Removal

Experimental teeth were secured to preweighed test tube receptacles loosely filled with cotton. Once secured to the test tube, a #2 Gates-Glidden drill was used to remove gutta-percha to the midroot level or to the point of binding against the canal. (This action created a reservoir for the solvent and improved the access for further instrumentation.) Ten microliters (0.01 ml) of solvent delivered by a micropipette was placed into the newly created reservoir. Hand instrumentation with Flex-R files was used to remove the remaining gutta-percha. The addition of solvent in 10 μl increments was used as needed to advance the file apically. The file was manipulated using half-turn rotation movements and then withdrawn. The file was advanced apically by repeating this procedure until the apical seat was reached or the remaining gutta-percha was removed, whichever came first.

Quantification of Apically Extruded Solvent

Once working length was achieved, the tooth was removed from the test tube and the test tube lid secured. The sealed test tube was weighed using a Mettler balance to the nearest 0.01 mg. The total amount of solvent used was recorded. The amount of solvent leached out through the apical foramen was determined by subtracting the pretreatment weight of the polypropylene test tube from weight of the same test tube after removal of the gutta-percha filling.

Controls

The negative control specimens were secured to preweighed 1.5 ml polypropylene test tubes loosely filled with cotton. After a time period approximating the time required for gutta-percha removal in the experimental groups, the tooth was removed from the test tube and the test tube lid closed. The sealed test tube was again weighed using a Mettler balance to the nearest 0.01 mg. The difference of the test tube weight before coupling with the teeth and after removal from the tooth was determined and recorded. This procedure was completed for each of the 10 negative control samples.

The 15 teeth selected as positive controls were randomly divided into three groups. Each specimen was then coupled to a preweighed 1.5 ml polypropylene test tube. Once secured to the test tube, a known volume of solvent was delivered into the canal space via the access cavity by an automatic micropipette. Three minutes after introduction of the solvent, the tooth was detached from the test tube and the lid of the test tube secured and weighed. The weight of the test tube before introduction of the solvent into the canal space was subtracted from the weight of same test tube 3 min after introduction of the solvent. This procedure was performed in five samples for each of the solvents (chloroform, halothane, and xylene). All weights were recorded to the nearest 0.01 mg using a Mettler balance.

TABLE 1. Average measurements, by group

Group	*n*	Mean Weight Change (mg)	Mean Percent Weight Change	SD
Experimental—Chl	10	0.32	0.033	0.038
Experimental—Hal	10	0.35	0.032	0.037
Experimental—Xyl	10	0.22	0.020	0.019
Negative control	10	0.16	0.015	0.010
Positive control—Chl	5	22.16	2.186	1.096
Positive control—Hal	5	30.78	2.908	1.208
Positive control—Xyl	5	29.17	2.852	0.817

Chl, chloroform; Hal, halothane; Xyl, xylene.

Statistical Analysis

The percent weight change for each sample in the experimental and control groups was calculated and compared using a one-way analysis of variance test.

RESULTS

The mean weight change and percent weight change for all groups are listed in Table 1.

The mean weight of apically extruded solvent was 0.32 mg for the chloroform group, 0.35 mg for the halothane group, and 0.22 mg for the xylene group. Data obtained from the positive control groups demonstrated the ability of the solvents to pass through the apical foramen. The mean weight of apically extruded solvent was 22.16 mg for the chloroform group, 30.78 mg for the halothane group, and 29.15 mg for the xylene group.

The percent weight change analyzed using a one-factor analysis of variance revealed that, although an increase was detected in the experimental groups when compared to the negative control group, it was not statistically significant ($p < 0.05$). The percent weight change between the positive control groups and the negative control group was statistically significant ($p < 0.01$).

DISCUSSION

In this study, the weight measurements reported in the experimental groups served to quantify the amount (dose) of solvent presented through the apical foramen during removal of gutta-percha from the root canal. It was assumed that this weight represented solely residual solvent. In all likelihood, the extruded substance consisted of a mixture of solvent, gutta-percha, and dentinal chips produced from the canal walls. Therefore, data presented represents a "worst case" scenario with the actual amount of solvent presented being less than that actually assessed.

The American Conference of Governmental Industrial Hygienists annually publish the *Threshold Limit Values and Biological Exposure Indices* to assist in identification of risk agents and the conditions and events under which they potentially produce adverse consequences to people or to the environment. The American Conference of Governmental Industrial Hygienists *Threshold Limit Values and Biological Exposure Indices* identify chloroform, halothane, and xylene as risk agents when present at levels exceeding values of 49 mg/m^3 for chloroform, 404 mg/m^3 for halothane, and 434 mg/m^3 for xylene (14). These values represent the maximum permissible exposures (by inhalation, ingestion, or direct contact) that it is believed that nearly all workers may be exposed to 8 h/day for 5 days/wk for their entire working history without adverse effect. No adverse effects are expected to the average person at exposure levels that fall below the threshold limit value (TLV) for a given substance. Conversely, if exposure levels exceed the TLV, the occurrence of adverse effects are possible and a hazard exists. The accepted practical value that is considered "action value" is 50% of TLV, at which point attempts to reduce the exposure amount to the average person are undertaken.

The average volume of air inhaled by the average adult (all levels of activities considered) has been determined to be 13 m^3/day (15). Using 8 m^3/day as a conversion factor, which is assumed to represent the amount of air breathed during working activity (16), translates the TLVs to daily maximum exposure level of 392 mg for chloroform, 3,232 mg for halothane, and 3,472 mg for xylene.

A comparison of the maximum daily exposure level of a solvent to the level of solvent that is actually presented to the patient during retreatment establishes a basis to assess (quantify) the risk to the patient associated with its use. The average exposure levels of chloroform, halothane, and xylene—as determined in this investigation—were 0.32 mg, 0.35 mg, and 0.22 mg, respectively. Dividing the maximum permissible level by the average actual exposure level establishes a safety factor. Assuming that the average exposure levels determined in this study represent a daily exposure, a 1,200-fold safety factor for chloroform, a 9,000-fold safety factor for halothane, and a 15,000-fold safety factor for xylene exist. However, the aforementioned averages represent a one time exposure. The safety factor for each solvent in all actuality would be magnitudes greater.

This investigation was undertaken to analyze the health risk to the patient associated with the use of solvents used for gutta-percha in endodontic retreatment. For a risk to exist with these solvents, there must be the possibility of adverse consequences associated with their use and the uncertainty of the occurrence of these consequences. If either is missing, there is no risk (17). As long as solvents based on acceptable dose response determinants are used at levels below daily maximum permissible levels [as defined by the no effect level (the TLVs)], no adverse health consequences are expected to occur. Both conditions necessary for a risk to exist are thereby eliminated (the possibility of adverse consequences and uncertainty of their occurrence), thus no risk.

Halothane toxicity, unfortunately, is not solely dose-dependent. Current evidence strongly suggests halothane hepatitis may be an immune-mediated drug toxicity characterized by the presence of specific antibodies that recognize several liver microsomal proteins produced in response to the metabolite of halothane (11, 18). These antibodies are thought to play a role in the pathogenesis of the idiosyncratic hepatic necrosis produced by halothane. An important feature of idiosyncratic toxicities, which makes them difficult to study in both humans and animals, is their relatively low frequency of occurrence and variable dose (11). The incidence of halothane hepatitis is in the order of one in 10,000 exposures (19). Therefore, with the use of halothane, it must be recognized that, in certain individuals, repeated exposure to halothane could initiate a drug hypersensitivity reaction with hepatic necrosis as a sequelae.

Zakariasen et al. (7) stated that, when chloroform is properly used in endodontic therapy (i.e. small quantities confined to the root canal space), it is unlikely to be a significant health hazard to the patient. The results of this study support this hypothesis in the fact that, although there was a weight difference between the experimental groups and the negative control group, it was not statistically significant.

TABLE 2. Delivery of TLV volume of solvent using a 1-ml syringe

Chloroform	Xylene	Halothane
0.26 ml ≈ 130 drops* 0.26 ml ≈ 99 drops†	4.0 syringes	1.7 syringes

* 28-gauge needle.
† 27-gauge needle.

The Food and Drug Administration ban on drugs and cosmetics containing chloroform (2) has cast confusion upon the dental profession as to whether the use of chloroform in the practice of dentistry is considered unsafe or has been prohibited. This ban only pertains to the use of chloroform in instances where close and repeated contact exposure to the skin may pose a potential risk for it to act as a carcinogen. The ban does not pertain to the use of chloroform in clinical practice (20), and use of the ban as a basis to eliminate use of chloroform in dentistry is inappropriate.

The vehicle of solvent delivery used in this study was the adjustable 50 μl automatic pipette. The automatic pipette is a laboratory tool and ill suited for clinical use. However, the 1-ml insulin syringe is a suitable alternative. This versatile syringe offers a disposable, inexpensive, and a readily available delivery vehicle capable of dispensing small increments of solvent to any desired target area within the oral cavity. The daily maximum permissible exposure levels for each of the solvents tested in this study in terms related to delivery by a 1-ml syringe are listed in Table 2.

This in vitro study was restricted to single-rooted teeth with completely formed apices recently obturated with well condensed gutta-percha, all favorable to minimizing the dose presented to the patient. Unfortunately, such conditions are not always encountered in vivo. Clinically, teeth requiring endodontic retreatment may be multirooted, have poorly obturated canals with poor apical adaptation or have been obturated many years before. Such conditions may predispose the patient to exposure levels greater than those presented in this study. This may be attributed to the necessity to use an increased volume of solvent required to facilitate the removal of the gutta-percha from the canal(s) or to a greater access of solvent to the surrounding tissues. Nevertheless, as long as the amount of solvent used is below the indicated TLV, no adverse effect is expected to occur. However, the utmost care should be taken in the handling and usage of these substances to minimize the exposure of both the patient and dental team. As Paracelsus stated several centuries ago, "all substances can be remedies or poisons depending on their mode of application" (13).

Based on the findings in this study, the following conclusions are made:

1. Minuscule quantities of solvent are expelled through the apical foramen during the removal of gutta-percha from the root canal.
2. The amount of solvent that may become available to the tissues surrounding the tooth structure is several orders of magnitude below the permissible toxic dose.
3. The controlled use of chloroform, halothane, or xylene at the appropriate dose levels as determined by this study poses no health risk to the patient.

This study was supported by Northwestern University.

The assertions contained herein are those of the authors and are not to be construed as official or as views of the Department of the Navy, Department of Defense, or of the U.S. Government.

Dr. Chutich is a former resident, Northwestern University Dental School, Evanston, IL, and is command endodontic consultant, Naval Dental Center, Jacksonville, FL. Dr. Kaminski is professor emeritus, Department of Oral Pathology, Northwestern University Medical and Dental Schools, Evanston, IL. Dr. Miller is a clinical assistant professor, Department of Restorative Dentistry, Northwestern University, Evanston, IL, and is in private practice in Homewood, IL. Dr. Lautenschlager is professor, Department of Biomaterials, Northwestern University Dental School, Evanston, IL. Address requests for reprints to Dr. Michael J. Chutich, 2056 Deer Run Trail, Jacksonville, FL 32246.

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