PEDIATRIC DENTISTRY/Copyright © 1989 by
The American Academy of Pediatric Dentistry
Volume 11, Number 1

Scientific Articles

Assessment of the systemic distribution and toxicity of glutaraldehyde as a pulpotomy agent

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Abstract

The systemic distribution of glutaraldehyde (GA) from a pulpotomized tooth of a rat was estimated to be 40 nanomoles or 25% of the applied dose. Metabolic studies disclosed that GA was eliminated in urine and expired gases; 90% was cleared from body tissues in 3 days. To evaluate the toxicity of GA, doses 500x greater than that systemically distributed from a pulpotomy site were infused into the jugular veins of rats. Twenty-four hours postinfusion the rats were evaluated in vivo for physiologic changes or sacrificed for biochemical and histologic evaluation of harvested tissues. Only one of the assays, a physiologic parameter, was altered by the 500x dose. Considering the relatively large dose administered and the limited effects, we conclude that GA would not be toxic when used as a pulpotomy agent.

Glutaraldehyde has generated considerable interest in recent years as an alternative pulpotomy agent. It has been investigated by in vitro techniques (Ranly and Lazzari 1983; Ranly et al. 1987; Jeng et al. 1987; Karp et al. 1987), analyzed in animal studies (Davis et al. 1982; Ranly et al. 1985; Fuks et al. 1986; Myers et al. 1986), and evaluated in humans (Kopel 1980; Garcia-Godoy 1986; Fuks et al. 1987; Hernandez Pereyra et al. 1987). Impetus for these studies have been prompted in part by the concern over the possible local and systemic toxicity of formocresol (Lewis and Chestner 1980; Myers et al. 1983; Grundy and Adkins 1984).

Results from animal and clinical studies using glutaraldehyde have been promising (Kopel 1980; Davis et al. 1982; Garcia-Godoy 1986; Hernandez Pereyra et al. 1987). This agent has been demonstrated to be a superior fixative (Ranly and Lazzari 1983) with low antigenic potential (Ranly et al. 1985). Its depth of penetration and zone of necrosis (Kopel et al. 1980; Ranly et al. 1987) appears to be considerably less than that of formocresol (Garcia-Godoy 1981). Autoradiographic evaluation of teeth treated with ^{14}C-glutaraldehyde demonstrated minimal diffusion into surrounding periodontal tissues (Myers et al. 1986).

Glutaraldehyde has been shown to be distributed systemically from a pulpotomy site (Myers et al. 1986), but its potential for somatic toxicity has not been evaluated. In previous studies, the systemic distribution and toxicity of formaldehyde was evaluated in the rat model (Ranly 1985; Ranly 1987). It was the intent of this study to determine the systemic distribution of glutaraldehyde from a pulpotomy site using similar methodology and to investigate its toxicity relative to the body load attained from the dental procedure.

Materials and Methods

Systemic Distribution and Metabolism Studies

Pulpotomy procedure — Eight male Sprague-Dawley rats, each weighing 225 ± 10 g, were anesthetized by an IP injection of pentobarbital and positioned on an operating table. Penetration of the pulp chamber of the maxillary left first molar was made with a 0.5 round bur under a binocular scope, and bleeding was controlled with endodontic paper points. A 0.4 µl aliquot of 4% glutaraldehyde containing labeled glutaraldehyde (^{14}C-[1, 5] glutaraldehyde, 10.5 mCi/mmol, custom synthesis [New England Nuclear; Boston, MA]) was deposited in the pulp chamber with the aid of a 1-µl syringe. After a timed 4-min interval, the chamber was blotted dry with a paper point and filled with zinc oxide-eugenol cement. Forty-five minutes later the rats were bled and then sacrificed by an ether overdose. Samples of liver and kidney were harvested for counting of incorporated ^{14}C-glutaraldehyde.

Intravenous administration of glutaraldehyde — Six groups of 225 ± 10 g male Sprague-Dawley rats (8 rats/group) were anesthesized prior to surgical exposure of the neck region. Labeled glutaraldehyde diluted with saline then was infused into the jugular vein. The dose levels administered to the rats in this manner represented 10, 15, 20, 25, 30, or 50% of the amount of

glutaraldehyde that was deposited into the pulpotomy site. These percentages were used to determine an intravenously administered dose, which effected a systemic incorporation of labeled glutaraldehyde comparable to that following a pulpotomy. Forty-five minutes following the infusion, the rats were sacrificed and their tissues harvested in the manner described above.

Metabolic studies — Six groups of 225 ± 10 g male Sprague-Dawley rats (4 rats/group) were infused with 0.96 μCi of ^{14}C-glutaraldehyde. One group was sacrificed by an ether overdose 5 min postinfusion in order to establish zero time values for liver, kidney, serum, and muscle samples. The other groups were sacrificed at each of the following time periods: 1, 6, and 24 hr, 3 and 7 days. Immediately following infusion with ^{14}C-glutaraldehyde, members from the 1, 6, and 24-hr groups were placed individually in glass metabolic cages, which had outlets for the capture of expired gases and a separate receptacle for urine. Another group, the 7-day rats, were placed individually in chambers 6 days postinfusion and maintained there for 24 hr. Air was drawn from the cage by a vacuum and was bubbled through 2 vessels containing 3 N NaOH. This solution trapped the expired $^{14}CO_2$ which was a metabolic byproduct of the administered glutaraldehyde. Samples of urine and NaOH solutions were retained for counting by liquid scintillation spectroscopy.

Investigation of Toxic Side-Effects

Infusion procedures — Buffered glutaraldehyde at a concentration 500x the level determined to escape from a pulpotomy site was infused into the jugular veins of anesthetized 225-g rats (6 rats/group). This dose in a volume of 50 μl was equivalent to 2 μMoles of glutaraldehyde. Twenty-four hours later the rats were evaluated by biochemical and histologic parameters. In one experiment, a 100x dose also was evaluated.

Phenosulfonphtalein (PSP — Sigma Chemical Co; St. Louis, MO) was infused into the jugular veins of rats treated with glutaraldehyde 24 hr previously. The dose of PSP administered was 0.2 mg/50 μl in a volume of 50 μl. The rats were gavaged with water and catheterized for the collection of urine over a 2-hr period. The collected urines were evaluated for PSP spectrophotometrically at 560 nm according to a method modified from Pla and Larson (1965) and reported as μg cleared by the kidneys.

Harvesting Tissue Samples

Following ether anesthesia, blood was collected from the dorsal aorta of rats and allowed to clot. The blood then was centrifuged and the serum separated for analyses.

Urine was harvested from rats that were restrained in acrylic cages. The urine was collected in ice-cooled graduate centrifuge tubes with an external catheter (PE 240 tubing) according to the method of Petty (1982). The tubes were completely shielded from fecal contamination. After 2 hr the volumes of urine were recorded, and aliquots were taken for further processing.

Kidney and liver tissue were harvested for histopathologic examination 24 hr postinfusion with glutaraldehyde. The samples were fixed in 10% neutral buffered formalin and prepared conventionally for routine paraffin sectioning. Sections were cut at 5 μm and stained with H&E.

Evaluation of Blood Factors

Creatinine — Serum creatinine was determined using a diagnostic kit (# 555 — Sigma Chemical Co; St. Louis, MO). This assay is based on the yellow-orange color that forms when the metabolite is treated with alkaline picrate. It was read at 510 nm and reported as mg/dl serum.

Serum glutamic-oxalacetic transaminase (SGOT) — SGOT was determined using a diagnostic kit (# 505 — Sigma Chemical Co; St. Louis, MO). The assay of this enzyme is based on the transfer of amino groups from aspartic acid to α-ketoglutaric acid. The products of this reaction are determined colorimetrically after their reaction with 2, 4-dinitrophenylhydrazine at 490 nm. SGOT activity is expressed in Sigma-Frankel (SF) units/ml, derived from a calibration curve.

Serum glutamic pyruvic transaminase (SGPT) — SGPT was determined using a diagnostic kit (# 505-P — Sigma Chemical Co; St. Louis, MO). The assay of this enzyme is based on the transfer of amino groups from alanine to α-ketoglutaric acid. The colorimetric reaction and expression of activity are the same as for SGOT.

Evaluation of Urine Factors

Proteins — For the assay of urinary proteins, the tubes containing the collected urine were vortexed and duplicate 50 μl samples were taken for analysis by the method of Bradford (1976). After color development, the samples were read on a spectrophotometer at 595 nm. Protein was reported as μg/ml of urine. The total amount of protein excreted also was reported in mg, calculated from the measured volume of urine.

Lactate Dehydrogenase (LDH) — The determination of LDH in urine followed a standard clinical protocol. Urine collected for 2 hr then was dialyzed overnight in distilled water at 4° C to remove inhibitors. Next, the bag was blotted dry, reweighed, and assayed for LDH. The assay used is based on the catalysis of lactic acid to pyruvate and the reduction of NAD to NADH, which is

read spectrophotometrically at 340 nm. The formula used to calculate the total activity in the urine adjusted for volume effects of dialysis and normalized the length of collection. The units of enzyme activity (defined as nmol NADH formed/ml/min) are reported, therefore, for 8-hour volumes.

In Vitro Determination of Kidney Function

Renal tubular transport capabilities of the kidney postinfusion was measured in vitro, using a modification of the method of Cross and Taggart (1950). This procedure involved the measurement of the accumulation of p-aminohippurate (PAH) by rabbit kidney slices. Following 2-hr urine collection, rats were anesthetized with ether and the kidneys were excised. The kidneys were cut in half longitudinally and then sliced into thin sections with a Stadie-Riggs microtome (Model 6727-C10 — Arthur H. Thomas Co; Philadelphia, PA). These sections of tissue weighing an average 178 mg then were placed in weighed flasks, containing 2.7 ml of buffer with 0.001 M PAH. After 1 hr of incubation in a reciprocal action water bath at 37° C, the incubation media was decanted from the flasks. The PAH remaining in the media was determined by the method of Bratton and Marshall (1939). The accumulation into the slices was calculated by subtraction and reported as µg/mg wet tissue.

Results

Systemic Distribution and Metabolism Studies

The studies with glutaraldehyde estimated the systemic distribution to be 25% of the applied dose (Table 1). This amounts to a body load of 40 nanomoles of glutaraldehyde. After 45 min the tissue/fluid ratio (g tissue/ml serum) of isotopic activity was 3 for the liver and 4.5 for the kidney. Similar ratios also were observed in the metabolic clearance studies.

The clearance of ^{14}C-glutaraldehyde from several tissues was determined for 7 days (Table 2). The zero time load in the serum and muscle was virtually eliminated in 1 week, and only a small portion (8% in the liver, 7% in the kidney) remained in major organs.

Glutaraldehyde was rapidly metabolized and expired as CO_2 or excreted in the urine (Table 3). At the end of 24 hr, 42% of the administered load of label was eliminated. After 6 days, both routes still were being used for elimination.

Toxicity Studies

Serum (SGPT, SGOT, creatinine) and urinary parameters (protein and LDH) were not changed significantly by the infusion of glutaraldehyde (Table 4). The uptake of PAH by the kidney slices was significantly higher in the experimental group. The clearance of PSP was significantly lower in the group receiving the 500x dose of glutaraldehyde, but it was not depressed in the rats infused with a 100x dose.

Discussion

In order to be able to compare toxic levels of glutaraldehyde to the amount distributed systemically from a pulpotomy site, our first objective was to determine the distribution of the labeled agent from treated teeth of rats. It was our intent to use this value as a reference level for toxicity studies. In this way, toxic doses could be equated to the number of concurrent pulpotomies required to achieve a similar systemic load.

Glutaraldehyde was distributed from a pulpotomy site into the tissues of the body. The body load estimated by our indirect methodology was approximately 40 nanomoles. This value represented 25% of the applied dose and was considerably higher than the 3-5% estimated by Myers et al. (1986) using dogs. However, the percentage absorbed was also a function of the applied dose. A better estimate for the distribution of glutaraldehyde is its clearance from the pulp chamber. Myers et al. (1986) calculated the clearance of glutaraldehyde from pulpotomized teeth of dogs (20-25 kg) to be 9.32 µl/hr. The clearance from the rat molar was about 0.1 µl/hr for a 225-g rat. On a comparable

TABLE 1. Systemic Distribution of ^{14}C-Glutaraldehyde (45 Min Post-Treatment)

Tissue	Pulpotomy[a]	50% Dose[b]	30% Dose[c]	25% Dose[d]	20% Dose[e]	15% Dose[f]	10% Dose[g]
Liver	603 ± 65[1]	1311 ± 109	840 ± 59	602 ± 46[1]	406 ± 49	376 ± 39	204 ± 54
	(.18)@	(.39)	(.25)	(.18)	(.12)	(.11)	(.06)
Kidney	871 ± 72[2]	1803 ± 101	1092 ± 61	913 ± 55[2]	625 ± 48	605 ± 64	315 ± 68
	(.26)	(.54)	(.33)	(.27)	(.19)	(.18)	(.10)
Serum	183 ± 21[3]	604 ± 34	590 ± 26	200 ± 30[3]	93 ± 15	0	0
	(.06)	(.19)	(.18)	(.06)	(.03)	0	0

[a] .16µMoles (.254µCi); [b] .08µMoles (.12µCi); [c] .05µMoles (.07µCi); [d] .04µMoles (.06µCi); [e] .032µMoles (.048µCi); [f] .024µMoles (.036µCi); [g] .016µMoles (.024µCi).

* Reported as dpm/g wet wt tissue or ml serum. All values reported as Mean ± S.E.M.

@ Values in parentheses represent glutaraldehyde in nanomoles calculated from specific activity.

[1,2,3] Differences not statistically significant.

TABLE 2. Clearance of ^{14}C-Glutaraldehyde From Rat Tissues

	Post-treatment Periods					
	5 min	1 hr	6 hr	24 hr	3 day	7 day
Liver	13,641[a]	11,098	4957	3040	1129	1049
	(100%)	(81%)*	(36%)	(22%)	(8%)	(8%)
Kidney	45,936[a]	19,352	7353	5209	3272	3262
	(100%)	(42%)	(16%)	(11%)	(7%)	(7%)
Serum	18,495[b]	4505	2430	1255	367	215
	(100%)	(24%)	(13%)	(7%)	(2%)	(1%)
Muscle	3664[a]	2466	480	501	157	127
	(100%)	(67%)	(13%)	(14%)	(4%)	(.7%)

[a] dpm/gm wet tissue; [b] dpm/ml serum.
* Values in parentheses represent radioactivity as a per cent of initial tissue load.

TABLE 3. Routes of ^{14}C-Glutaraldehyde Elimination

	Periods of Collection Post-infusion			
	1 hr	*6 hr*	*24 hr*	*24 hr/ 6th day**
CO_2	138,001[a]	486,109	499,878	8644
	(6%)@	(23%)	(23%)	(0.4%)
Urine	249,266[a]	369,236	396,071	2345
	(12%)	(17%)	(19%)	(0.1%)

* 24 hr collection beginning on day 6.
[a] Total dpm/Collection Period.
@ Values in parentheses represent per cent of initial load (0.96 μCi).

weight basis, the latter value would adjust to approximately 10 μl/hr. Thus the amount of glutaraldehyde solution which actually egressed from pulpotomized teeth of rats and dogs was similar when calculated relative to body weights. Therefore, we felt justified in using a rat as a model for systemic distribution and toxicity studies, since the systemic absorption seems proportional in the 2 species.

In addition to being a small body load of glutaraldehyde (approximately 1.7×10^{-8} g /g body weight), it was rapidly metabolized to CO_2 (and possibly other molecules). These findings are in agreement with earlier studies which demonstrated the rapid metabolism of glutaraldehyde (Myers et al. 1986; Karp et al. 1987). It is interesting that this xenobiotic molecule was eliminated so dominantly by metabolic breakdown.

Significant amounts of the label were excreted in the urine, but it is unknown whether intact glutaraldehyde or its metabolites were involved. Although glutaraldehyde is a reactive molecule and would be expected to cross-link randomly, the majority of it was eliminated rather quickly from the system.

A variety of biochemical parameters were selected in an attempt to determine acute manifestations following infusion of glutaraldehyde. The 500x dose was selected arbitrarily as a starting point to evalute the potential toxicity of glutaraldehyde pulpotomies.

TABLE 4. Systemic Effects of Glutaraldehyde

Assay	*Control* N = 6	*500X Dose* N = 6	*Sign.**
SGPT (U/ml)	55 ± 18@	67 ± 10	N.S.
SGOT (U/ml)	107 21	122 15	N.S.
Serum creatinine (mg/dL)	0.55 .11	0.65 .16	N.S.
Urinary protein (μg/ml)	174 46	207 66	N.S.
Total urinary protein (mg)	2.3 .8	2.2 .9	N.S.
LDH (U/8hr)	146 43	112 43	N.S.
PAH (μg/g)	44 10	79 16	$P<.001$
PSP (μg)	155 ± 13	94 ± 12	$P<.001$
		100X Dose	
PSP (μg)	153 ± 24	153 ± 25	N.S.

* Significance determined by Student's *t* test.
@ Values are presented as the mean ± S.D.

General cytotoxicity was evaluated by the assay for SGOT released in the blood by damaged cells. While often associated with the liver, this enzyme is not limited to this organ; it is present in some extrahepatic organs such as heart, skeletal muscle, and kidney. For this reason, it is theoretically a good measure of generalized cellular injury (Henry et al. 1974). Another serum enzyme, SGPT, is found mainly in the liver; its release is more suggestive of hepatic necrosis (Henry et al. 1974). However, serum levels of both enzymes may increase as a result of leakage from cells with altered permeability of membranes due to systemic effects of an agent rather than of hepatic necrosis caused by a chemical. The inference of hepatotoxic effects, or lack of them, as deduced from studies of levels of serum

enzymes, must be corroborated by histologic studies (Pla and Hewitt 1982). Accordingly, we examined the livers histologically and found no evidence of abnormality.

Potential nephrotoxicity was evaluated using assays for glomerular and tubular damage. Proteinuria is a consequence of altered filtration in the glomeruli. On the other hand, creatinine excretion is relatively constant from day to day and can be used as a measure of glomerular filtration. Elevated creatinine values are seen in cases of uremia (Ganong 1973). Neither of these values underwent statistically significant changes following the infusion of glutaraldehyde.

The agent p-aminohippuric acid has long been useful in vivo for the determination of renal plasma flow; it is secreted rapidly by the tubular cells (Ganong 1973). The in vitro assay used in this study is based on the ability of tubules to transport PAH, in this case from the incubation media into the tubules of kidney slices. Interestingly, the uptake of PAH was stimulated by the glutaraldehyde. We are unable to explain these results, but we interpret them to represent a functional stimulation. Perhaps the glutaraldehyde was converted to an intermediary in oxidative metabolism, since it has been reported that tricarboxylic acid cycle intermediates can stimulate the transport of PAH by renal tubules (Kippen and Klinenberg 1978). Had actual enzymic damage occurred, the uptake would have been expected to fall rather than rise.

The clearance of PSP from the blood was used as an endogenous test of kidney function. The high dose of glutaraldehyde (500x) decreased the clearance of this agent, but the lesser dose (100x) was without effect. We conclude, in the absence of any kidney histopathology at either dose, that the 500x load of glutaraldehyde transiently modified the handling of PSP by renal tissues.

According to Wright and Plummer (1974), the measurement of several enzymes in the urine is valuable for the detection of acute kidney damage by toxic compounds. Supposedly, the enzyme LDH is a "marker" for cytoplasmic damage to cells of the nephron. According to our results, the excretion of this enzyme in the urine was not affected by infusion with glutaraldehyde.

Even when injected as a bolus at a level considerably higher than that associated with a pulpotomy, glutaraldehyde did not appear to be particularly toxic. By histologic evaluation and most biochemical parameters, no significant changes were noted. Exceptions were the increased uptake of PAH and the decreased clearance of PSP when the 500x dose was administered. In the absence of histopathology and the other negative findings, we conclude that these changes were metabolic and reversible.

Conclusions

We estimated by an indirect method the systemic distribution of 4% glutaraldehyde from a pulpotomy site to be approximately 25% of the applied dose. This constituted a body load of 40 nanomoles and a clearance rate from the tooth of approximately .1 µl/hr. More than 90% of the glutaraldehyde which accumulated in body tissues was eliminated in 3 days, either by metabolic conversion to CO_2 or excretion in the urine. Evaluation of blood, urine, and tissues following the infusion of relatively large doses of glutaraldehyde demonstrated virtually no toxic effects. We conclude that the use of glutaraldehyde as a pulpotomy agent in humans would be free of any significant systemic toxicity.

This study was supported by NIDR grant DE0750-01.

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