ORIGINAL REPORT: PHASE I CLINICAL TRIAL

Pharmacokinetics of Iodine and Fluoride following Application of an Anticaries Varnish in Adults

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Abstract: Researchers have suggested that combining topical fluoride with an antiseptic to reduce cariogenic bacteria may be more effective than fluoride application alone in preventing dental caries. In previous studies, povidone iodine (PVP-I), a widely used bactericidal antiseptic, and sodium fluoride (NaF), used to foster remineralization of enamel, were applied sequentially topically and shown to be safe and effective. The study aim was to characterize the kinetics of iodine and fluoride following topical application of a single combination PVP-I and NaF anticaries varnish in healthy adults. Sixteen participants (aged 23 to 57 y) participated in a pharmacokinetics study following the application of 0.4 mL varnish containing 10% (w/v) PVP-I and 5% (w/v) NaF. Serum and urine samples were collected at various time points over 24 h following application of varnish. Iodine and fluoride concentrations were analyzed, and for each time point, baseline concentrations were subtracted from observed values. Following varnish

application, 2 of 16 participants had nearly undetectable baseline-corrected iodine and fluoride levels, suggesting minimal absorption, lack of release of iodine and fluoride from the varnish, or inconsistent dosing. The average peak concentrations were 57 ± 33 ng/mL iodine and 60 ± 34 ng/mL (0.060 ± 0.034 ppm) fluoride and occurred within 3 h of application. The average elimination half-life was 5.5 ± 1.4 h and 3.1 ± 1.6 h for iodine and fluoride, respectively. Renal clearance of iodine and fluoride was similar to literature values. No adverse events related to the study varnish were observed by the investigative team or reported by the participants. In this study, serum fluoride and iodine transiently increased but were within normal range 24 h after application of the varnish. This study has shown that the combination of PVP-I and NaF in a proposed anticaries varnish was well tolerated.

Knowledge Transfer Statement: This clinical study demonstrated that a dental varnish combining 10% (w/v)

povidone iodine and 5% (w/v) sodium fluoride is well tolerated. Serum fluoride and iodine transiently increased but were within normal range after 24 h. Further studies should be conducted to assess the efficacy of a combination in preventing dental caries, especially in high-risk populations.

Keywords: clinical study, healthy volunteers, dental, dental pharmaceutical preparations, dental caries prevention and control

Introduction

Fluoride is a well-recognized compound used to prevent dental caries. Most commonly, people consume fluoride through fluoridated community water, toothpaste, mouth rinses and gels, and varnish. Topical sodium fluoride (NaF)-containing varnishes have been shown to be effective in the prevention of dental caries in young patients (Weyant et al. 2013; Moyer 2014). Although the exact mechanism for NaF varnish's ability to prevent dental caries is not fully understood, investigators have suggested that NaF is able to foster remineralization

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of tooth enamel (Gao et al. 2016). While dental fluoride has been shown to have biological effects on the virulence factors of *Streptococcus mutans* in vitro, there is no evidence that the fluoride levels in available products are sufficient to have meaningful clinical effects on *S. mutans* (Buzalaf et al. 2011). Inclusion of antiseptics with topical fluorides may provide added benefit reducing or eliminating oral cariogenic bacteria (Milgrom et al. 2009). Iodine was tested against various oral bacterial species and shown to have preferential activity against *S. mutans*, a species implicated in the causation of dental caries (Tam et al. 2006; Furiga et al. 2008).

Povidone iodine (PVP-I) is a Food and Drug Administration (FDA)–approved and widely used bactericidal antiseptic and has been studied with NaF. Two cohort studies have tested the effect of sequentially applying PVP-I (10%) followed by 5% NaF varnish. In children aged 5 to 6 y, PVP-I and NaF were found to protect erupting first permanent molars from developing dental caries (Tut and Milgrom 2010). In children aged 12 to 30 mo, sequential application of PVP-I and NaF reduced the rate of new decay by 31% compared to NaF treatment alone (Milgrom et al. 2011).

To date, a combination PVP-I and NaF anticaries varnish has not been tested. In support of the development of a combination PVP-I and NaF varnish, an efficacy study in young children was designed and is currently ongoing (Milgrom et al. 2017). A second study was designed to determine circulating iodine and fluoride concentrations and excretion patterns in vivo, and the results are reported herein. Following application of the combination varnish to the teeth, some amount of the varnish will be swallowed and absorbed through the gastrointestinal (GI) tract. Minimal amounts are likely to be absorbed through the oral mucosa. We conducted a pharmacokinetic study to determine the serum concentrations of iodine and fluoride and total urinary excretion of iodine and fluoride following topical application of the combination PVP-I and NaF varnish to the teeth.

Materials and Methods

The reporting guidelines for Clinical Pharmacokinetic Studies (ClinPK) are followed in this article (Kanji et al. 2015).

Participant Recruitment

The study was conducted under IND 128835 from the FDA. The study was approved by the Western Institutional Review Board (#20161181). We enrolled healthy adult participants from November 2016 to February 2017 from the greater Seattle, Washington, region. Inclusion criteria were that participants must be aged 18 y or older, had at least 20 teeth, healthy as determined by medical history by the attending clinician, and not taking prescription or over-the-counter medications. Participants were excluded if they were pregnant, weighed less than 110 pounds, had oral mucositis or ulcerative lesions, had a sensitivity to shellfish or iodine or fluoride varnish, or had known hypothyroidism, hyperthyroidism, dermatitis herpetiformis, hypocomplementemic vasculitis, nodular thyroid with heart disease, multinodular goiter, Graves disease, or autoimmune thyroiditis.

Procedures

Following informed consent, basic demographics and health history were obtained. A brief visual examination was conducted to note any evidence of inflammatory or ulcerative changes to the gingival or other oral tissues. Participants were instructed not to consume seafood or shellfish the day prior to the study day through the 24-h blood draw period and to use nonfluoride toothpaste on the study day through the 24-h blood draw. Fluoride-free collection tubes were used for blood collection. Prior to application of the varnish, baseline blood and urine samples were collected from each participant. Teeth were brushed with a soft toothbrush to remove debris and dried with cotton prior to application of the varnish.

The combination varnish, containing 10% (w/v) PVP-I and 5% (w/v) NaF,

was commercially prepared by an FDA registered laboratory and used within 6 mo. The varnish is identical to that being used in an ongoing FDA-supervised clinical trial (Milgrom et al. 2017). The varnish was vortexed for 2 min before use to break up any undissolved shellac. A total volume of 0.4 mL of the varnish was applied with a dental applicator brush. The maximum total applied dose was estimated to be 8 mg of iodide and 12 mg of fluoride, but the actual dose for each participant is unknown due to variation in the volume applied and residual varnish remaining on the brush. Participants were not allowed to eat for at least 2 h following application of the varnish and were directly observed during the first 12 h after application of the varnish. Procedures were carried out in the University of Washington Medical Center, Institute of Translational Health Sciences, Translational Research Unit and the Regional Clinical Dental Research Center, School of Dentistry, University of Washington.

Sampling and Analytical Analysis

Blood samples (6 mL) were collected at 30 min and 1, 2, 3, 4, 6, 8, 12, and 24 h following application of the test varnish. Participants collected urine for 24 h, and the total volume was recorded. Samples were processed and those aliquoted for iodine analysis were refrigerated until analysis; those aliquoted for fluoride analysis were frozen at -20°C until analysis.

Blood and urine samples were analyzed for iodine by inductively coupled plasma–mass spectrometry (Mayo Medical Laboratories) and for fluoride by ion selective electrode (University of Washington, Environmental Health Laboratory and Trace Organics Analysis Center). The limit of detection for both serum and urine analyses was 10 ng/mL for iodine and 10 ng/mL (0.01 ppm) for fluoride.

Data Analysis

For the pharmacokinetic analysis, baseline serum iodine and fluoride

Table 1.
Participant Demographics.

Characteristic	Healthy Adult Volunteers (N = 16)
Age (y) ^a	41.4 ± 13.4 (23 to 57)
Male (n)	8
Race (n)	
Caucasian	11
African American	1
Asian	3
More than 1 race	1
Ethnicity (n)	
Not Hispanic or Latino	14
Unknown or not reported	2

^aMean ± standard deviation and (range) are provided for age.

concentrations were subtracted from other timed serum concentrations to adjust for baseline endogenous levels of iodine and fluoride. Baseline-corrected concentrations that had a negative value (i.e., measured concentration was lower than baseline concentration) or resulted in concentrations at the limit of detection for multiple time points (i.e., 10 ng/mL for fluoride) were excluded. Pharmacokinetic parameters were estimated using Phoenix WinNonlin (Certara). The elimination rate constant (k_{elim}) was determined by nonlinear regression of the terminal slope. Upon visual inspection, inclusion of the 24-h time point tended to decrease the estimated k_{elim} (increase the half-life). It appeared that the 24-h time point represented a mixture of endogenous iodine and fluoride and that absorbed from the varnish. Thus, data from the 24-h time point were excluded from the determination of k_{elim} . Two areas under the curve (AUCs) were calculated. The $\text{AUC}_{0-\infty}$ was calculated using a log-linear trapezoidal rule of baseline-corrected serum concentrations and extrapolated to infinite time by $C_{\text{last}}/k_{\text{elim}}$, where C_{last} was the last concentration used in the estimation of k_{elim} . The $\text{AUC}_{0-24 \text{ h}}$ represents the exposure to exogenous iodine or

fluoride following application of the PVP-I and NaF varnish. The $\text{AUC}_{0-24 \text{ h}}$ was calculated using a log-linear trapezoidal rule of total iodine or fluoride serum concentrations from time = 0 to 24 h. The $\text{AUC}_{0-24 \text{ h}}$ represents the exposure to both endogenous and exogenous iodine and fluoride over 24 h. The total urinary recovery of iodine and fluoride was determined by multiplying the concentration measured in a 24-h urine sample by the total volume of urine of the 24-h urine sample. The renal clearance of iodine and fluoride was calculated as the total urinary recovery/ $\text{AUC}_{0-24 \text{ h}}$.

For each participant, the time to peak concentration (T_{max}), observed and baseline-corrected peak concentrations (C_{max}), and observed 24-h concentration ($C_{24 \text{ h}}$) are reported. The elimination half-life, AUCs, and renal clearance are summarized.

Results

Participants

Sixteen healthy adults participated in the study. The participant demographics are summarized in Table 1. No adverse events, determined by the investigators and medical monitor as related or

possibly related to the application of the combination PVP-I and NaF varnish, were observed (gingival inflammation or soft tissue changes) or reported by participants (nausea, vomiting, difficulty swallowing or breathing, swelling around the lips or skin of the face, itchiness around the lips or skin of the face, hives or rash, stomachache or diarrhea).

Iodine Pharmacokinetics

Mean iodine concentrations and pharmacokinetic parameters are summarized in Table 2, and serum iodine versus time curves are shown in Figure 1. The baseline serum iodine concentrations ranged from 34 to 84 ng/mL. After correction for baseline levels, 2 of 16 participants had very low iodine levels following application of the PVP-I and NaF varnish (participants 5 and 16). The peak baseline-corrected concentrations of iodine ranged from 7 to 132 ng/mL and occurred between 0.5 and 3 h after application of the varnish. As described in the Materials and Methods, the 24-h iodine concentrations appeared to be a combination of exogenous and endogenous iodine. The uncorrected values at the 24-h time point were approximately comparable to baseline levels and ranged from 42 to 97 ng/mL. The estimated half-life of iodine was $5.1 \pm 1.8 \text{ h}$. The exposure to exogenous iodine ($\text{AUC}_{0-\infty}$) varied by 36-fold (34 to 1,238 ng·h/mL).

The amount of iodine recovered in urine over 24 h varied by nearly 8-fold (0.3 to 2.6 mg) (Table 2). The amount of iodine excreted was strongly correlated with total serum iodine $\text{AUC}_{0-24 \text{ h}}$ ($r = 0.66$; Fig. 3A). The renal clearance of iodine varied by approximately 6-fold (4.5 to 26 mL/min).

Fluoride Pharmacokinetics

Mean fluoride concentrations and pharmacokinetic parameters are summarized in Table 2, and serum fluoride versus time curves are shown in Figure 2. The baseline serum fluoride concentrations ranged from <10 to 50 ng/mL (<0.010 to 0.050 ppm). After

Table 2.

Summary of Observed Serum Fluoride and Iodine Concentration and Pharmacokinetic Parameters and Urinary Recovery for Baseline-Corrected Values ($N = 16$).

	Observed Iodine	Baseline-Corrected Iodine	Observed Fluoride	Baseline-Corrected Fluoride
Baseline (ng/mL)	54 ± 13		25 ± 13	
$T_{\max}$ (h)	1.7 ± 0.7	1.7 ± 0.7	0.8 ± 0.3	0.8 ± 0.3
$C_{\max}$ (ng/mL)	111 ± 36	57 ± 33	76 ± 36	60 ± 34
$C_{24\text{ h}}$ (ng/mL)	62 ± 16		24 ± 13	
$AUC_{0-24\text{ h}}$ (ng·h/mL)	1,810 ± 486		703 ± 350	
$AUC_{0-\infty}$ (ng·h/mL)		539 ± 315		315 ± 206
$t_{1/2}$ (h)		5.5 ± 1.4		3.1 ± 1.6
Total urinary recovery (mg) ^a	1.26 ± 0.71		2.51 ± 1.28	
Renal clearance (mL/min) ^b	11.3 ± 5.6		64.0 ± 27.4	

Values are presented as mean ± standard deviation.

$AUC_{0-24\text{ h}}$, area under the curve from $t = 0$ to 24 h, calculated using total serum concentration data (endogenous and exogenous iodine or fluoride); $AUC_{0-\infty}$, area under the curve from $t = 0$ to ∞ , calculated using baseline-corrected serum concentration data; $C_{24\text{ h}}$, observed concentration at 24 h; $C_{\max}$, observed peak concentration; $t_{1/2}$, terminal elimination half-life; $T_{\max}$, time of peak concentration.

^aTotal urinary recovery: (24 h urine concentration) × (24 h urine volume).

^bRenal clearance: total urinary recovery/ $AUC_{0-24\text{ h}}$.

Figure 1. Kinetics of iodine following application of the povidone iodine and sodium fluoride varnish. **(A)** Observed serum iodine concentrations ($n = 16$) and **(B)** baseline-corrected iodine concentrations with extrapolated values (open symbol) ($n = 16$) versus time. The 24-h timepoint was not used in the pharmacokinetic analyses.

correction for baseline levels, 2 of 16 participants had no detectable fluoride levels following application of the PVP-I and NaF varnish (participants 5 and 16), and 4 of 16 participants had 3 or fewer time points of fluoride concentrations.

Overall, baseline-corrected peak concentrations of fluoride ranged from 20 to 150 ng/mL (0.020 to 0.150 ppm) and occurred within the first hour after application of the PVP-I and NaF varnish. Although fluoride concentrations were

detectable until the 24-h time point for most participants, they approached baseline levels by 6 h for 10 of 16 participants. The half-life and AUC of fluoride were not able to be estimated in 4 of 16 participants due to an insufficient

Figure 2. Kinetics of fluoride following application of the povidone iodine and sodium fluoride varnish. **(A)** Observed serum fluoride concentrations ($n = 16$) and **(B)** baseline-corrected fluoride concentrations with extrapolated values (open symbols) ($n = 14$) versus time. Baseline-corrected concentrations that resulted in concentrations at the limit of detection for multiple time points (i.e., 10 ng/mL for fluoride) were excluded.

number of detectable baseline-corrected fluoride concentrations as described above. For the 12 of 16 participants, the estimated half-life of fluoride was 3.1 ± 1.6 h, and the exposure to exogenous fluoride (AUC_{0-24}) varied 13-fold from 66 to 847 ng·h/mL.

The amount of fluoride recovered in urine over 24 h ranged from 0.58 to 5.0 mg (Table 2). The amount of fluoride excreted was moderately correlated with total serum fluoride AUC_{0-24} ($r = 0.43$; Fig. 3B). The renal clearance of fluoride varied 7-fold from (21 to 145 mL/min).

Discussion

Baseline serum levels of iodine concentrations ranged from 34 to 84 ng/mL, which are within the reference range of 40 to 80 ng/mL (Allain et al. 1993). Similarly, baseline serum fluoride concentrations ranged from undetectable (<10 ng/mL) to 50 ng/mL, which are within the reference range of 19 to 76 ng/mL (Cardoso et al. 2006). Following application of the varnish, serum iodine and fluoride peaked rapidly within 3 h and 1 h, respectively, for participants with detectable baseline-corrected concentrations. The uncorrected peak serum iodine levels (111 ± 36 ng/mL) transiently exceeded the reference

range of serum concentrations and were equivalent to baseline levels by 24 h. The uncorrected peak fluoride levels (76 ± 36 ng/mL) exceeded the reference range for 8 of 16 participants. Depending on fluoride levels achieved, circulating concentrations of fluoride returned to baseline levels within 2 to 24 h for most participants. The half-life of iodine ranged from 3.4 to 8.3 h. No reported half-life of iodine was found in the literature. The half-life of fluoride of 2 to 6.8 h in these study participants is similar to those reported in the literature (Ekstrand and Ehrnebo 1983). After administration of sodium fluoride tablets, the plasma half-life of fluoride was estimated to be 5.78 h (Ekstrand and Ehrnebo 1983). Variability between study participants in iodine and fluoride levels may be due to difference in the amount of varnish applied, lack of release iodine and fluoride from the varnish, or differences in absorption.

For all participants, the total amount of iodine excreted (1.26 ± 0.71 mg) was higher than the reported reference range of urinary 24-h collection of 0.075 to 0.279 mg of iodine (Knudsen et al. 2000). Similarly, the total amount of fluoride excreted (2.51 ± 1.28 mg) was higher than reported urinary 24-h collection of 0.378 ± 0.051 mg of fluoride (Schiff

and Binswanger 1980). Our values exceeded the urinary iodine and fluoride excretion reference ranges because our study participants were treated with the combination anticaries varnish, whereas individuals in the cited literature were studied under normal dietary conditions. Urinary excretion of fluoride and iodine was strongly correlated over the 24-h period ($r = 0.68$; Fig. 3C). This finding is not unexpected as both iodine and fluoride are extensively cleared by renal excretion (Schiff and Binswanger 1980; Jahreis et al. 2001). The renal clearance of iodide was reported to vary between 28 and 67 mL/min in 3 healthy participants (Vought and London 1967), which was higher than the values seen in this study (11.3 ± 5.6 mL/min). The renal clearance of fluoride reported after administration of intravenous and oral fluoride in healthy adults (66.2 ± 27.8 mL/min) (Ekstrand et al. 1978) was similar to the values seen in this study (64.0 ± 27.4 mL/min). Both iodine and fluoride are subject to reabsorption as the renal clearances are lower than glomerular filtration (~110 mL/min).

There are several limitations to the study. The actual amount of PVP-I and NaF swallowed by each participant is unknown and likely to be highly variable. Thus, we could not calculate

Figure 3. Correlation of 24-h urinary recovery of iodine and total serum iodine AUC_{0-24 h} (A), 24-h urinary recovery of fluoride and total serum fluoride AUC_{0-24 h} (B), and urinary recovery of iodine and fluoride over 24 h following application of the povidone iodine and sodium fluoride varnish (C). AUC, area under the curve.

dose-adjusted serum concentrations of fluoride or iodine. In addition, we did not correct for the baseline excretion of iodine or fluoride in the participants as 24-h urine collections were not performed prior to application of the varnish. The reported urinary data include both iodine and fluoride from the varnish and other exposures (i.e., diet). Although participants were instructed to use fluoride-free toothpaste and not consume shellfish or seafood during the study, their diets were not monitored or recorded. Some individuals did not have appreciable changes to their fluoride concentration versus time profiles, and it is unclear whether this is due to low ingested doses or assay sensitivity at very low serum fluoride concentrations.

In this study, no adverse effects were observed, and none of the participants reported any adverse effects that were deemed to be related to the application of the varnish. Similarly, no adverse events were observed in children aged 6 to 83 mo receiving sequential application of topical PVP-I and NaF 3 times over the course of a school year (Tut and Milgrom 2010). The combination PVP-I and NaF varnish did not significantly alter iodine or fluoride plasma concentrations following a single clinical application. Only 1 study reported iodine concentrations following longer term usage of PVP-I. Ader et al. (1988) reported elevated serum iodine and urinary iodine excretion with no change in serum triiodothyronine (T_3) and thyroxine (T_4) concentrations

following 6 mo of daily use of PVP-I-containing mouth rinses. Although they observed a small increase in thyroid-stimulating hormone due to a physiological response to the excess iodine exposure, they determined that the increases were within the normal circulating concentrations, and no thyroid dysfunction was likely to develop during a 6-mo mouth-rinse treatment.

Although this study was conducted in adults, we would anticipate similar results in children. Iodine and fluoride are extensively cleared by renal excretion (Schiffel and Binswanger 1980; Jahreis et al. 2001). When corrected to standard body surface area, renal clearance and glomerular filtration rate approach adult values by the age of 2 y in a study of newborns, infants, and children (Rubin

et al. 1949). Following application of 2 to 5 mg of fluoride varnish, peak fluoride concentrations of 60 to 120 ng/mL were observed at 2 h in 4 children aged 4 to 14 y (Ekstrand et al. 1980). In addition, Ekstrand et al. (1980) reported the urinary fluoride output was in agreement with the total fluoride dose applied. Similarly, we found moderate correlations between urinary fluoride and iodine recovery and total serum exposure over 24 h. For vulnerable populations in whom blood sampling is challenging due to ethical or practical concerns, the urinary excretion rate parallels the plasma level of fluoride (Ekstrand and Ehrnebo 1983) and might be used as a surrogate biomarker of fluoride exposure. Although some factors, such as urinary pH, urine flow, and glomerular filtration rate, may influence fluoride and iodine excretion, renal clearance appears to be relatively constant from children older than 1 y and adults.

Overall, following application of the PVP-I and NaF combination varnish, the circulating levels of iodine and fluoride were transiently elevated and returned to baseline within 24 h for most participants. The pharmacokinetics of iodine and fluoride following application of the PVP-I and NaF varnish were comparable to literature values. Given the safety profile of this combination varnish and predictable pharmacokinetics, we believe that this varnish should be continued to be studied for efficacy in the prevention of caries.

Author Contributions

Y.S. Lin, contributed to conception, design, and data analysis, drafted and critically revised the manuscript; M.L. Rothen, contributed to conception, design, data acquisition, and interpretation, drafted and critically revised the manuscript; P. Milgrom, contributed to conception, design, data analysis, and interpretation, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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