Qualitative Evaluation of Fluoride Ions in Different Sodium Fluoride Tablet Formulations Used for Children

F. Mazhari DDS, MS*, M. Hassanzadeh-Khayyat PhD**, A. Makarem DDS, MS***, H. Oraphai PhD****

ABSTRACT

Introduction: Use of fluoride tablet is one of the several ways of fluoridation in children. The purpose of this study was to evaluate the systemic absorption of fluoride from a generic sodium fluoride tablet, in comparison with a commercial one.

Methods and Materials: This was a double-blind, cross over study. Following ingestion of 1 mg of fluoride in a generic or commercial form, urine samples were collected from 27 healthy boys aged 8-10 years old over a 24-hour period. The urine samples were analyzed by potentiometric method using fluoride ion selective electrode.

Results: Under the identical conditions, the mean 24-hour urinary fluoride excretion rate of the subjects before taking any generic and commercial fluoride tablets were 15.87±4.68 and 17.51±6.40 µg/hr, respectively. The average rates of 24-hour urinary fluoride excretion of the subjects were 25.74±6.75 and 28.21±9.23 µg/hr after the ingestion of generic and commercial fluoride tablets, respectively. The mean cumulative amounts of fluoride ion excreted in 24-hour urine collection were 28% and 22% of the administered doses of commercial and generic fluoride tablets, respectively.

Discussion: Results indicated that the systemic absorption of the fluoride ion released from the generic tablet is not significantly different from the commercial one. Therefore, it can be suggested that the tested generic tablets is bioequivalent to the commercial ones.

Key Words: Systemic Absorption, Children Sodium Fluoride Tablet.

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In this study, the systemic absorption of fluoride from a generic sodium fluoride tablet was compared with the systemic absorption of a commercial sodium fluoride one in children. Usually, the plasma concentration of fluoride is measured for determination of the amount of drug absorption, which needs to take several blood samples from children in certain intervals after dose administration \(^3,4\). This kind of study is almost impossible in children \(^3\). One of the recommended methods for the fluoride monitoring in children, to ensure that the absorption of fluoride from various sources is at an appropriate level, is measurement of urinary fluoride excretion and its comparison with normal values \(^5\text{-}12\). Urinary excretion correlates with the plasma fluoride concentration very well, which is regarded as the most valid indicator of the fluoride supply to the organism \(^13\).

The rate of urinary fluoride excretion varies throughout the day and night, in relation to the time of fluoride ingestion, particularly where fluoride supplementation is given once daily e.g. in the form of fluoride tablets. When urine analysis is carried out to assess fluoride excretion it should ideally cover a 24-hour sample collection, although it is not a particularly convenient method for monitoring the fluoride excretion of the population in general \(^14\). However, many researches indicate that collecting the urine is a variable and valuable method for monitoring urinary fluoride excretion rate \(^15,16\).

In addition to the use of urinary fluoride excretion rate, to monitor fluoride absorption by comparing it with normal value, it can also be used as a basis for estimation of fluoride intake \(^17\).

The aim of this study was therefore to use of urinary fluoride excretion rate to estimate and compare systemic absorption of fluoride from the two different formulations (generic and commercial tablets) after administration for children.

### Methods and Materials

#### Subjects
Approval to conduct the study was obtained from the local research ethics committee. Twenty seven normal healthy children aged between 8-10 years old (average of 9) living in a boarding unit, were participated in this investigation. All children were in good general health and had not received any medication for two weeks prior to the initiation of study. The subjects were using a similar diet and enjoying the same community environment. They were using the same kind of toothpaste and their water supply was containing 0.2 ppm of fluoride.

#### Experimental design
In this study the generic tablet, made in school of pharmacy, was compared with a commercial sodium fluoride tablet Zy-mafluor, Germany (both containing 2.2mg of NaF equal to 1mg of fluoride ion). Each subject received 1 mg of fluoride per day for three days in two different occasions (generic or commercial fluoride tablets). Sampling was started on third day. The study was designed as a randomized double-blind crossover investigation with a two weeks wash out period.

#### Sampling
Total 24-hour urine specimens were carefully collected in three eight-hour separate portions and stored in separate large wide-necked screw-topped polyethylene bottles. Urine samples were refrigerated until analysis. The three eight-hour separate portions of urine were collected from 22.00 to 6.00, 6.00 to 14.00, and 14.00 to 22.00 o'clock.

In addition to collecting urine samples after fluoride administration for the subjects, the 24-hour urine specimens (as three eight-hour separate portions) were also collected before dose administration in two separate occasions (before administration of either generic or commercial forms). These urine samples were analyzed for fluoride and used...
as a baseline (background) for estimation of fluoride intake. When collection of urine was incomplete, the entire sample was excluded from the study.

**Assays and procedures**

The volume of each individual sample was measured and recorded. Fluoride ion concentration was determined using a fluoride ion specific electrode (Metrohm AG) after diluting each sample (1:1) with the TISAB III ionic buffer solution \(^{17, 18}\). Calibration curves were prepared using standard aqueous fluoride and TISAB buffer solutions which both were specified by the manufacturer prior and during the analysis of the samples. A linear standard curve was constructed in the range of 0.5 to 5 ppm of fluoride ion. The fluoride content of each sample (in milligrams) was calculated as the sample fluoride concentration (ppm of fluoride ion) and multiplied by the sample volume. Knowing the time interval of each collection (8 hours), the urinary fluoride excretion rate was calculated for each sample in micrograms of fluoride per hour. The total fluoride excretion over the 24-hour period of time was calculated as the sum of the fluoride content of the three urine samples collected over the period of 24-hour (one sample per every eight hours). Repeated measurement and Wilcoxon's tests were used for comparison between the groups.

**Results**

The mean urinary flow rate for the twenty seven subjects over the 24-hour period, over the each of the eight-hour period of urine collection, and before and/or after oral administration of generic and commercial fluoride tablets are shown in table 1. Figure 1 shows the comparison between the urinary fluoride excretion rates in 24-hour periods of urine collection before taking any fluoride tablets in two different occasions. The mean urinary fluoride excretion rates of the subjects over the 24-hour period and also over the each of the eight-hour periods of urine collection, before and after taking generic and commercial fluoride tablets is shown in table 2. Figure 1 also shows the comparison of the urinary fluoride excretion rates in 24-hour periods of urine collection after commercial and generic fluoride tablet administrations.

The total amount of fluoride ion excreted after oral administration of commercial and generic fluoride tables (both containing 2.2 of NaF equal to 1 mg of fluoride ion) was calculated for each subject. The mean cumulative amount of fluoride ion excreted over the 24-hour period of urine collection is shown in table 3.

<table>
<thead>
<tr>
<th>Occasion</th>
<th>M.U.F.R. during the periods of urine collection (ml/min)</th>
<th>M.U.F.R. over 24-hour period (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22.00-6.00 (o'clock)</td>
<td>6.00-14.00 (o'clock)</td>
</tr>
<tr>
<td>Before administration of generic tablet</td>
<td>0.31</td>
<td>0.26</td>
</tr>
<tr>
<td>After administration of generic tablet</td>
<td>0.34</td>
<td>0.29</td>
</tr>
<tr>
<td>Before administration of commercial tablet</td>
<td>0.29</td>
<td>0.27</td>
</tr>
<tr>
<td>After administration of commercial tablet</td>
<td>0.29</td>
<td>0.39</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Mean urinary excretion rate (M.U.E.R.) of fluoride ion in twenty seven healthy children over the 24-hour period before and after administration of 1 mg of fluoride as generic or commercial tablets.

<table>
<thead>
<tr>
<th>Administration time</th>
<th>M.U.E.R. of fluoride during each period of urine collection (μg/hr)</th>
<th>M.U.E.R. of fluoride in 24-hour period (μg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22.00-6.00 (o'clock) 6.00-14.00 (o'clock) 14-22.00 (o'clock)</td>
<td></td>
</tr>
<tr>
<td>Before administration of generic tablet</td>
<td>17.44±8.37 13.78±4.01 16.10±8.90</td>
<td>15.87±4.68</td>
</tr>
<tr>
<td>After administration of generic tablet</td>
<td>39.28±11.79 13.20±4.66 24.73±7.90</td>
<td>25.74±6.75</td>
</tr>
<tr>
<td>Before administration of commercial tablet</td>
<td>16.21±7.90 16.50±9.37 19.62±7.18</td>
<td>17.51±6.40</td>
</tr>
<tr>
<td>After administration of commercial tablet</td>
<td>36.37±13.52 21.27±11.18 26.98±10.56</td>
<td>28.21±9.23</td>
</tr>
</tbody>
</table>

Table 3. Mean cumulative urinary excretion (M.C.U.E) of fluoride ion in twenty seven healthy children before and/or after oral administration of 1mg of fluoride as generic and commercial tablets.

<table>
<thead>
<tr>
<th>Administration time</th>
<th>M.C.U.E. of fluoride ion (μg) during each periods of urine collection</th>
<th>M.C.U.E. of fluoride (μg) in 24-hour period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22.00-6.00 (o'clock) 6.00-14.00 (o'clock) 14.00-22.00 (o'clock)</td>
<td></td>
</tr>
<tr>
<td>Before administration of generic tablet</td>
<td>139.55 110.27 128.66</td>
<td>378.48</td>
</tr>
<tr>
<td>After administration of generic tablet</td>
<td>314.21 105.60 197.86</td>
<td>617.67</td>
</tr>
<tr>
<td>Before administration of commercial tablet</td>
<td>129.68 131.99 156.67</td>
<td>418.56</td>
</tr>
<tr>
<td>After administration of commercial tablet</td>
<td>290.92 170.16 215.85</td>
<td>676.93</td>
</tr>
</tbody>
</table>

Figure 1. Comparison between mean urinary excretion rates of fluoride ion in twenty seven healthy children before and/or after oral administration of 1mg of fluoride as a generic or commercial tablet, over the 24-hour period.
Discussion
The average 24-hours urinary flow rate for all the subjects was 0.37±0.06 ml/min (ranged from 0.31 to 0.44 ml/min, table 1). As it is shown in figure 1, the urinary fluoride excretions rate in 24-hour periods of urine collection are fairly close in two different occasions, before taking any fluoride (15.87±4.68 and 17.51±6.40 µµµµg/hr, respectively). Statistical analysis showed no significant differences between the urinary fluoride excretion rates, in two different occasions, over the period of twenty-four hours and/or over the each of the eight-hour periods of urine collection, before taking any fluoride tablet which confirms the similarity of the subjects' diet and community environment.

Ingestion of the sodium fluoride tablet increased the amount of excreted fluoride. The averages of 24-hour urinary fluoride excretion rates of the subjects were 25.74±6.75 and 28.21±9.23 µµµµg/hr after administration of generic and commercial fluoride tablets, respectively (figure 1). These results are very close to the results of a similar report by Musset (1992) in which urinary fluoride excretion rate was 26.34±8.73 µµµµg/hr after administration of sodium fluoride tablet, equal to 1mg of fluoride ion 19.

Statistical analysis showed no significant differences between the urinary fluoride excretion rate, over 24-hour period and each of eight-hour periods of urine collection, after administration of the commercial and generic fluoride tablets. This shows the relatively similar systemic absorption of fluoride from the two sodium fluoride tablets (commercial and generic).

Statistical analysis of 24-hour urinary fluoride excretion rates before and after administration of either commercial or generic fluoride tablets showed significant differences (P<0.0001). This difference indicates the significant systemic absorption of fluoride ion after administration of each tablet (commercial and/or generic). It is important to mention that the urinary fluoride excretion rate was considerably high in the first eight-hour period after the tablet administration, in comparison with the other two urine collection periods (second and third eight-hour after ingestion)(table 2). These indicate the rapid absorption and excretion of fluoride in the body. However, the reason for higher urinary fluoride excretion rate in the third eight-hour period is due to the lunch and afternoon tea. These results are similar to the other reported data 19.

The mean cumulative amount of fluoride ion excreted in 24-hour period of urine collection in two different occasions, was 398.52 µg before taking any fluoride which was used as a background. The mean cumulative amounts of fluoride ion excreted in 24-hour period of urine collection after administration of a commercial and generic fluoride tablets were 278.41 µg (about 28% of administered dose) and 219.15 µg (about 22% of administered dose), respectively (after subtracting the background). This shows the close amounts of fluoride excreted in urine after administration of either the generic or commercial fluoride tablets. This also shows that from administered fluoride, less than 30% excreted over a 24-hour period. Considering the fluoride short half-life it seems that over 70% of the administered dose has been absorbed. Comparison of the urinary fluoride excretion rate and total amounts of fluoride ion excreted after administration of generic and commercial tablets indicates that the generic tablets are bio-equivalent to the commercial ones.

References