Salt vs. Free-base Nicotine in E-Liquids Does Not Impact Nicotine Plasma Levels

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Abstract

E-Liquids are commonly made with free-base nicotine or protonated nicotine in various salts. Salt forms are perceived as less harsh by vapers. A crossover in-patient clinical study was performed to evaluate the impact of the nicotine form on plasma levels. Subjects vaped different nicotine strengths (3 – 50 mg/ml) of the same E-Liquid flavor (Tobacco Gold No. 1) made with either free-base nicotine or nicotine protonated with lactic acid (nicotine lactate). A total of 36 subjects vaped the products under controlled conditions: a 2-3 second puff every 30 seconds for a total of 10 puffs. The subjects also smoked their own brand cigarettes or chewed nicotine gum in an in-patient facility. Blood samples were drawn at time zero up to 180 minutes. Own-brand cigarette nicotine plasma levels peaked in 6 minutes with a maximum concentration of 18.7 ng/mL. The 35 and 50 mg/mL Tobacco Gold nicotine lactate E-Liquid peaked at 6 and 7 minutes at maximum concentrations of 14.6 and 16.2 ng/mL, respectively. The Tobacco Gold nicotine free base 18 mg/mL peaked at 10 minutes at a concentration of 5.3 ng/ml. This was equivalent to the Nicorette gum (5.9 ng/mL) which peaked at 45 minutes. The Tobacco Gold nicotine free base 3 mg/mL product peaked at 10 minutes with a plasma level of 1.9 ng/mL, less than the Nicorette gum. The plasma levels were proportional to the nicotine strength irrespective of the form (lactic acid salt or free-base) demonstrating that nicotine form (either salt or free-base) has no effect on nicotine absorption.

Methods

This was a randomized, open-label, crossover study designed to evaluate the nicotine pharmacokinetics (PK) of Twist brand Tobacco Gold No. 1 E-Liquids (**Figure 1**) compared to Nicorette 4 mg nicotine gum and own brand cigarettes in healthy adult male and female smokers. The Tobacco Gold No. 1 E-Liquid was tested at nicotine concentrations of 3, 18, 35, and 50 mg/mL. The 3 and 18 mg/mL nicotine was a nicotine free-base formula and the 35 and 50 mg/mL were lactic acid salts. The formulas were similar except for the form and concentration of nicotine. Each subject was provided with an Aspire Nautilus™ tank-system atomizer (**Figure 2**) equipped with a 1.8 ohm coil. The airflow hole was set to 1.1 mm. The battery was set to 12 watts. The Aspire Nautilus was chosen because it is the system that was used for the CORESTA HPHC method validation program. Subjects vaped 10 times (maximum 3 ± 2 seconds per puff) at approximately 30 ± 5–second inter-puff intervals. Subjects also puffed their own brand cigarette 10 times at 30 second intervals. Mint flavor Nicorette Gum (4 mg nicotine complexed with polacrilex) was chewed for 30 minutes as per label instructions.

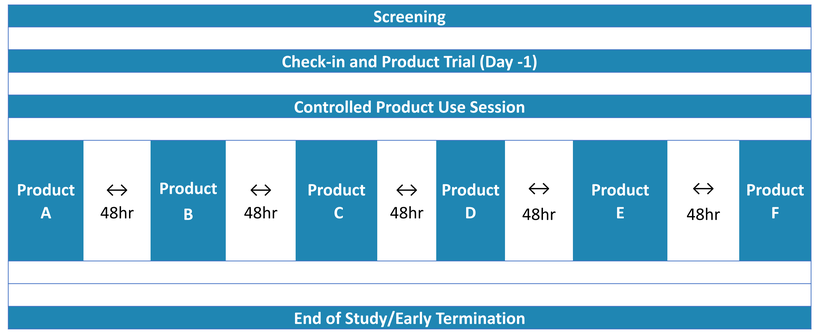
Subjects had to have a history of smoking an average of ≥10 cigarettes daily for at least 1 year and tested positive for urine cotinine (≥200 ng/mL) at Screening. Subjects participated in a standard Screening Visit and a Confined Assessment Phase, which included a Product Trial Session on Day -1 and Product Use Sessions, which consisted of morning Controlled Product Use Sessions. Each study day of product use was separated by approximately 48 hours. Subjects vaped the study products, puffed their own brand cigarette or chewed the gum in a random order. Blood sampling was within 5 minutes of start of product use (T_0) and at 2, 5, 10, 15, 30, 45, 60, 90 and 180 minutes after product administration. **Figure 3** shows the study design.

Figure 1. Twist Brand Tobacco Gold No.1 E-Liquid

Figure 2. Aspire Nautilus Tank

Methods

Figure 3. Study Design



Product A: Tobacco Gold No. 1 flavor, 3 mg/mL free-base nicotine

Product B: Tobacco Gold No. 1 flavor, 18 mg/mL free-base nicotine

Product C: Tobacco Gold No. 1 flavor, 35 mg/mL nicotine lactic acid salt

Product D: Tobacco Gold No. 1 flavor, 50 mg/mL nicotine lactic acid salt

Product E: Own-brand cigarette, regular (non-menthol) or menthol flavor

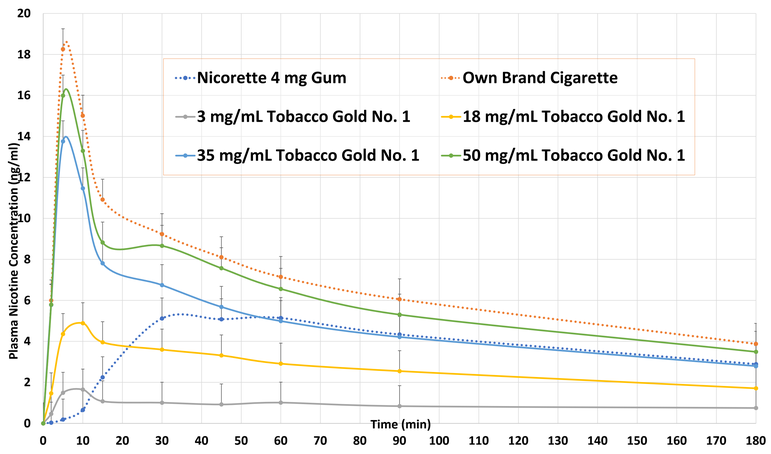
Product F: Nicorette gum, Mint flavor, 4 mg nicotine

Results

A total of 39 per day for a mean duration of 23.1 years. Approximately half of subjects used menthol cigarettes (48.7%) and the other half used non-menthol cigarettes (51.3%).

Nicotine plasma levels were measured after controlled use of the products. **Figure 4** shows the baseline adjusted plasma nicotine concentrations of each product and **Table 1** shows the derived nicotine pharmacokinetic parameters. Own-brand cigarette nicotine plasma levels peaked in 6 minutes with a maximum concentration of 18.7 ng/mL. The nicotine salt based 35 and 50 mg/mL Tobacco Gold No. 1 peaked at 6 and 7 minutes at maximum concentrations of 14.6 and 16.2 ng/mL, respectively. The freebase nicotine 18 mg/mL Tobacco Gold No.1 peaked at 10 minutes at a concentration of 5.3 ng/ml. This was equivalent to the Nicorette gum (5.9 ng/mL) which peaked at 45 minutes. The 3 mg and 6 mg products, also with freebase nicotine, peaked at 6 or 10 minutes with plasma levels ranging from 1.9 toA 3.9 ng/mL, all less than the Nicorette gum. The rate of nicotine plasma rise (C_{max}/T_{max}) was greatest for own-brand (3.1 ng/mL/min) followed by 2.4 and 2.3 for the 35 and 50 mg/mL Tobacco Gold No. 1. The rate of rise for the 18 and 3 mg/mL Tobacco Gold No. 1 was 0.5 and 0.2 respectively. Nicorette gum was slowest at 0.1. The total amount of nicotine absorbed was greatest for own-brand (AUC = 1239 ng*min/mL) followed by the 50 mg/mL Tobacco Gold No. 1 (1114) and the 35 mg/mL Tobacco Gold No. 1 (890). Nicorette Gum was next at 670. The 3, 6, and 18 mg/mL product AUCs were all less than the gum (range 158-178).

Figure 4. Baseline Adjusted Plasma Nicotine Concentrations



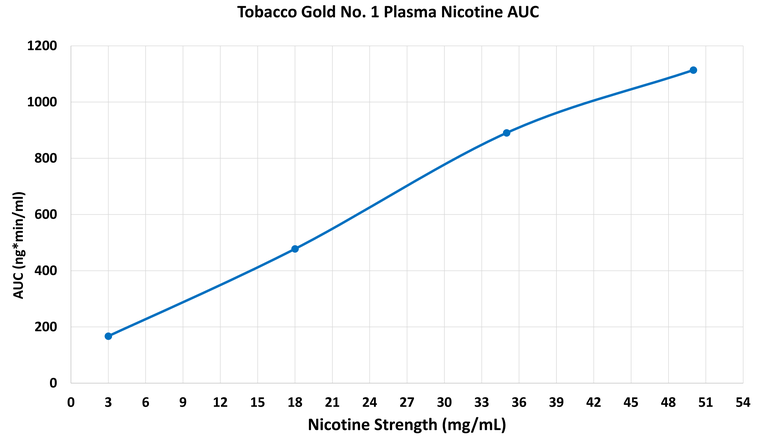
Results

Table 1. Nicotine Pharmacokinetic Parameters

Parameter	Tobacco Gold No. 1 3 mg/mL n = 36 - 37	Tobacco Gold No. 1 18 mg/mL n = 36	Tobacco Gold No. 1 35 mg/mL n = 35	Tobacco Gold No. 1 50 mg/mL n = 37	Own-Brand Cigarette n = 37	Nicorette Gum 4 mg n = 35 - 36
C_{max} (ng/mL)						
Mean	1.9	5.3	14.6	16.2	18.7	5.9
SD	1.29	4.68	14.36	16.08	12.96	4.13
T_{max} (minutes)						
Median	10.0	10.0	6.0	7.0	6.0	45.0
$AUC_{(0-t)}$ (ng*min/mL)						
Mean	167.1	477.6	890.3	1113.8	1239.4	669.9
SD	76.87	275	720.1	921.01	490.73	429.49
$AUC_{(0-180)}$ (ng*min/mL)						
Mean	166.7	477.6	889.8	1113.1	1238.2	680.9
SD	76.63	275.02	719.5	921.0	490.17	430.10

Figure 5 shows the plasma nicotine AUC as a function of the amount of nicotine in the E-Liquid. The 3 and 18 mg/mL E-Liquids, as noted before, are made with free base nicotine and the 35 and 50 mg/mL are lactic acid salts of nicotine. **The AUC increases in proportion to the nicotine concentration in the E-Liquid irrespective of the nicotine form (free base or salt).** This demonstrates that nicotine form (either lactic acid salt or free-base) has no effect on nicotine absorption.

Figure 5. Plasma Nicotine as a Function of Nicotine Concentration in E-Liquid



Conclusions

Plasma nicotine levels increased with increasing nicotine strengths. The maximum plasma nicotine concentration (Cmax) for the Twist products was less than own-brand cigarettes. The area under the curve was also less than own-brand cigarettes. The time to maximum plasma concentration (Tmax) was equal to or slower than own brand cigarettes. A comparison of free-base to the lactic acid nicotine salt AUCs indicated that **the salt formulation did not affect nicotine absorption**.

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